Université de Montréal

Addressing gaps in colorectal cancer screening in Canada: Multilevel determinants of screening, pathways to screening inequalities, and program evaluation

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RÉSUMÉ

Contexte : Le cancer colorectal occupe présentement le deuxième rang des cancers les plus diagnostiqués au Canada et le troisième rang des cancers causant le plus grand nombre de décès. Malgré les avantages du dépistage préventif pour l'identification précoce du cancer colorectal, seulement 20% à 30% des adultes canadiens âgés de 50 à 74 ans participent au dépistage de façon régulière. De plus, il existe plusieurs inégalités sociales au niveau de la participation au dépistage.

But : Les objectifs généraux de cette thèse sont de développer une meilleure compréhension des déterminants sociaux du dépistage colorectal et d'explorer les voies potentielles d'intervention—à la fois en identifiant des mécanismes qui expliquent les disparités sociales de dépistage et en évaluant si les stratégies actuelles d'intervention au niveau de la population permettent de promouvoir le dépistage et de réduire les inégalités sociales de dépistage.
La thèse comprend trois objectifs spécifiques :

1) Examiner l'association entre le revenu du quartier et la participation au dépistage colorectal;
2) Examiner si l'accès à un médecin régulier agit comme médiateur de l'inégalité de dépistage observée entre les nouveaux arrivants au Canada et les personnes nées au Canada;
3) Évaluer les retombées de deux types de programmes de dépistage du cancer colorectal au Canada (soit des programmes « systématiques » qui impliquent l'envoi et la réception de tests de dépistage à tout résident âgé de 50 à 74 ans par courrier; et des programmes « centrés sur la décision du patient » qui renvoient la responsabilité aux patients de demander le test par l'intermédiaire d'une ligne téléphone, d'un site web, ou de leur médecin, et ensuite de retourner le test en personne) sur la participation au dépistage et sur les inégalités sociales de dépistage.

Méthodes : Les analyses ont été effectuées à partir des données recueillies auprès des répondants âgés de 50 à 75 ans de l'Enquête sur la santé dans les collectivités canadiennes (ESCC) qui ne présentaient aucun facteur de risque familial ou médical connu de cancer colorectal (personnes à risque moyen). Les données de l'ESCC fournissent l'information sur l'âge, le sexe, l'état matrimonial, le niveau de scolarité, le revenu, le statut immigrant et de

minorité visible, l'accès à un médecin de famille, la ruralité du lieu de résidence, la province de résidence, et la participation à vie (au moins une fois) au dépistage du cancer colorectal, et le dépistage récent (soit par test de selles dans les des deux années précédentes ou par un test endoscopique dans les cinq années précédentes). Les données du Recensement canadien de 2006 ont été utilisées pour caractériser le revenu du quartier des répondants. Les analyses effectuées comprennent, entre autres, des équations d'estimation généralisées (objectif 1), des analyses de médiation incluant des analyses de régression et de pondération par la probabilité inverse (objectif 2), et des analyses évaluatives de type « différences entre les différences » (« Difference-in-Differences ») par le biais d'analyses de régression (objectif 3).

Résultats : Les résultats indiquent que le dépistage colorectal est déterminé par des facteurs individuels et contextuels. Cette thèse a révélé un gradient dans le dépistage de cancer colorectal selon le revenu du quartier au Canada, indépendamment des caractéristiques sociales et économiques des individus. Cette observation permet d'entrevoir l'influence des contextes sociaux et environnementaux sur le dépistage du cancer colorectal. De plus, les résultats suggèrent que l'accès aux médecins n'est pas un médiateur de l'association entre l'immigration et le dépistage du cancer colorectal. D'autres mécanismes explicatifs doivent être explorés pour mieux comprendre les causes intermédiaires. Enfin, les programmes dits systématiques et patient-dépendants sont tous les deux associés à une augmentation de participation au dépistage. Cependant, ces deux types de programmes ne semblent pas réduire les inégalités sociales de dépistage. En fait, le programme patient-dépendant semble augmenter la disparité de dépistage entre ceux avec et sans un médecin de famille. Il est possible que la réduction des inégalités sociales du dépistage doive nécessiter la mise en place de stratégies d'intervention davantage ciblées.

Conclusions : Cette thèse contribue à l'avancement des connaissances sur les déterminants sociaux du dépistage du cancer colorectal au Canada. Les résultats suggèrent que les contextes socioéconomiques méritent d'être explorés dans la surveillance et les recherches futures sur le dépistage colorectal. Parmi les pistes de recherche porteuses, on compte des recherches portant sur les mécanismes explicatifs des inégalités sociales et des études sur les interventions potentielles pour promouvoir le dépistage parmi les plus populations plus vulnérables.

Mots clés (versions françaises des mots clés MeSH): Tumeurs colorectales, détection précoce de cancer, endoscopie, déterminants sociaux de la santé, inégalités, caractéristiques de l'habitat, mesures épidémiologiques, méthodes épidémiologiques, politique de santé, évaluation de programme.

SUMMARY

Background: Colorectal cancer is the second most diagnosed cancer in Canada and the third most common cause of cancer mortality. Despite the known benefits of early and regular use of preventive screening tests, only 20% to 30% of Canadian adults aged 50 to 74 years participate in regular screening, and social disparities in screening participation exist.

Purpose: The overall aims of the proposed thesis are to contribute to a better understanding of the social determinants of colorectal cancer screening in Canada and to explore potential pathways for intervention—both by identifying mechanisms that explain existing social disparities and by evaluating whether or not current population-level intervention strategies affect screening uptake overall and among vulnerable populations. The specific objectives of the thesis are as follows:

1) To assess the association between area-level socioeconomic deprivation and colorectal cancer screening participation;
2) To assess whether or not access to primary care physician mediates differences in screening uptake between recent immigrants and non-immigrants in Canada;
3) To evaluate the impact of two types of colorectal cancer screening programs ("systematic mail-based programs" that deliver and collect screening kits via-mail to all residents aged 50 to 74 years, and "patient-reliant programs" that rely on individuals to access test kits via a designed phone-line, website, or their physician, and return kits in-person) on screening participation, and screening disparities.

Methods: Analyses were conducted utilizing data from 50 to 75-year-old respondents from the population-based Canadian Community Health Study (CCHS) who had no known familial or medical risk factors of colorectal cancer (i.e., those at 'average risk'). CCHS data provided information on respondents' age, sex, marital status, educational attainment, income, immigration status, visible minority status, access to a primary care physician, area and province of residence, and both lifetime (i.e., ever vs. never) and non-recent colorectal cancer screening (i.e., no stool-based screening in the previous two years or no endoscopic-based screening in the previous five years). Data from the 2006 Canadian Census provided

information on respondents' local area-level income. Different types of analyses were used, including generalized estimating equations (Objective 1), regression- and inverse probability weighting-based mediation analyses (Objective 2), and regression-based difference-in-differences analyses for program evaluation (Objective 3).

Results: First, findings suggest that colorectal cancer screening is determined by both individual- and local area-level or region-wide factors. This thesis observed a gradient in lifetime colorectal cancer screening according to local area-income in Canada independent of individual-level social and economic factors. This finding highlights the potential influence of social and environmental contexts on colorectal cancer screening uptake. Second, access to primary care physicians was not found to mediate the association between recent immigration and colorectal cancer screening. This finding suggests that alternative interventions to reduce immigration-based disparities should be explored. Lastly, both systematic and patient-reliant programs were observed to improve overall screening participation. However, both types of programs did not appear to reduce known social and economic screening inequalities. In fact, the patient-reliant program studied was observed to increase the screening disparity between those with and without a primary care physician. These results indicate that reductions in social inequalities related to colorectal cancer screening may require more targeted strategies.

Conclusions: This thesis contributes to the literature on the social determinants of colorectal cancer screening in Canada by exploring area-level determinants of screening as well as mechanisms that explain screening inequalities and by evaluating the effectiveness of various colorectal cancer screening programs at improving screening uptake and reducing screening inequalities. Findings support the notion that the role of socioeconomic contexts, above and beyond individual-level factors, merit attention both in future research on and surveillance of colorectal cancer screening. It also indicates that modifiable pathways to known screening disparities require continued exploration, and that future work should assess the acceptability, feasibility, and effectiveness of complimentary targeted interventions to promote screening both overall and among those most vulnerable.

MeSH Keywords: Colorectal neoplasms, Early Detection of Cancer, Endoscopy, Social Determinants of Health, Inequalities, Residence Characteristics, Epidemiologic Measurements, Epidemiologic Methods, Health Policy, Program Evaluation.

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LIST OF ABBREVIATIONS

Acronym	Meaning
CAD	Canadian dollars
CCHS	Canadian Community Health Survey
CCO	Cancer Care Ontario
CDE	Controlled Direct Effect
CI	Confidence Interval
CMA	Census Metropolitan Area
CPAC	Canadian Partnership Against Cancer
CRC	Colorectal Cancer
CRCHUM	Centre de recherche du Centre hospitalier de l'Université de Montréal
CSHP	Cancer Screening Health Promotion Model
CV	Curriculum vitae (résumé)
DAG	Directed Acyclic Graph
DD/DiD	Difference-in-Differences
DDD/DiDiD	Difference-in-Difference-in-Differences
ESPUM	École de santé publique de l'Université de Montréal
EMM	Effect measure modification
GEE	Generalized estimating equation
MAN	Manitoba
NB	New Brunswick
NDE	Natural Direct Effect
NFLD	Newfoundland
NS	Nova Scotia
NIE	Natural Indirect Effect
NIH	National Health Institute (National Cancer Institute)
OR	Odds ratio
PCP	Primary Care Physician
PD	Prevalence Difference
PE	Proportion Eliminated
PEI	Prince Edward Island
PR	Prevalence Ratio
RR	Relative Risk
SASK	Saskatchewan
SPCRC	Saskatchewan's Screening Program for Colorectal Cancer
TE	Total Effect
WHO	World Health Organization

This thesis is dedicated to my friends Bonnie, Sam, and Allie, and all those who have lost someone to colorectal cancer

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PREFACE

Welcome, dear reader. If you are here, it is likely that you—like me—are interested in the fields of social epidemiology, cancer epidemiology, and applied public health research. I came to these research domains through an interdisciplinary training journey. Schooled in Liberal Arts (DEC, Heritage College, 2006-2008), Environmental Studies and Feminist Studies (BA, McGill University, 2008-2012), and in Psychiatric Epidemiology (MSc, McGill 2012-2014), I turned to the domains of public health and social epidemiology out of keen interest in understanding how systems of power create and perpetuate social divides and inequalities, how individuals are influenced by the spaces and communities in which they live, and how social and policy contexts influence population-level health.

The unifying thread of my program of research to-date (my academic CV is described in Appendix I) has been the guiding principle of health equity. Specifically, I am interested in studying the social determinants of health, and ways to modify these determinants (namely through health and social policies) to promote both population health and health equity. In pursuing a PhD in public health, with a specialization in epidemiology, at the Université de Montréal, my aims were twofold. First, I intended to develop a strong background in public health theory that could direct the orientation of, and ensure the public health-relevance of, my future research. Second, I aimed to perfect my knowledge of epidemiologic methods, particularly in statistical analysis and causal inference, to prepare myself for a productive and rigorous career in population health research. Grounded in public health theory and rigorous methodology, this thesis bridges my research interests and training objectives.

I am humbled and deeply appreciative that I could complete my doctoral training in the substantive field of cancer prevention. The burden of colorectal cancer in Canada is devastating, and the fact that preventive colorectal cancer screening participation remains so low in the country merits research attention. This thesis addresses three burning public health questions: What factors are keeping colorectal cancer screening rates so low? Why are certain populations less screened than others? And do some interventions currently implemented increase screening and decrease screening inequalities? Addressing these questions, this thesis was designed to provide evidence that could help reduce the burden of this cancer for all Canadians.

"Equity in health implies that ideally everyone could attain their full health potential and that no one should be disadvantaged from achieving this potential because of their social position or other socially determined circumstance. […]

Three distinguishing features, when combined, turn mere variations or differences in health into a social inequity in health. They are *systematic*, *socially produced* (and therefore modifiable) and *unfair."*

— Margaret Whitehead and Göran Dahlgren.
In *Concepts and principles for tackling social inequities in health*, 2006

CHAPTER 1: INTRODUCTION

1.1 The burden of colorectal cancer in Canada: Incidence and mortality

Though colorectal cancer incidence in Canada has been declining since the 1980s, in part due to uptake of preventive screening tools and to reductions in population-level exposure to risk factors such as smoking,[1,2] it remains the second most commonly diagnosed cancer in Canada.[3] In 2017 alone, an estimated 26,800 new cases were diagnosed. Like other cancers, colorectal cancer and its treatment can be painful, distressing, and debilitating.[4] Among new cases, over one third are expected to die from the disease (the case fatality rate is 36% for men and 38% for women).[1] An estimated 9,400 people died from colorectal cancer in 2017 (mortality rates were 28.1/100,000 in men and 19/100,000 in women)—making it the third most common cause of cancer death in Canada.[3] The breadth of suffering caused by colorectal cancer in Canada can be characterised as tragic. This, not only because of the large number of Canadians affected by the disease but also because much of the burden is known to be preventable through primary and secondary prevention strategies.

1.2 Strategies for colorectal cancer prevention

1.2.2 Secondary prevention: Early, regular screening

Preventive colorectal cancer screening aims to identify growths in the colon and rectum before they become cancerous or invasive (i.e. likely before any symptoms are exhibited).[2] The Canadian Cancer Society has proposed preventive screening guidelines for adults aged 50 to 74 years, who are at average risk of developing colorectal cancer—that is, those without a personal or family history of colorectal cancer, inflammatory bowel disease, or previously identified benign polyps,[5] all of whom require a personalized screening schedule.

In average-risk adults, screening is not recommended to begin before the age of 50 years due to the low prevalence of adenomatous (noncancerous, but precursory) polyps in adults under that age.[6,7] Approximately 93% of new cases occur in adults aged over 50 years.[8] To note, however, are proposed changes to guidelines to propose screening begin at 45 years, given growing rates of colorectal cancer incidence among adults aged 45 to 50 years.[9] In turn,

screening after the age of 75 years is not recommended in average-risk adults given, among other factors, increased risk of harm from screening procedures.[10] Current guidelines recommend that average-risk adults aged 50-74 years have a stool test (either a fecal occult blood test [FOBT] or fecal immunochemical test [FIT]) at least every 2 years to identify signs of polyp growth.[5]

These tests involve collecting small stool samples over the course of three consecutive days, in which microscopic traces of blood can be identified (full details on tests procedures are described in Appendix IV). If blood is present, it may be from digestive matter scraping against growing precancerous or cancerous polyps in the colon or rectum. The specificity (or "true negative rate") of both the FIT and FOBT is approximately 92%, indicating that a high proportion of individuals without blood in their stool (i.e. "true negatives") are correctly identified as such using these two tests.[11] The sensitivity (or "true positive rate") of the tests is lower, however—ranging from 14% to 31% for FOBT and 34% to 85% for FIT[11]—which is why and endoscopic follow-up is needed (a colonoscopy's sensitivity is approximately 97%[12]).

Indeed, stool tests that come back positive for the presence of blood are followed-up with an endoscopic procedure (either a colonoscopy or flexible sigmoidoscopy, also described in detail in Appendix IV), during which polyps are identified and, when possible, removed. Though endoscopic procedures are relatively painless (in fact, colonoscopies require sedation), the preparation required before the test is intensive. Participants are required to drink only liquids for at least 24 hours before the test, to consume laxatives the night before, and to fast the morning of the test,[13] to allow for an effective examination of the rectum and colon for polyp growth. If the endoscopic procedure yields a negative result (indicating an absence of pre-cancerous or cancerous lesions), guidelines suggests that stool-based testing should be resumed every two years—sigmoidoscopies are not needed for another five years, and colonoscopies are not needed for another ten years.[14] Throughout this thesis, a person is considered to be "up-to-date" on screening or to "have been screened recently" if they either completed a stool-based test in the previous two years, or a sigmoidoscopy in the previous five years, or a colonoscopy in the previous ten years. A person is considered to have been screened in their lifetime if they have completed, at least once, either a stool-based test, a sigmoidoscopy, or a colonoscopy.

It is estimated that the use of stool-based screening every two years can reduce mortality by 15-20% in average risk adults.[15-17] Ninety percent of cases identified at an early stage (i.e. when the cancer was still localized in the colon or rectum) survive five years after diagnosis.[2] In contrast, five-year survival is only 68% once the cancer has spread regionally and 10% once it has metastasized.[2] By helping to identify cases at an earlier stage, screening saves lives. It is estimated that if 30% of those eligible participated in regular stool-based screening in Canada, 21,000 deaths could be averted between the years 2015 and 2030.[1] If participation reached 80%, 40,000 deaths could be averted.[1] The proposed Canadian participation target is currently 60%.[8] Beyond theses health benefits, preventive screening also yields economic advantages. Approximately 560 million Canadian dollars are spent yearly on colorectal cancer treatment,[18] and these costs are expected to grow as the Canadian population ages and the burden of colorectal cancer grows.[1] In economic terms, preventive screening is more cost-effective than a no-screening, purely treatment-based approach[19] (more details on the economic evaluation of screening can be found in Appendix V).

1.3 The Canadian prevention gap: Low screening participation

Despite convincing evidence of the economic and life-saving importance of screening, self-reported screening data suggest that only 20% to 30% of adults aged 50 to 74 years with no known familial or medical risk factors (i.e. those at "average risk") are up-to-date on colorectal cancer screening (i.e. have received a stool-based test in the previous two years, a sigmoidoscopy in the previous five years, or a colonoscopy in the previous ten years),[20,21] and most have in fact never been screened in their lifetime.[5,22] In contrast, approximately 63% of women aged 50 to 74 years are believed to be up-to-date for breast cancer screening in Canada and 79% of women aged 25 to 69 years are estimated to be up-to-date for cervical cancer.[20]

On average, colorectal cancer screening participation rates among both average- and higher-risk adults vary by province. The provinces and territories, sorted in decreasing order of the proportion of all 50- to 74-year-old adults, regardless of risk status, who had received either stool-based screening in the previous two years, or endoscopic screening in the previous ten years in 2012, were: Manitoba (67% up-to-date on screening), Ontario (64%), Prince Edward

Island (62%), Alberta (60%), Saskatchewan (53%) Nova Scotia (52%), British Colombia (50%), New Brunswick (47%), Newfoundland (46%) and Quebec (43%).[23] The prevalence was 41% for the territories, when combined.[23]

Further, disparities in colorectal cancer screening among population sub-groups have been reported. Screening prevalence differences have been observed according to income, rural residence, education, access to primary care physicians, and immigration status. In 2008, 26% of average-risk Canadians in the highest income quintile had never received a stool-based test versus 44% in the lowest income group in 2008.[24] That same year, 22% of average-risk Canadians living in urban areas were screened recently via stool-based test versus 18% in rural-dwelling Canadians.[24] In 2001, a study in Alberta reported that 26% of average-risk men without a high school education had been screened recently via stool-based test versus 77% in those with a high school diploma; and that approximately 10% of average-risk Alberta residents who had not received a screening recommendation from their physician were up-to-date on either stool- or endoscopic-based screening, versus 60% in those who had received a physician recommendation.[25] In 2014, approximately 19% of average-risk individuals who recently immigrated to Canada (i.e. immigrated in the previous 10 years) were reported to have been screened recently via stool- or endoscopic-based screening, compared to 30% of average-risk adults who were born in Canada.[21]

Since non-recent screening is associated with later-stage at diagnosis and higher levels of colorectal cancer mortality,[26] under-screened populations tend to bear a disproportionate amount of the overall colorectal cancer burden. This inequitable distribution of cancer burden has detrimental social and economic impacts on Canadian society[27] and according to the principle of distributive justice,[28] is both avoidable and unjust.[29] The low, overall participation in colorectal cancer screening in Canada, and even lower screening participation among vulnerable populations[30-33] (i.e. those most likely to be "at-risk" for non-recent screening[34,35]), requires public health attention and will be the focus of this thesis.

1.4 Why are screening rates so low? Determinants of colorectal cancer screening

A question that arises when considering low screening participation rates pertains to the determinants of screening participation: what factors are operating to keep screening rates so low? The literature on the determinants of colorectal cancer screening began to emerge in the mid-1990s (publication trends are described in greater detail in Appendix VI) and many determinants have now been identified. Described in detail in Chapter 2, they include logistic factors such as lack of discretionary time,[36-38] health service-related factors such as not having a primary care physician,[30-32] or not being exposed to a provincial organised colorectal cancer screening program,[39,40] psychological factors such as fear of the test or test result, or perceiving the screening tests to be embarrassing or unpleasant,[36,38,41] and social and economic factors such as not being in a relationship, having lower educational attainment or lower income, or having recently immigrated to Canada.[30-32,42,43]

Missing from extant literature, however, are two areas of knowledge. First, Canadian literature has yet to assess whether or not determinants may be operating beyond the level of individual characteristics—i.e. independent or "above and beyond" individual-level characteristics. No Canadian study has assessed neighbourhood-level determinants of colorectal cancer screening, as has been done in other countries[25,33,44] and for preventive breast and cervical screening in Canada.[45,46] This gap in Canadian literature is problematic insofar as the environments in which people live are known to affect individual health behaviours, regardless of (or above and beyond) individual-level characteristics. Areas of residence tend to shape opportunities for and barriers to the promotion of health[47] and present relevant targets for public health intervention. Area-level determinants of screening and pathways to screening inequalities therefore represent important gaps in Canadian literature that this thesis aims to address.

Second, though social disparities in screening have been observed (i.e. by income level, immigration status, access to primary care physicians), Canadian literature lacks evidence of how known determinants may operate or intersect to drive social disparities in screening. Currently, no study has assessed the modifiable mechanisms that explain known screening disparities, nor have any applied relevant methodological techniques to assess whether or not observed correlates of screening may be mediators of known social disparities in screening. Knowing which factors mediate screening disparities is needed to inform interventions to improve

screening participation overall and among population sub-groups. Currently, several types of interventions have been implemented in Canada to promote screening—some of which have yet to be formally evaluated.

1.5 What is being done about low screening participation? Current Canadian interventions

Two broad approaches exist in Canada to promote colorectal cancer screening: an opportunistic screening approach and an organised program approach. "Opportunistic screening" is the term used to describe screening participation in the absence of any defined screening program. In an opportunistic screening setting, screening occurs on an ad hoc basis wherein individuals visit their physician or a primary care clinic and—either upon the physician's recommendation, or their request—receive screening services.[48] This prevention approach relies on the availability of diagnostic procedures, individuals' regular use of primary care services, awareness of prevention modalities, and physician's readiness to recommend screening.[49] Organised screening programs are the current alternative to opportunistic screening. As of 2007, all Canadian provinces except Quebec began establishing organised programs to promote stool-based screening uptake[1] (Quebec intends to roll out its program between 2018 and 2019;[50] it currently uses an opportunistic screening approach). All current programs send invitation letters at regular intervals to encourage residents aged 50 to 74 years to participate in screening.[48] In addition to these invitation letters, existing programs differ in their approaches of distributing screening tests. Some programs systematically distribute screening tests by mail to all adults aged 50 to 74 years (these can be considered "systematic" organised screening programs) while others rely on patients to request and/or pick-up screening tests (these can be considered "patient-reliant" organised screening programs). More details on provinces' programs can be found in Appendix VII and in subsequent sections of this thesis.

Traditionally, the aim of an organized screening program is to maximize screening coverage while ensuring an optimized use of resources. Organised screening programs are designed to promote screening while protecting against over-screening and poor screening quality and follow-up.[49] These organised programs are thought to be better at improving screening uptake compared to opportunistic programs by reducing reliance on the prescribing

habits of physicians, and on individuals' knowledge, or regular use of health services.[49] Indeed, studies of programs in England, Korea (each using administrative data), and in the Canadian provinces of Manitoba (using administrative data) and Ontario (using self-reported survey data) suggest that the implementation of programs that involve sending out screening kits are accompanied by increases in screening participation rates (i.e. by 6% to 14% over the course four to six years; study results are discussed in greater detail in Chapter 2).[39,40,51,52]

However, in Canada, only Ontario and Manitoba's programs have been evaluated.[39,40] The other seven provincial programs have not yet been evaluated. Further, among the latter seven programs, variability exists in intervention design. They vary, for example, in their reliance on individuals' initiative in achieving every step in the screening process (i.e. acquiring the test, collecting stool samples, submitting the samples for testing). Some programs involve sending out screening kits via-mail (and enable tests to be returned via-mail once completed) (i.e. "systematic" organised screening programs), whereas others rely on individuals to pick-up and return screening tests at designated locations (i.e. "patient-reliant" organised screening programs) (Appendix VII summarizes program features by province). Evaluation studies have yet to take this heterogeneity into account when considering how organised screening programs may influence population-level screening participation.

Also missing from the Canadian literature is an assessment of how known social disparities in screening in Canada[21,25,30-32,44,53] are affected by organised screening programs (i.e. whether they persist, are exacerbated, or reduced). The few studies that have examined this question indicate that most socioeconomic disparities persist despite organised screening programs[39,51,54-57]—this is because systemic barriers to screening are thought to remain even after program implementation[58] (such as language barriers, limited number of health centers, lack of transportation services, area-level deprivation,[49] and disparities in service utilization[59]). It is therefore unclear whether or not "patient-reliant" and "systematic" organised screening programs in Canada reduce screening disparities.

1.6 Thesis objectives and structure

Given the low prevalence of colorectal cancer screening and existing social disparities in screening in Canada, the overarching goals of this thesis are to advance knowledge on the social determinants of colorectal cancer screening in Canada and to explore potential pathways of intervention—both by identifying mechanisms that explain existing social disparities and by evaluating how current population-level intervention strategies affect screening uptake overall and among vulnerable populations. Towards this end, this article-based thesis addresses the three following specific objectives:

1) To determine whether or not local area-level features such as area-level income are associated with having ever been screened or having been screened recently, independent of individuals-characteristics such as individual-level income;

2) To assess whether or not access to primary care physicians mediates differences in screening uptake between recent immigrants and non-immigrants in Canada;

3) To quantify the impact of two types of organized colorectal cancer screening programs—programs that send out screening kits systematically to all age-eligible adults (systematic programs) and programs that send invitation letters but rely on individuals to request, and subsequently and return screening kits in-person (patient-reliant programs)—on screening participation overall, and on screening disparities (by income, education, rural residence, access to primary care physicians). Both types of programs are compared to a non-treatment comparison population (exposed exclusively to opportunistic screening).

The structure of this thesis is as follows: it begins by summarizing knowledge on the social determinants of colorectal cancer screening—summarizing findings using a consolidated conceptual framework (Chapter 2). This literature review is then followed by a detailed description of the methodologies and data sources used in this thesis (Chapter 3), and the three empirical manuscripts that address each of the three thesis objectives (Chapter 4-6).

In the first manuscript (Chapter 4), the association between area-level income and colorectal cancer screening is examined using generalised estimating equation models. The

second manuscript (Chapter 5) aims to broaden current understandings of the mechanisms through which social disparities in colorectal cancer screening are produced. It uses three mediation analysis methods (one regression-based, the other inverse probability weight-based) to assess whether access to primary care physicians mediates the association between immigration status and screening participation. Lastly, the third manuscript (Chapter 6) uses a quasi-experimental "Difference-in-Differences" (DD) framework to quantify the impact of two systematic programs (in Saskatchewan and Nova Scotia) and one patient-reliant program (in Prince Edward Island), using the populations of New Brunswick and Newfoundland—where no programs were implemented in the time-window studied—as comparisons. The DD framework was applied using a regression-based method.[60]

Finally, Chapter 7 summarizes the thesis' main research findings and contributions, as well as overall limitations and strengths. The potential implications of the thesis' research findings are discussed, as are directions for future research.

1.7 Unique contribution of the doctoral candidate within the broader research program

This body of work was developed and led by the author of this thesis (Alexandra Blair), under the supervision of Dr. Geetanjali D. Datta and Dr. Lise Gauvin. Knowledge produced in this thesis is embedded within Dr. Datta's broader program of research on the social epidemiology of cancer, cancer prevention, and the social determinants of health and complementary to Dr. Gauvin's work on social inequalities as they related to health behaviours. The doctoral candidate's contributions are unique in the following ways:

Dr. Datta's program of research explores social determinants of outcomes across the cancer control continuum. Through this thesis, A. Blair contributes to this body of work by focusing specifically on the social determinants of colorectal cancer screening and colorectal cancer screening equity in Canada. This thesis is cast within a unique literature, which the candidate describes in detail in Chapter 2. Also, the work described in this thesis, is grounded in theory and conceptual frameworks used in Dr. Gauvin's work, but addresses an entirely different

set of health behaviours. As a result, the area pursued in this thesis is unique from the work conducted by the supervisors.

The programs of research led by Drs. Datta and Gauvin rely on advanced epidemiologic and quantitative methods. In keeping with this approach while innovating, the doctoral candidate explored and applied several emerging but not yet widely used social epidemiologic methods and analytic designs—including multiple mediation analysis techniques (described in detail in Chapters 3 and Chapter 5) and several sensitivity analyses to assess and quantify potential source of bias. Rigorously delving into the appropriate application of these emerging methods is a unique contribution of the candidate. That is, for each paper, A. Blair prepared the necessary datasets, conducted all data analyses, drafted the manuscripts, and completed text edits following co-author feedback. Further information on the individual contributions of each co-author is provided at the outset of all three manuscripts in Chapters 4, 5 and 6 of the thesis.

Finally, the study of systematic and patient-reliant organised colorectal cancer screening programs in Nova Scotia, Saskatchewan and Prince Edward Island (Objective 3; Chapter 6) is a new area of research. This evaluation of provincial programs is complementary to work lead by Dr. Datta on the impact of cervical and colorectal cancer screening policy changes in Ontario as well as work conducted by Dr. Gauvin using natural experiment approaches to the effects of built environment transformations on travel and physical activity behaviours.

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CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Though colorectal cancer screening is performed at an individual level, it is –like many other health-related outcomes—a behaviour that is socially patterned and can therefore be studied from an epidemiologic or "population health" lens. At a population-level, individuals bearing certain characteristics are less likely to be up-to-date on screening than those without those same characteristics. Correlates of screening behaviour, which will be discussed in greater detail below, can be considered population-level "risk factors" [61] of never having been screened for colorectal cancer or not having been screened recently. Population health theories suggests that clustering of risk factors can occur such that certain sub-populations bear greater risk of being "at risk" of concurrent health-threatening exposures.[34,35] These sub-populations are often described as "vulnerable"[35]—not only because of their lived experience of concurrent risk factors, but also because of their vulnerability to negative health outcomes. In the case of colorectal cancer, certain populations are vulnerable to elevated risk all along the cancer control continuum—from likelihood of regular screening, to likelihood of screening follow-up and treatment. In this chapter, known determinants of colorectal cancer screening will be summarized, and intersections between factors will be discussed. The literature summary below does not represent a systematic review of the literature. Rather, it is aimed to provide readers with a substantive description of the known determinants of colorectal cancer screening. The literature described below was identified in the PubMed database using search terms pertaining to colorectal cancer screening and social determinants of health (e.g., "colorectal cancer screening"; "fecal occult blood test"; "endoscopy"; "social determinants"; "income"; "education"; "regular medical doctor"; "race"; "immigration"; "neighbourhood"; "organised screening program"; "Canada") and from the bibliographies of identified relevant publications—including key systematic reviews.[21,33,43,62-64] The summary of the determinants of colorectal cancer screening below is structured according to a consolidated conceptual framework that draws from the Social Determinants of Health framework,[65] and behavioural models.[66,67]

2.2 Consolidated conceptual framework

The determinants of colorectal cancer screening are reviewed below. They can be summarized according to a consolidated conceptual framework, developed by Datta,[68] that draws from the Social Determinants of Health framework,[65] Ronald Andersen's Behavioural Model to Explain Health Service Utilization,[66] and Gelberg et al.'s Behavioural Model for Vulnerable Populations[67]—which was an adaptation of Andersen's original behavioural model. This consolidated framework (Figure 1) posits that determinants of screening participation fall into three categories: predisposing factors that make individuals more or less inclined to be screened; enabling factors that facilitate and encourage screening participation; and need-related factors—all of which are governed by health and social policies, organizations, and systems of resource distribution. Each article in this thesis draws from this consolidated framework in operationalizing exposure, covariate and outcome measures, and designing analyses. Insofar as targeting modifiable factors has been identified as an important next step in cancer prevention,[69] all three articles in this thesis focus on modifiable "enabling" determinants of screening. These include the "community-level factors" of area-level income (Objective 1), the "personal resource" of having a primary care physician (Objective 2), and the "community-level factor" of being exposed to an organised screening program (Objective 3).

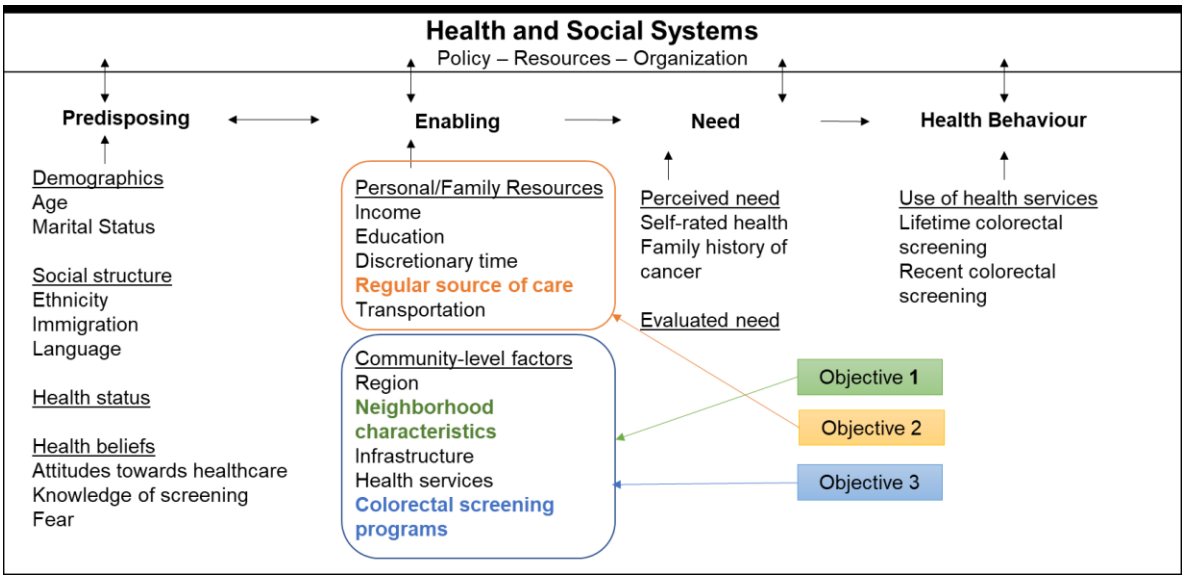

Figure 1: Consolidated conceptual framework of predisposing, enabling, and need-related predictors of colorectal cancer screening, adapted by Datta (2012) using Andersen (1995) and Gelberg (2000)'s Health Behaviour models and the Social Determinants of Health framework (described in Solar, 2007); with indication of the modifiable "enabling" determinants of screening addressed by each of the thesis objectives.

2.3 Determinants of colorectal cancer screening

Determinants of colorectal cancer screening have principally been identified through epidemiologic studies of large, population-based surveys, which provide self-reported data on colorectal cancer screening as well as social and demographic characteristics.[25,70,71] Self-reported survey data are considered among of the best sources of data for the assessment of social determinants of screening, as they can offer information on numerous social and demographic characteristics on large, population-based samples. Social and demographic factors captured in these surveys can be used to minimize confounding bias in multivariate analyses of the determinants of screening. Indeed, most studies that have examined correlates of screening do so using multivariate regression analyses that are adjusted for key social and demographic factors such as age, sex, marital status, education, and income. Below, known determinants are summarized.

2.3.1 Predisposing factors: Demographic markers, health status and beliefs

Predisposing factors are those that make individuals more or less inclined to be screened. They encompass demographic factors, indicators of social identity, as well as health beliefs and psychological predisposition. Known demographic correlates of screening in Canada are age and marital status. Canadian literature has found that younger adults (aged 50-60 years) are less likely to be recently screened compared to older adults (60-74 years).[30-32] This may be because of younger adults' lower perceived susceptibility to cancer incidence, or because of the observed correlation between younger age and lower likelihood of receiving a physician's recommendation for screening.[72] Secondly, in Canada, individuals who are not married or in a partnered relationship are also less likely to be screened.[42,43] This may be because spouses monitor and encourage each other to pursue health promoting behaviours such as screening.[73] Pursuing screening as a spousal unit may facilitate screening—as is indicated by the observation that screening co-invitation for married couples is associated with an increased likelihood of screening uptake.[43] Beyond these two factors, mixed findings are reported with regards to the predisposing demographic factor of gender. Some studies report that women and men demonstrate similar patterns of stool-based testing,[71] while others report that screening is slightly

higher in women than in men.[8] A small qualitative study in Canada found that women were also more likely to undergo endoscopic screening.[74]

Second, makers of social identity that are associated with lower likelihood of screening include having been born outside of Canada, non-white ethnicity, and First Nation, Inuit, or Métis identity.[30-32] Among racial minorities in Canada, persons from South Asian decent are among the most under-screened.[75] Differences in screening according to these social identifiers may be due to differences in cultural beliefs pertaining to cancer and screening.[76,77] Ethno-cultural differences have been observed, for example, in feelings of fatalism (regarding cancer diagnosis and mortality)[78] in perceived acceptability of screening tests (e.g. 8% of White respondents in an American study reported stool-based screening test as embarrassing versus 21% in Latino respondents).[79] In Canada, recent immigrants may lack knowledge of where or how to access screening services,[21] and those whose mother tongue is neither English nor French may face barriers with regards to language in accessing health services.[53]

Third, general health status influences individuals' predisposition to use health services such as screening tests. General health status may influence one's mobility[80] or self-efficacy (i.e. their perceived ability to perform a specified behaviour).[81] The relation between health status and screening likelihood appears to follow a U-shaped curve: likelihood of screening is highest among those with high self-rated health, and decreases with worsening self-rated health (low levels of physical activity and smoking behaviour are also correlates of lower screening participation)[30-32]; however, among those with lower self-reported health, likelihood of screening among those diagnosed as having a chronic disease (i.e. hypertension, cardiovascular disease, diabetes, arthritis, ulcers, asthma or emphysema) is higher than those without a diagnosis—mostly likely due to increased, regular contact with health professionals who can make screening recommendations.[43]

Fourth, known psychological predisposing factors include perceiving the screening tests to be embarrassing or unpleasant,[36] a fear or anxiety about finding out about health problems and about the test result,[36,38,41] and fear of pain or injury.[36] Though screening modalities for other cancers can also be perceived as unpleasant, uncomfortable and embarrassing, dislike of

colorectal cancer screening tests is reported to be a stronger barrier to colorectal cancer screening than for cervical and breast cancer screening.[82] This is because of the invasive nature of endoscopic procedures, discomfort around stool self-sampling, and the particularly intensive preparation needed before endoscopic procedures. Many of these psychological factors differ by sex.[74] Women are often more anxious about injury from perforation caused by endoscopic procedures and embarrassed to discuss screening with health professionals. In contrast, men are more likely to report fatalism (causing avoidant procrastination), and perceive screening to be unnecessary and to cause vulnerability (rather than embarrassment).[74]

2.3.2 Enabling factors: Individual and community-level resources

Enabling factors are those that facilitate and encourage screening participation. Aligned with the materialist hypothesis that health behaviours and outcomes are influenced by the material conditions in which people live, and the resources to which they have access,[83] enabling factors encompass the various resources available to individuals or their communities that make screening more accessible and realizable.

Individual-level resources that are known to be associated with colorectal cancer screening participation in Canada include education, employment and higher income.[30-32] Income and education, two important determinants of an individual's socioeconomic status or social positioning,[65] influence health literacy and one's ability to engage with cancer screening information,[81] or navigate health services (i.e. making health care appointments[84]). Also tied to these socioeconomic factors is the enabling factor of having discretionary time to perform the tasks pertaining to screening[36-38] (this includes the ability to take time off work[37] or away from family obligations,[36] or the ability to afford any external costs, such as those pertaining to transport[36]).

Beyond individual-level socio-economic factors, access to health care resources is also an important enabling factor. Having a primary care physician is a key predictor of screening, as physicians represent an essential source of information regarding screening and screening recommendations.[25,30,31,71,85] Although Canada has a universal health care system, approximately

15% of Canadians do not have access to a primary care physician (with higher rates observed in Quebec (25%), the Yukon (26%), the Northwest Territories (58%) and Nunavut (83%)),[86] and may therefore be less likely to receive regular screening recommendations. Similarly, prior or regular use of health services facilitates use of behaviours such as screening. Preventive colorectal cancer screening occurs primarily in those already accessing the health care system[25,30,31,38,71,85,87]: in men, previous screening for prostate cancer is a predictor of colorectal cancer screening;[71] and in women, use of hormone replacement therapy, cervical or breast cancer screening are correlated with colorectal cancer screening.[25,30,31,71,85]

Above and beyond individual-level socioeconomic and health service-related factors, local-area level features are also believed to enable health behaviours such as screening by shaping individuals' access to infrastructure, services, social capital, community support.[47,88] In Canada, the one documented community-level predictor of non-recent screening is living in a rural setting.[25,44] This may be because of lower access to health and social services in rural settings in the country. For example, individuals living in the most rural areas in Canada are often less likely to have a primary care physician.[89] Outside of Canada, studies have found that other community-level factors are associated with screening above and beyond individual-level socio-demographic and economic characteristics. These include local area-level primary care provider density,[90,91] low income,[37,92-94] low educational attainment,[91] perceived social and physical disorder (i.e. visible garbage, fear of crime),[95] and low neighbourhood satisfaction.[96] However, these community-level features have been understudied in association to colorectal cancer screening in Canada. Since local community areas and neighborhoods are important spaces for potential public health intervention[47] (i.e. via neighborhood-based interventions in targeted community health clinics[97]), and since the hypothesized mechanisms linking local-area level features to colorectal cancer screening (i.e. resource deprivation, lower social support and social capital[47]) are likely to operate in Canada, area-level determinants of colorectal cancer screening represent an important topic for future research.

Beyond the local area-level, an important region-wide enabling determinant of screening is exposure to an organized screening program. Though currently no systematic review of the effectiveness of population-wide colorectal cancer screening programs at increasing screening

participation has been conducted, individual studies report positive associations between organised programs and screening. Improvements in screening participation rates were observed in Ontario (increase from 16% to 22% participation from 2003 to 2009), England (57% to 66% participation from 2006 to 2012), Korea (10% to 21% participation from 2004 to 2008), and Winnipeg, Manitoba (43% to 57% participation from 2007 to 2012)[39,40,51,52] following program implementation. In contrast, a small drop in screening was observed in France following a country-wide extension of the national screening program (34% to 31%, from 2009 to 2010).[55] These communication-based programs are thought to increase screening participation by increasing population-wide awareness of colorectal cancer and the relevance of prevention strategies.[49] A limitation of existing evaluation studies, however, is their inconsistent use of methodologies to minimize sources bias such as confounding. The study of program effects in Manitoba,[40] for example, did not use a control population against which to compare screening trends (and account for secular trends in screening).[98] Future studies require systematic use of rigorous evaluation methodologies to minimize bias.

Further, as mentioned previously, it is unclear whether organized screening programs implemented in Canadian provinces reduce known social disparities in screening. Studies that have assessed program impacts on screening disparities by individuals' socioeconomic status yield a bleaker picture: income and education-based screening disparities appear to persist despite the establishment of screening programs.[39,51,54-57] This follows other previously observed patterns of public health program uptake, that have inspired the "Inverse Equity Hypothesis." This hypothesis states that health promoting programs are often most utilized by privileged groups—those most informed, most affluent —with a lagged effect for the economically, socially, educationally, linguistically, culturally, or racially marginalized.[59,99-101] Until subpopulations benefit from the intervention, disparities can be unchanged or even increase. In the case of colorectal cancer screening programs, it may be that effects for populations of lower socioeconomic status are lagging because the established programs (which send information packets and screening tests via mail) fail to tackle socioeconomic barriers to screening, such as a lack of enabling resources such as transportation services and local health centers.[49,58] Beyond socioeconomic status, however, no study has evaluated how various types of organized programs reduce screening disparities according to other enabling factors, such as region of residence (i.e.

urban or rural dwelling) or access to primary care physicians. Future evaluation studies in Canada must consider the programs' effects on screening disparities, ideally according to multiple social factors to understand the pathways through which programs influence screening uptake.

2.3.3 Need-related factors: Perceived and evaluated need

Need for colorectal cancer screening can be perceived by the individual or evaluated by an external source—such as peer or health care provider. The receipt of screening recommendation from a health care provider is a key determinant of colorectal cancer screening,[75] one that directly influences an individual's perceived need for screening. However, physicians do not systematically recommend screening to their patients. Rather, recommendations tend to be given in relation to physicians' personal beliefs about the importance of screening,[102] their perception of low patient acceptance for screening, of the intensity of the pre-screening preparation, of costs to the health care system, of test availability, possibility of complications, waiting times, and test accuracy.[103] Beyond the personal beliefs of physicians, other factors can impede physicians from making screening recommendations during clinical encounters. These barriers include meeting patients for reasons other than a regular medical check-up, needing to prioritize other preventive services, and communication difficulties across languages.[104]

Inconsistent patterns of screening recommendation are especially problematic within certain vulnerable populations as they perpetuate screening disparities. For example, an Ontario-based study observed that physicians are less likely to recommend colorectal cancer screening to individuals of visible minorities, immigrants, and persons of lower income.[75] These systemic inequalities in screening recommendation can influence population-level disparities in colorectal cancer screening.

Among the proposed solutions to the problem of differential screening recommendation is to provide better training for physicians and health care providers with regards to screening guidelines,[105] and to reduce reliance on their screening prescription habits[49] —namely by finding alternative ways to inform individuals about the importance of screening. Organised screening

programs that communicate screening guidelines directly to residents represent such an alternative. However, studies have yet to assess how various organised screening programs in Canada affect known screening disparities between those with and without a primary care physician.

2.3.4 Systems-level factors: Structural determinants of screening disparities

Predicating known predisposing, enabling, and need-related determinants are factors that operate at the level of health and social systems (Figure 1). System-level determinants of health and health behaviour have also been called the "structural determinants of health" and the "social determinants of health inequities".[65] They encompass structures such as laws, policies, programs, and social or built environments, as well as the socioeconomic and political contexts in which people live. The Social Determinants of Health framework posits that these system-level factors reinforce and perpetuate norms and cultures and influence distributions of resources across sub-populations, and generate social stratification (i.e. social hierarchies).[65]

These social systems are believed to drive the unequal distribution of predisposing, enabling, and need-related factors between groups occupying unequal positions in society—thereby influencing population-level propensity for screening uptake.[65] For example, population-level wealth distribution affects individual predisposition for screening, and shapes who has access to enabling resources. Health literacy, psychological barriers to screening (i.e. fear, embarrassment, fatalism, lack of confidence, mistrust of health services, and learned helplessness), and logistic barriers such (i.e. lack of discretionary time, greater perceptions of inconvenience, and inability to take time off work), all tend to follow a socioeconomic gradient.[33,36-38,81,84,106] This socioeconomic gradient in predisposing and enabling determinants may explain why socioeconomic disparities in screening are observed.

Beyond socioeconomic disparities in screening, system-level factors can also shed light on the aetiology of the other screening disparities—such as the observed 10% gap in lifetime colorectal cancer screening prevalence between recent immigrants and individuals born in Canada. [107] Though this disparity has been repeatedly documented in Canada,[30-32,75] the

mechanisms driving this disparity remain poorly understood. On a proximal level, ethno-cultural differences in screening beliefs and perceptions (i.e. predisposing characteristics)[76-79] may explain why recent immigrants to Canada are disproportionately under-screened compared to individuals born in Canada. However, population health theory[65] and the proposed consolidated framework (Figure 1) suggest that this screening disparity may be due to systemic differences in access to enabling resources according to immigration status.

In Canada, despite the numerous strengths of the Canadian integration system (including the protective legal frameworks provided by the Canadian Multiculturalism Act[108] and by sections 15 and 27 of the Canadian Charter of Rights and Freedoms), immigrants to Canada are often disproportionately burdened by discrimination,[10911,29] and by stressors such as inadequate housing, precarious employment, and barriers to health care. [110] Recent immigrants are more likely to face linguistic and cultural barriers in accessing care,[53] and are less likely than Canadian-born individuals to have access to a primary care physician.[111] Restricted access to these health promoting resources[65] is thought to explain in part why individuals who immigrate to Canada—who, upon arrival are disproportionately healthy, educated, and skilled[112]—see their health status decline over time, and eventually converge, with that of Canadian-born residents.[76] Disproportionate under-exposure to factors that facilitate screening may also explain why recent immigrants are less likely to be screened for colorectal cancer.

It should be noted, however, that the hypothesized deterministic relations or "pathways" between Canada's integration system (i.e. the social structures and policies that define the country's openness to immigrants[113,114]), immigrants' access to enabling resources, and subsequent screening behaviour have yet to be empirically assessed. Identifying modifiable mediators of this disparity could inform potential interventions to improve screening participation overall, and increase screening equity.[115]

2.4 Methodological considerations

In reading the previous studies on the determinants of colorectal cancer screening, three broad methodological considerations emerge. Discussed below, they include: 1) how colorectal

cancer screening outcomes are operationalized; 2) what types of associations between factors are explored; and 3) how sources of bias in observational studies are handled and minimized. Largely overlooked in the existing literature, these considerations directly inform the design of the studies presented in this thesis.

2.4.1 Defining screening outcomes

A point that few of the studies summarized above (in section 2.3) explore at length is the consideration of how colorectal cancer screening outcomes are defined and operationalized. Based on current screening guidelines, adults aged 50 to 74 years with no known familial or medical risk factors are considered up-to-date on colorectal cancer screening if they have either received a stool-based test in the previous two years, a sigmoidoscopy in the previous five years, or a colonoscopy in the previous ten years. Those who were not screened according to those timeframes (i.e. those who have not been screened recently) fall into two groups: 1) those who have never been screened in their lifetime; and 2) those who have been screened in their lifetime, but not recently (as summarized in Table 1 below). Most existing studies on the determinants of colorectal cancer screening collapse the two latter groups into one: "those who have not been screened recently" (i.e., to Grouping 3 in Table 1 below). This form of categorization does not distinguish between those who had never been screened and those who had been screened in their lifetime but not recently (Table 1, Grouping 2); nor does it allow identification of risk factors of lifetime never screening (as would operationalization according to Table 1, Grouping 1).

Table 1: Defining recent and non-recent colorectal cancer screening

<table>
<tr><th>Operationalization</th><th colspan="3">Screening experience</th></tr>
<tr><td>Grouping 1</td><td>Never screened</td><td colspan="2">Screened in lifetime</td></tr>
<tr><td rowspan="2">Grouping 2</td><td rowspan="2">Never screened</td><td>Screened in lifetime, not-recently screened[a]</td><td>Recently screened[b]</td></tr>
<tr><td colspan="2">Not recently screened</td><td>Recently screened</td></tr>
<tr><td>Grouping 3</td><td colspan="3"></td></tr>
</table>

[a] "Not recently screened" indicates screening not having had a stool-based test in the previous two years, nor a sigmoidoscopy in the previous five years, nor a colonoscopy in the previous ten years.
[b] "Recently screened" indicates having received either a stool-based test in the previous two years, or a sigmoidoscopy in the previous five years, or a colonoscopy in the previous ten years.

Distinguishing between those who had never been screened, and those who had been screened in their lifetime but not recently is relevant for two reasons. First, the outcome of having never been screened is particularly relevant in the Canadian context, where most age-eligible adults have never been screened, and are therefore at elevated risk of being diagnosed at a more advanced stage.[116] Second, it is possible that those who have never been screened and those who have been screened, but not recently, have two distinct risk factor profiles—as has been observed for screening at other cancer sites.[117] Some factors may be more relevant for screening initiation than continued screening participation, or vice versa. Knowledge of these differential risk factor profiles can benefit future public health interventions. As discussed in greater detail in the next chapter (Chapter 3), all three manuscripts of this thesis carefully consider which type of outcome grouping should be used, based on the study's objectives.

2.4.2 Exploring mechanisms underlying observed associations

A second methodological consideration of existing studies are the types of associations assessed. The studies summarized above (in section 2.3) all aimed to explore direct associations between various factors and screening outcomes. In these studies, multivariate regression models tend to be specified without consideration of the potential relationships between risk factors. This type of analytic design has been described as falling within a "black box" paradigm of epidemiologic research, insofar as the mechanisms explaining associations remain unexplored (and are therefore "hidden from the viewer").[118] Though studies within this paradigm continue to yield relevant information for public health, they are of more limited use for the design of interventions on modifiable pathways to health.[118] This thesis aims to address this gap in extant colorectal cancer screening literature by exploring the modifiable mechanisms that explain social disparities in colorectal cancer screening.

Various methodological tools are available to study the mechanisms that explain or underlie social disparities. However, these have been underused in existing literature of the social determinants of colorectal cancer screening. One of these tools are directed acyclic graphs (DAGs), which permit a graphical representation of the assumed temporality and directionality

of associations between factors.[119] In the name "Directed Acyclic Graph," the term "directed" indicates direction and temporality of associations, and the term "acyclic" indicates that no bidirectional or cyclical associations are represented). Though they are principally used to identify on which variables to condition (i.e., through statistical adjustment, stratification, etc.) in order to control for confounding,[119] their use also ensures transparency regarding the assumed temporality and direction of relationships between measures in analyses. In this thesis, DAGs are used in all three of the manuscripts to represent conceptualized relationships and guide study design. They are described in detail in Chapter 3.

Another set of under-utilized tools in existing literature are techniques of mediation analysis. Mediation analyses can be utilised to assess both direct and indirect associations between various factors and a screening outcome. Decomposition of direct and indirect effects can provide useful information for public health. For example, it can provide an estimate of the proportion of a social disparity that could be eliminated if an intervention was designed to modify respondents' exposure to a mediating factor.[120] At the time this thesis was written, no study had applied mediation techniques to assess potential mediators of social disparities in colorectal cancer screening. The second manuscript of this thesis seeks to fill this gap, namely by using mediation analysis to assess whether having a primary care physician mediates the screening disparity between recent immigrants and individuals born in Canada.

Furthermore, multiple approaches to mediation analysis have been proposed in causal inference and biostatistics literature. Some use regression modeling,[121,122] while others combine regression modeling with inverse probability weighting techniques,[123] or use a purely inverse probability weighting-based approach.[120] The aim of using inverse probability weights is to create synthetic populations that are balanced in terms of the measured covariates, through which contrasts in average outcomes can be estimated[60]—yielding population-average effects or associations (rather than effects that are conditional on the strata of covariates included in a purely regression-based approach).[120] Though population average effects yielded from inverse probability weighting-based analyses are especially relevant for public health interpretation, they rely on distinct operational assumptions—namely regarding the validity of estimated inverse probability weights. At the time this thesis was written, few if any epidemiologic studies (within

or beyond the domain of cancer epidemiology) had applied multiple mediation techniques across which to compare the stability of findings or had explored the sensitivity of findings to potential violation of the assumptions required for each approach. The second manuscript of this thesis seeks to fill these gaps in the literature by applying three techniques of mediation analysis: one purely regression-based, one based on inverse probability weighted-regression, and one purely based on inverse probability weighting.

2.4.3 Tackling sources of bias

Lastly, several sources of bias can affect observational studies of the social determinants of colorectal cancer screening. Principle among these is confounding.[124] Epidemiologic methods offer several tools to tackle confounding bias—either by minimizing it by design, or by quantifying the sensitivity of findings to potential unmeasured confounding (and interpreting results accordingly).

Confounding can be minimized through design, namely by conditioning analyses on known covariates of both exposures and screening outcomes. Indeed, most of the literature on social determinants of colorectal cancer screening reviewed (section 2.3) do utilize analytic methods that condition on known social and demographic correlates of screening, such as age, sex, marital status, education, and income. However, among the studies reviewed, those designed to assess the effectiveness of organised screening programs have under-utilized analytic methods to control for confounding—particularly confounding by secular trends (be they in screening or in other population-level factors). For example, of the two existing Canadian studies that assess organised screening programs in Ontario and Manitoba, only Ontario's study utilized a control population against which to compare changes in screening.[39,40] Use of pre- and post-intervention data in a comparison population allows for the assessment of initial comparability of treated and comparison groups and, given a sufficient similarity between groups, enables an interpretation of post-intervention changes in outcomes in the treated group (but not in the comparison group) to be attributable to the intervention and not to secular trends in other determinants of screening.[125] In this thesis, the third manuscript's evaluation of systematic and patient-reliant organised

screening programs utilized a non-treated comparison population against which to compare screening trends.

Another approach to analyzing data from observational studies consists of quantifying the potential sensitivity of their findings to bias. Though most studies summarized above (section 2.3) contextualize their findings in relation to potential sources of bias in their discussions, few studies provide analyses that assess the potential sensitivity of their findings to these identified sources of bias. Where possible, all three manuscripts of this thesis were constructed to fill this gap in the literature. As will be discussed in greater detail below (Chapter 3), sensitivity analyses included: (1) assessing the consistency of findings when using different timeframe cut-offs for the measurement of recent screening[5,22]; (2) assessing the sensitivity of findings to potential unmeasured confounding—by estimating both how large an association would have to be between an unmeasured factor and the exposure and outcome to "explain away" observed associations[126] and by using falsification techniques[127,128]; (3) and assessing the consistency of findings across available analytic methods. Where sensitivity analyses put the validity of results into question, these findings are discussed.

2.5 Summary and literature gaps addressed in this thesis

In summary, existing literature suggests that colorectal cancer screening is determined by predisposing, enabling, and need-related factors. These factors are believed to be experienced at multiple levels of population aggregation (from the level of individuals to their local areas, their communities, and provinces). However, Canadian literature is limited in its assessment of community- or local area-level determinants of colorectal cancer screening [Gap 1], as has been done for other cancer sites.[45,46] Local areas of residence tend to shape opportunities for, and barriers to, the promotion of health, and are important targets for public health intervention.[47] Knowing which local area features influence screening in Canada, above and beyond individual-level characteristics, is therefore relevant both for improving understanding of pathways to screening in this country, and for public health planning. This thesis therefore aims to fill this identified gap in Canadian literature through its first objective:

> [Objective 1] To determine whether or not area-level features such as area-level income are associated with having ever been screened or having been screened recently, independent of individual social, demographic and economic characteristics

Identifying community-level determinants of screening such as local area-level income will allow for a more complete understanding of the determinants of colorectal cancer screening in Canada.

The literature is still lacking, however, in terms of evidence of the processes or "pathways" that link predisposing, enabling, and need-related determinants, and drive social disparities in screening [Gap 2.1]. The proposed conceptual framework suggests that the inter-relation between factors is determined by over-arching health and social systems.[65] These systems are believed to structure the distribution of enabling resources across populations, thereby shaping population-level social disparities in screening participation. However, few if any empirical studies, in Canada or abroad, have sought to test mediating pathways to explain social disparities in screening [Gap 2.2] (i.e. the disparity in screening according to immigration status). This gap in the literature will therefore be address in the second objective of the thesis:

> [Objective 2] To assess whether or not access to primary care physicians mediates differences in screening uptake between recent immigrants and non-immigrants in Canada.

Knowing whether access to primary care physicians mediates the immigration-based disparity in lifetime colorectal cancer screening in Canada, is important for future public health planning and intervention design.

Details on the mechanisms underlying social disparities in screening will also be beneficial for the improvement of current interventions. Currently in Canada, all provinces but Quebec[1] have implemented organised screening programs to reach the proposed Canadian target of 60% regular screening participation.[8] Though these programs are believed to increase

screening participation overall,[39,40,51,52] evaluation studies have varied according to methodological rigour [Gap 3.1] in controlling for sources of bias such as secular trends and other confounding factors. It also remains unclear whether or not organized screening programs implemented in Canadian provinces reduce known social disparities in screening, or whether program effects vary according to the program design [Gap 3.2]. Existing provincial programs vary according to their reliance on individuals' initiative in achieving every step in the screening process (i.e. acquiring the test, collecting stool samples, submitting the samples for testing)—with some distributing and collecting kits via mail ("systematic" programs) and others on individuals to pick-up and return screening tests at designated locations ("patient-reliant" programs). Knowing which types of programs both increase screening participation overall and reduce screening disparities can help improve current programs or inform directions for future targeted interventions. This thesis therefore aims to fill this third gap in Canadian literature with the following objective:

> [Objective 3] To quantify the impact of two types of organized colorectal cancer screening programs—programs that send out screening kits systematically to all age-eligible adults (systematic programs) and programs that send invitation letters but rely on individuals to request screening kits (patient-reliant programs)—on screening participation overall, and on screening disparities (by income, education, rurality, access to primary care physicians).

Through these three objectives, this thesis aims to contribute to a better understanding of the social determinants of colorectal cancer screening in Canada and to provide information that can guide future interventions to promote screening and reduce screening inequalities.

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CHAPTER 3: METHODOLOGY

3.1 Data sources and access

This thesis relies on secondary analyses of data from the Canadian Community Health Survey (CCHS) and the Canadian Census. These data were accessed at the Quebec Inter-University Center for Social Statistics at the Université de Montréal (QICSS) (3535 Queen-Mary, bureau 420, Montréal, QC, H3V 1H8), respecting data access protocols stipulated in Canada's Statistics Act (1985).[129]

3.1.1 The Canadian Community Health Survey

The Canadian Community Health Survey (CCHS) is a cross-sectional survey administered by Statistics Canada. The CCHS collects health-related information on Canadians at the level of provincial health regions in order to support surveillance programs at provincial and national levels.[130] Its target population includes individuals aged twelve years and older, living in all ten Canadian provinces and three northern territories.[131] Excluded from the survey's target population are individuals living on First Nation reserves, Crown lands, or in very remote regions, as well as individuals who are institutionalized, or who are members of the Canadian Armed Forces.[131] The CCHS sample is considered representative of 98% of the Canadian population aged twelve years and above.[131]

For sampling purposes, the CCHS considers each province to be comprised of distinct Health Regions—of which there are approximately 130 in total throughout the country.[131] Each territory is considered to be a single Health Region.[131] Sample size allocation throughout the country is performed in three steps: first according to the population size of each province or territory; then according to the number of Health Regions they contain; and third, according to the square root of each Health Regions' population size.[131] Area frames for each Health Region were those used for the Canadian Labour Force Survey—a monthly survey of the Canadian labour market, also run by Statistics Canada.[132] Sampling was conducted in multiple stages: dwellings were first selected from a list of dwellings in each area frame; households in the identified dwellings formed the household sample, and individuals aged 12 years or older were randomly selected from each household.[131] The CCHS questionnaire was administered via

computer-assisted interviewing, either in-person (88% of households) or by telephone (12% of households). Each participant was given a weight according to their contribution to the total population. The CCHS weighting strategy has been described in detail previously;[133] weights account for weighting in the Labour Force Survey, for household counts and non-response at the area frame-level, and for method of data collection (in-person versus telephone-based interviews). Response rates for the CCHS were 84.7% in 2001,[134] 80.7% in 2003,[135] 78.9% in 2005,[136] 78% in 2008,[137] 68.9% in 2012,[138] 66.8% in 2013 and 65.6% in 2014.[139] From 1992 to 2005 the CCHS collected data every two years (N≈130,000 respondents at each wave), and starting in 2007 data collection occurred annually (N≈65,000 respondents at each wave).[130] All three thesis studies utilize multiple cycles or "waves" of CCHS data. Objective 1 uses additional data from the Canadian Census.

3.1.2 The Canadian Census

The Canadian Census provides information on demographic, social, and economic features of the Canadian population.[140] Up until 2006, the long-form Canadian Census was conducted every five years, and participation was mandatory. The 2011 long-form census (renamed the National Household Survey) was made voluntary. Consequently, response rates dropped by approximately 17%, and community-level data for approximately 1,100 communities could not be released due to unacceptably low participation rates.[141] The long-form census was reinstated in 2016, but these data were not utilized in this thesis as they were not available at the time when the analyses were conducted.

For the thesis' first objective (Objective 1), the Canadian Census provides information on the income profiles of CCHS respondents' local-areas. The study linked CCHS respondents in 2005 and 2007 to Census data from 2006. CCHS and Canadian Census data were linked using CCHS respondents' Census Dissemination Area codes. Since Canadian neighborhood socioeconomic profiles tend to be stable over time, often changing over a longer time period than one to two years,[142] we assumed that neighborhood characteristics had not changed drastically within a 1-year interval before and after 2006, and that it was appropriate to link 2006 Census data to CCHS participants in 2005 and 2007.

3.2 OBJECTIVE 1

The first manuscript of this thesis aimed to determine whether or not local area-level features such as area-level income are associated with having ever been screened or having been screened recently, independent of individuals-level characteristics such as income.

3.2.1 Design

Using multiple waves of the CCHS, this study used a pooled cross-sectional design to maximize study power. It utilized data from the 2005 and 2007 cycles of the CCHS. These two CCHS cycles are the closest cycles to the 2006 Canadian Census, the most recent census year for which long-form data describing area-level income are available). Results from pooled CCHS cycles represent the average associations across cycles.

3.2.2 Study population

For this study, the population of interest was average-risk adults aged 50-75 years, with available information on colorectal cancer screening. Adults are considered average-risk if they did not have a first-degree relative with colorectal cancer, a personal history of colorectal cancer, inflammatory bowel disease, or previously identified benign polyps.[5] Thus, excluded from this study are participants who reported screening due to "family history of colorectal cancer," "follow-up of a problem," and "follow-up of colorectal cancer treatment."[143] Persons reporting screening due to "age", "race", or as "part of regular check-up/routine screening" were included (questionnaire items on reasons for screening are described in detail in Appendix VIII). Preliminary analyses suggest that approximately 54% of CCHS respondents aged 50 to 75 who said they had been screened for colorectal cancer at least once in their lifetime, reported doing so for "higher risk" reasons (i.e. personal or family history reasons), whereas 46% reported "average risk" reasons (i.e. age, race, routing screening). Overall, those reporting screening for "higher risk" reasons represented approximately 15% of adults aged 50 to 75 in CCHS cycles 2005 and 2007. Removing these higher-risk respondents yielded a proportion of non-recent

screening in average risk respondents (80%) that is similar the reported Canadian average of 77%.[20]

Additionally, the study population was restricted to those who lived in urban areas. In the CCHS, respondents' area of residence is considered "urban" or "rural" based on their stated postal codes. A postal code is a reference used for mail delivery in Canada, comprised of six alpha-numeric digits.[144] Postal code areas overlap with Census Dissemination Areas (the conversion between the two area units is performed by Statistics Canada using its Postal Code Conversion File).[144] Dissemination Areas are the smallest geographic unit division for which census data is publicly released in the country. They encompass relatively homogenous and stable populations of between 400 to 700 residents.[145] Statistics Canada classifies Dissemination Area as "rural" or "urban" according to population concentration. Urban areas are those that have a population concentration of at least 1,000 residents or of 400 residents per square kilometer.[144] Since population density is lower in rural areas, rural Dissemination Areas tend to be disproportionately large compared to urban Dissemination Areas. Studies have demonstrated that local area-level exposures derived from the Census are less accurate in rural settings due to the disproportion size of these Dissemination Areas.[146] Therefore, since rural Dissemination Areas potentially fail to capture the immediate local-area lived experience of material and social deprivation as they are more likely to do in urban areas, rural-dwelling respondents (approximately 30% respondents aged 50 to 75 in CCHS cycles 2005 and 2007) were excluded from the analysis.

3.2.3 Directed acyclic graph (DAG) of study measures

Drawing from the thesis' conceptual framework (Chapter 2: Figure 1) and from existing literature, the assumed associations between relevant factors in the association between area-level income and colorectal cancer screening are described in the Directed Acyclic Graph (DAG) below (Figure 2). Age, sex, marital status, educational attainment, access to a primary care physician, and place of birth are all assumed to be associated with local area-level income and with colorectal cancer screening. These measures therefore represent the minimal sufficient adjustment set for estimating the total effect of local area-level income on screening.

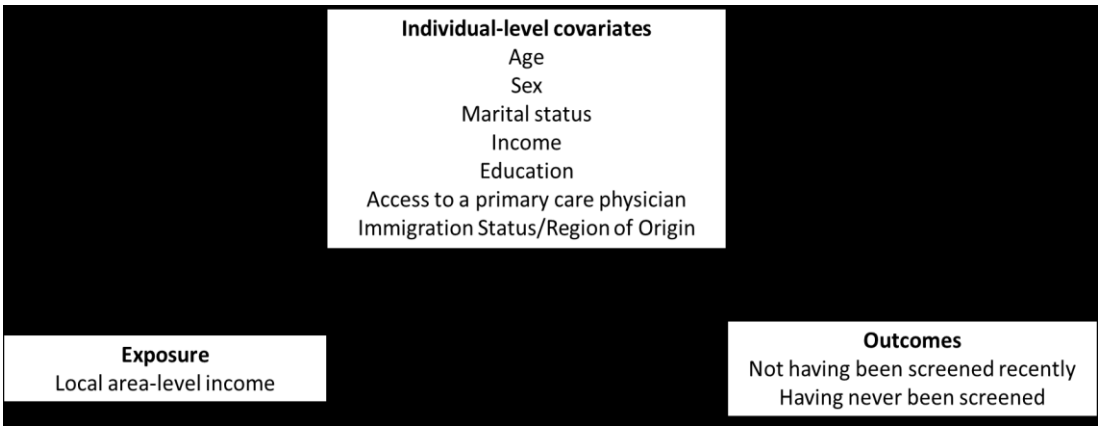

Figure 2: Directed Acyclic Graph (DAG) of the assumed directionality of associations between area-level income, individual-level characteristics (covariate matrix), and screening behaviour.

All the measures depicted in the DAG were used in the study. These measures are based on self-reported CCHS data and were operationalized as categorical variables. Due to small cell sizes for certain covariates and to restrictions placed by Statistics Canada to protect the confidentiality of respondents,[129] these categorical measures were restricted to at most four categories.

3.2.4 Outcome measures

In this study, the outcomes of interest were 1) having never been screened, and 2) not having been screened recently for colorectal cancer. In the CCHS, participants are asked the following two questions: "An FOBT is a test to check for blood in your stool, where you have a bowel movement and use a stick to smear a small sample on a special card. Have you ever had this test? [If yes] When was the last time?" and "A colonoscopy or sigmoidoscopy is when a tube is inserted into the rectum to view the bowel for early signs of cancer and other health problems. Have you ever had either of these exams? [If yes] When was the last time?" Potential answers range from less than one year ago, to 10 or more years ago (time responses are described in Appendix VIII). Current Canadian Cancer Society guidelines recommend that adults 50-74 receive a fecal screening test every two years, a sigmoidoscopy every 5 years, or a colonoscopy every 10 years.[5] The CCHS does not specifically ask respondents to identify the type of

endoscopy they received (colonoscopy or sigmoidoscopy). Therefore, respondents are considered as having not been screened recently if they neither received a stool test in the past two years, nor received an endoscopy in the past 5 years. This classification may produce measurement bias (e.g. those screened via colonoscopy in the previous 6 years are considered non-recently screened), however we preferred using a conservative estimate of the level of preventive screening in Canada than an over-estimation of screening that eclipses true gaps and screening inequalities. In this study, stool- and endoscopic-based screening were combined to account for the potential reality that certain individuals may by up-to-date on screening due to a recent stool-based test, without having received endoscopic screening recently or in their lifetime (or vice versa). Combining stool- and endoscopic-screening history for each respondent was done to minimize the potential misclassification of respondents' screening status.

This study uses both outcome timeframe measures (having never been screened, and not having been screened recently for colorectal cancer). Focusing on these two distinct outcomes enabled an assessment of predictors of two distinct screening events: initial screening participation, and continued screening uptake. Divergence of predictors can inform public health intervention targeted either to those who have never been screened, or those who have, but are not up-to-date in their screening.

3.2.5 Exposure measure

In this study, the exposure of interest was local area-level income. Mean income was computed by Statistics Canada for all Dissemination Areas (DAs). As the smallest Census divisions for which area-level data is released in the country, Dissemination Areas are believed to capture the immediate area-level socioeconomic resources available to residents. We categorized these mean income measures into quartile groups (quartile group 1 representing areas with lowest mean income, and quartile group 4 representing areas with highest income).

3.2.6 Covariate measures

Sociodemographic measures

Sociodemographic covariates used in this study were sex, age, and marital status. Age was dichotomized according to a cut-off of 60 years (comparing those aged 50 to 59 years-old to those 60 to 75 years-old). This age cut-off was used to compare screening in younger age-eligible adults to screening in older adults (namely those who were more likely to be retired). Though age 65 marks the age of eligibility for full retirement pensions in Canada,[147] the average age of retirement in the country is 60 years.[148] Approximately 60% of adults aged 55 to 64 years are partially retired, and 30% are fully retired.[148] Retirement marks a new stage in life course, especially with regards to discretionary time which is known to be a predictor of screening participation.[36-38] Further, older adults are assumed more likely to have been concurrently exposed to screening recommendations. For the variable of marital status, those who were married or in a common law relationship were compared to those who were divorced, widowed, or separated, and to those who were single. Sex, age, and marital status were treated as covariates in all three studies, to address potential confounding of the measured associations.

Income

Individual-level income was treated as a covariate in this study, to account for possible confounding between area-level income and individual screening behaviour. Information on respondents' household income from all sources, before taxes and deductions, in the previous 12 months was used. In the CCHS, respondents were asked "What is your best estimate of the total income received by all household members, from all sources, before taxes and deductions, in the past 12 months? Capital gains should not be included in the household income. Income can come from various sources such as from work, investments, pensions or government. Examples include Employment Insurance, Social Assistance, Child Tax Benefit and other income such as child support, alimony and rental income." Respondents are requested to state the estimated value of household income in Canadian Dollars (CAD). Respondents could refuse to answer the question or state "I do not know." From 2005 onward, all missing income data in the CCHS were imputed by Statistics Canada using a nearest neighbor method, based on available income-related data, household and postal code characteristics.[149] These imputed income values were

used in this study. Household income values were separated into quartile groupings based on the overall sample's distribution of income. Quartile 1 represents lowest income and quartile 4 represents highest income. For Objective 1, individual-level income was treated as a covariate, to account for possible confounding between area-level income and individual screening behaviour.

Education

Educational attainment was treated as a covariate, to account for possible confounding either between area-level income and individual screening behaviour In the CCHS, respondents were asked "What is the highest certificate, diploma or degree that [you have] completed?", to which possible answers were "Less than high school diploma or its equivalent," "High school diploma or a high school equivalency certificate," "Trade certificate or diploma," "College, CEGEP or other non-university certificate or diploma (other than trades certificates or diplomas)," "University certificate or diploma below the bachelor's level," "Bachelor's degree (e.g. B.A., B.Sc., LL.B.)," or "University certificate, diploma, degree above the bachelor's level." Since lack of high school graduation is an important predictor of non-recent cancer screening,[150] those who obtained less than high school diploma or its equivalent were compared to those who had a high school diploma or greater (which included both those who did and did not graduate from college).

Access to a primary care physician

Access to a primary care physician was treated as a covariate, to account for possible confounding between area-level income and individual screening behaviour. In the CCHS, respondents were asked "Do you have a regular medical doctor?" and could answer "Yes", "No", "I do not know," or refuse to answer. Screening among respondents with a physician (those who answered "Yes" to the above item) was compared to those without (those who answered "No"). Among CCHS respondents aged 50 to 75 years, approximately 1% reported "I do not know" or refused to answer.

Immigration

Immigration status was treated as a covariate in this study. Respondents were considered to be immigrants to Canada if they stated a country other than "Canada" when asked "In what country were you born?" and answered "No" to the question "Were you born a Canadian citizen?" Respondents' region of origin was treated as a covariate to account for potential confounding between area-level income and individual screening behaviour. Region of origin was measured based on respondents' reported country of birth. Reported countries of birth other than Canada were categorized according to the United Nations Statistics Division's Geographic Regions classification system and organized into two groups: group 1 includes the United States, European countries, and countries in Oceania; and group 2 includes countries in Latin America and the Caribbean, Africa, and Asia. These two groupings were designed to roughly capture differences in socio-cultural experiences of health care and colorectal cancer screening environments (including policies, infrastructure) pre-immigration—with immigrants from group 1's "Western" nations assumed to be more likely to have been exposed to health care systems and colorectal cancer screening policies (including organized screening programs) that are similar to those in Canadian provinces and territories.[48,151]

3.2.5 Sample weights

In the CCHS, each respondent is attributed a sampling weight according to their contribution to the total population. Described in greater detail elsewhere,[133] weights account for weighting in the Labour Force Survey (the nation-wide, monthly survey used to design the CCHS sampling frame[152]), for household counts and non-response at the area frame-level, and for method of data collection (in-person versus telephone-based interviews). In conjunction with sampling weights, Statistics Canada provides bootstrap weights (500 per respondent) to estimate variance. These 500 weights represent 500 replicates of the survey sample, accounting for the complex sampling design of the survey.[153] Both sampling and bootstrap weights were used in this first thesis study.

3.2.6 Analyses

To examine the association between local area-level income and two colorectal cancer screening outcomes (having never been screened, and not having been screened recently), the following statistical analyses were performed:

Descriptive analyses

The first analysis performed for this objective was the calculation of descriptive statistics for the demographic, socioeconomic, and screening characteristics of area-level income groups. Covariates of individual-level age, sex, marital status, income, education, immigration status, and access to a primary care physician were used.

Multivariate analyses

Analyses of the association between local area-level income and the screening outcomes were then performed. These analyses were designed to accommodate the sampling and bootstrap weights provided by Statistics Canada (500 weights for each participant), and the hierarchical data structure of the CCHS. Respondents are nested within Dissemination Areas (DA) (on average 6 [minimum 1 & maximum of 68] individuals are nested within each DA) and, according to the principle of spatial autocorrelation, are assumed to be more likely correlated due to their closer proximity.[154]

To account for these features of the data, a macro-based analysis proposed by SAS Corporation was applied.[155] A macro is typically a block of statistical code that is designed to repeat a similar process (e.g. a model or command) over a certain number of pre-specified arguments (e.g. repeated each time with a distinct variable, or with distinct weights).[156] Here, the macro syntax proposed by SAS[155] was adapted for our data by both Alexandra Blair and Dr. Samiratou Ouédraogo (a postdoctoral fellow at the School of Public Health of the Université de Montréal), and was used to loop through a generalized estimating equation (GEE) log-link Poisson model (with an assumed exchangeable covariance structure) 500 times—each time using a new,

unique bootstrap weight to construct robust 95% confidence intervals for the exposure and covariates' prevalence ratio (PR) estimates. These bounds are assumed to be robust to any mis-specification of effects due to over-dispersion.[157]

The macro's GEE-based approach was able to account for potential within-Dissemination Area data correlation, which would violate the assumption of independence between observations in traditional regression approaches.[158] Unlike multi-level approaches that model within-subject or within-area covariance structure, GEE approaches pre-specify the assumed covariance structure, treating it as a nuisance rather than an estimate of interest.[158,159] In the study for Objective 1, an exchangeable or "compound symmetric" covariance structure was assumed (i.e. the same for all respondents living in the same Dissemination Area). This GEE-based approach allows an interpretation of modeling output as the average association between area-level income and screening across Dissemination Areas. Here, the model used was a Poisson model, rather than a logistic model to minimize over-estimation of the associations[160] due to the common outcome (approximately 80% of adults aged 50 to 75 years are not up-to-date on colorectal cancer screening in Canada).[20] Poisson model estimates can be interpreted as the screening prevalence ratios (PR) for the factors included in the model. To complement measures on a relative scale, prevalence differences (PD) were also computed using Poisson models specified with an identity-link. PDs refer to the difference in adjusted prevalence (%) of screening for each of the factors in the model. All models were adjusted for age, sex, marital status, income, education, immigration status, and access to a primary care physician. All analyses were conducted using SAS 9.4.[161]

Sensitivity analyses

As a first sensitivity analysis, potential effect measure modification (EMM) of the absolute and relative associations by immigration status, regular physician access, and household income were also tested using product terms between each factor and the exposure (local area-level income). Second, given our conservative operationalisation of recent endoscopic screening (i.e., having received a sigmoidoscopy or colonoscopy in the previous five years), analyses were repeated with an alternative cut-off of 10 years. Results were similar and were not reported in the study. Third, since the validity of estimates relied on the assumption of non-confoundedness

between the exposure and outcome measures, Ding and VanderWeele's Bounding Factor formula[126] was applied to test the sensitivity of our findings to potential unmeasured confounding. This sensitivity analysis assesses how large an unmeasured factor's (or matrix of factors') relation with the exposure and outcome would have to be to bring effect estimates to cross the null (PR=1). Using the lower bound of the 95% confidence intervals estimated ($PR_{observed}$), the formula[126] to estimate the maximum association ($PR_{maximum}$) between unmeasured factor and exposure and outcome reads as follows:

$$PR_{maximum} = PR_{observed} + \sqrt{[(PR_{observed} * (RR_{observed} - 1)]}$$

The estimated value ($PR_{maximum}$) can then be interpreted based on extant knowledge of the determinants of both area-level income and screening determinants. The potential for residual confounding can be discussed considering these findings.

3.2.7 Power considerations

The ability of the latter analyses to correctly reject a null hypothesis (H0) (i.e., that no association between area-level income and screening is present, PR = 1) depends on several factors. In this context, study power depends on the prevalence of screening outcomes, the number of Dissemination Areas studied, the average number of respondents residing in the same Dissemination Area (i.e., cluster size), and the degree of correlation of the characteristics of individuals dwelling within the same Dissemination Area (i.e., intraclass correlation). Testing the association between local area-level income and colorectal cancer screening becomes less efficient when the number of Dissemination Areas decreases, the size of Dissemination Area clusters grows, and/or when the intraclass correlation between persons living in the same Dissemination Area increases. Analyses of how large a sample would have to be to detect various effect sizes, given analysis parameters, were performed using an approached proposed by Liu and Liang (1997)[162]—results of which are described in Appendix IX. Given the large number of Dissemination Areas utilized in this national sample (approximately n=7,200), and the relatively few respondents present in each Dissemination Area (average of n=6), it is estimation

that the available CCHS sample was sufficiently powered to detect associations between area-level income and screening of approximately PR=1.05 or greater.

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3.3 OBJECTIVE 2

The second objective of this thesis was to assess whether or not access to primary care physicians mediates differences in screening uptake between recent immigrants and non-immigrants in Canada.

3.3.1 Design

Like the first manuscript, this second manuscript uses a pooled cross-sectional design to maximize study power. It utilizes data from the 2003, 2005, 2007-2014 cycles of the CCHS. Results from pooled CCHS waves represent the average associations across waves.

3.3.2 Study population

The population of interest for this study were 50 to 75-year-old respondents from the CCHS with no known familial or medical risk factors of colorectal cancer (i.e., those at "average risk"[5]). Those reporting screening for "higher risk" reasons (i.e. due to "family history of colorectal cancer," "follow-up of a problem," and "follow-up of colorectal cancer treatment.") represented approximately 20% of adults aged 50 to 75 in CCHS cycles 2003 to 2014.

The study focused on two groups of respondents: those who were either white and Canadian-born, and those who had immigrated to Canada recently (≤10 years) and were either white or of visible minorities. The study sample was restricted to these groups for two reasons. First, longer-term immigrants (>10 years since arrival) were excluded given their similar overall prevalence of never having been screened for colorectal cancer (45.6%, 95% CI: 44.4%, 47.1%) as Canadian-born respondents (46.3%, 95% CI: 45.8, 46.8%). The application of mediation analysis to explain differences in screening between longer-term immigrants and Canadian-born respondents was therefore not pertinent, as no distinct inequality was present.

Second, visible minority Canadian-born respondents were excluded so that two specific contrasts could be made, which could help elucidate the mechanisms underlying immigration-

based disparities in screening. The first contrast was between white Canadian-born respondents and white recent immigrants. The screening disparity between the latter two groups (adjusting for relevant covariates) is assumed to be attributable to the experience of recent immigration alone (i.e. experience of a new country, a new health system, etc.) rather than to racial or ethnic discrimination. The second contrast was between white Canadian-born respondents and visible minority recent immigrants. The screening disparity between the latter two groups (adjusting for relevant covariates) is assumed to be attributable to the intersecting[115,163] (or "joint") experience of recent immigration and visible minority status (e.g. through processes of racial or ethnic marginalization). Differences in the size of these two inequalities are assumed to offer an indication of the effect-modifying potential of visible minority status lived by recent immigrants.

3.3.3 Direct acyclic graph (DAG) of study measures

Drawing from the thesis' conceptual framework (Chapter 2: Figure 1) and from existing literature, the assumed associations between relevant factors in the association between recent immigration, access to a primary care physician, and colorectal cancer screening are described in the Directed Acyclic Graph (DAG) below (Figure 3). Age, sex, marital status and educational are assumed to be associated with the exposure (recent immigration), the primary mediator studied (access to a primary care physician), additional potential mediators (income, rural residence) and the outcome (never having been screened). Additionally, exposure to a mail-out based organised provincial screening program (measure discussed in detail below) is also considered to a be a confounder in the associations between the exposure, mediator, and outcome. In the DAG, the arrow from exposure to an organized screening program to recent immigration (A) is denoted with an asterisk (*) to offer readers further information: the directionality of this arrow reflects the assumptions that 1) recent immigration entails a set of experiences, some of which are mutable and can vary according to the country of arrival's integration policies, and 2) organized screening programs (which represent a provincial investment in health promotion and health service accessibility—or least, the promotion of service and screening awareness) could shape recent immigrants' experiences in navigating a new health system. Together, these covariates

represent the minimal sufficient set of factors to adjust for confounding between the exposure and the mediators, the mediators and the outcome, and the exposure and the outcome.

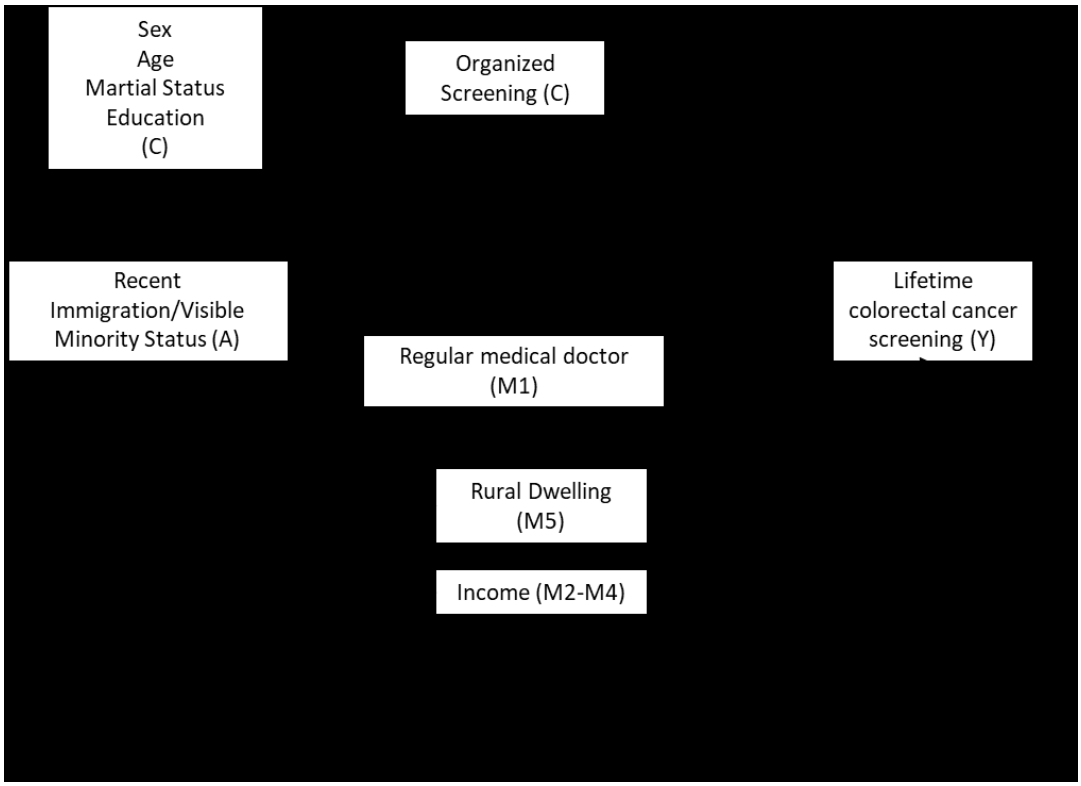

Figure 3 Directed Acyclic Graph (DAG) of the assumed directionality of associations between recent immigration, access to a primary care physician, income, rural residence, social and demographic, exposure to provincial systematic organised screening program, screening.

3.3.4 Outcome measure

The outcome measure for this second study was slightly different from the outcomes used in the first paper. Only the outcome of having never been screened was used, since preliminary analyses of the CCHS suggested that recent immigrants and Canadian-born respondents report similar of rates of having been screened recently (i.e. stool-based testing in the previous two years, or endoscopy use in the previous five years). Respondents who answered "Yes" to the CCHS question "An FOBT is a test to check for blood in your stool, where you have a bowel movement and use a stick to smear a small sample on a special card. Have you ever had this

test?" or to the question "A colonoscopy or sigmoidoscopy is when a tube is inserted into the rectum to view the bowel for early signs of cancer and other health problems. Have you ever had either of these exams?" were considered to have been screened at least once in their lifetimes. In this study, stool- and endoscopic-based screening were combined to account for the potential reality that certain individuals may by up-to-date on screening due to a recent stool-based test, without having received endoscopic screening recently or in their lifetime (or vice versa). Combining stool- and endoscopic-screening history for each respondent was done to minimize the potential misclassification of respondents' screening status.

The outcome of having never been screened is relevant for public health planning in Canada, insofar as most Canadians who have not been screened recently for colorectal cancer have in fact never been screened in their lifetime.[22,164] Further, since having never been screened is associated with later-stage cancer at diagnosis and higher risk of mortality, targeting never-screened populations is therefore also believed to be a relevant approach to reduce the incidence of late stage diagnosis and the overall burden of colorectal cancer.[26]

3.3.5 Exposure measures

In this study the joint exposures of interest were recent immigration and visible minority status. These two measures were combined in order to account for intersecting experiences of recent immigration and racialization.[115,163] Racialization is defined as the social process of "othering" through which certain populations are identified as distinct, and therefore unworthy of equal treatment.[165] It is the process that exposes individuals to, and legitimizes and perpetuates racism—be it in interpersonal and structural in form.

In this study, we use the construct of "visible minority status" as a proxy for racialized status, and the potential marginalization it entails. The term "visible minority status" applied in official Canadian policies and documents, such as the Canadian Census and Canada's Employment Equity Act, was constructed to identify persons who are "non-Caucasian in race or non-white in colour."[166] The term "visible minorities" grew in popularity between the 1970s and 1990s in Canadian political praxis.[167] As the country embraced the paradigm of multiculturalism

and introduced anti-discrimination frameworks such as those encoded in the Canadian Charter of Rights and Freedoms, the expression "visible minority" was used to replace terms such as "ethnic" or "racial" minority.[167] In the field of Critical Race Theory, some detractors oppose this shift in terminology insofar as it distances political semantics away from an acknowledgment of race (as construct)[166] and of the structured power dynamics defined by paradigms such as white supremacy.[168] The grouping of racial or ethnic minorities into one category has also been criticized for masking of heterogeneity in the lived experiences of population sub-groups (both among populations captured as "white" and those identified as "visible minorities"). [166] Acknowledging these limitations, we use the dichotomous measure of "white" versus "visible minorities" (which includes, here, individuals self-identified as indigenous) to capture two groups with differential likelihoods of experiencing racial discrimination. Indeed, as reported in the 2002 Canadian Ethnic Diversity Survey, 20% of individuals categorised as "visible minorities" reported having experienced discrimination or unfair treatment in the previous five years "sometimes or often" (proportions were specifically 21% among those who were first-generation Canadians and 18% among those who were at least second-generation Canadians), compared to 5% among those were not identified as "visible minority" respondents.[165,169]

In the CCHS, respondents' visible minority status was operationalized using a questionnaire item on racial and ethnic identity. CCHS respondents were asked "People living in Canada come from many different cultural and racial backgrounds. Are you: (1) White? (2) Chinese? (3) South Asian (e.g., East Indian, Pakistani, Sri Lankan)? (4) Black? (5) Filipino? (6) Latin American? (7) Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese)? (8) Arab? (9) West Asian (e.g., Afghan, Iranian)? (10) Japanese? (11) Korean? (12) Other [Specify]?" Respondents could also respond "I do not know" or refuse to answer. A "Cultural/ Racial Background" variable was then derived by Statistics Canada for the CCHS, with categories of "Aboriginal identity", "White only," "Black only," "Korean only," "Filipino only," "Japanese only," "Chinese only," "South Asian only," "Southeast Asian only," "Arab only," "West Asian only," "Latin American only," "Other racial or cultural origin (only)" and "Multiple racial or cultural origins." In this study, the variable of "visible minority status" (yes/no) captured two groups: those categorized as "White only" by the derived "Cultural/Racial Background" variable, and all other respondents, hereafter described as "visible minorities."

In the CCHS, respondents were also asked "In what year did you first come to Canada to live? Including first coming to live in Canada on a work or study permit or by claiming refugee status. If you moved to Canada more than once, enter the first year you arrived in Canada (excluding holiday time spent in Canada)." If the respondent could not give the exact year of arrival in Canada, they were asked to provide a best estimate of the year.[139] In this study, individuals were considered to have immigrated recently to Canada if they arrived in the previous 10 years. A 10-year cut-off was used to reflect the observed period it takes, on average, for new residents to feel a sense of familiarity in the Canadian setting, and to report similar income earnings as average Canadian residents.[170]

Variables or recent immigration and visible minority status were used to assess two contrasts: a comparison of screening between white Canadian-born respondents and white recent immigrants; and a comparison of screening between white Canadian-born respondents and visible minority recent immigrants. Screening among white recent immigrants and visible minority recent immigrants was compared to screening among white Canadian-born respondents to isolate the associations between the single exposure of recent immigration and screening, and the association between the joint exposure of visible minority status and recent immigration and screening. In the latter contrast, utilizing a categorization that captured both visible minority status and recent immigration status simultaneously was done in order to account for the intersecting experiences of recent immigration and racialization.[115,163]

3.3.6 Mediator measures

The principal mediator of interest was access to a primary care physician. And, as it is the convention to consider other potential mediating factors in the analysis of direct and indirect effects,[120] we identified two factors in the literature to be treated as additional potential mediators in the analyses: household income and area of residence. The full mediation analyses (i.e. the estimation of the TE, CDE, and PE) described below were not run for these additional mediators. Rather, the identification of potential additional mediating factors among the covariates of the study is recommended insofar as these factors must be treated differently in the estimation of the

TE, compared to the estimation of the CDE for the primary mediator of interest. These potential additional mediators were excluded from TE analyses, insofar as they were not assumed to confound the association between recent immigration and screening. In contrast, they were included as potential confounders of the principal mediator-outcome association in CDE analyses, given that they were assumed to determine both likelihood of access to a primary care physician and screening (Figure 3).

Access to a primary care physician

The measure of access to a primary care physician developed for the first thesis study was utilized again in this second study. In the following sections "M1" refers to a dichotomous variable of access to a primary care physician. Respondents were considered to not have a primary care physician (M1=1) if they answered "No" to the question "Do you have a regular medical doctor?"

Income

In the CCHS, respondents are asked about their own personal income, and about their household's income (i.e. "What is your best estimate of the total income received by all household members, from all sources, before taxes and deductions, in the past 12 months?"). If respondents either do not answer or do not know how to answer to the latter question, they are prompted with the following questionnaire item: "Can you estimate in which of the following groups your household income falls? Was the total household income in the past 12 months… [1] Less than $50,000 or [2] $50,000 or more?" Depending on the response, the interviewer then offers more specific income ranges (e.g. "less than $5000", "$5,000 to $10,000," etc. up to "$150,000 and over").

From CCHS cycles in 2005 onward, all missing income data were imputed by Statistics Canada using a nearest-neighbor donor imputation strategy.[149] The CCHS' income imputation method used a four-step modeling-based approach. In the first step, a model was fit for personal income (for male and female respondents separately), with age, education, source of income,

health region, marital status, household size, home ownership status, employment status, and number of children in the household. Data on the latter covariates were collected for every member of the household participating in the CCHS. Once the model was fit, an estimate of the predicted value of personal income for each respondent (regardless of true reported income) was produced, based on the respondents' responses to the latter covariate characteristics. In the second step, the predicted personal income values are summed for all CCHS respondents living in the same household—yielding a preliminary predicted value of household income. In the third step, each respondent is assigned the median household income value for their postal code, using the Canadian Census T1 Family File. In the fourth step, a final model is fit, with the log-transformed predicted values of preliminary household income (from steps 1 and 2) and median postal code income values (from step 3) as covariates, along with other health-related covariates chosen to capture daily activity limitations that may affect income levels (e.g. presence of Alzheimer's disease in the home, heavy drinking, activity limitation, daily smoking, general health status, immigrant status). As in step 1, predicted values of final modeled household income were derived for all respondents (regardless of true reported household income). The sample was then divided into groups (or "imputation classes"), based on the amount of income information provided for the household income questionnaire items listed above, such that there was a minimum of 10 potential "donors" of income data in each imputation class and 30% of respondents in each class were potential donors. Within each imputation class, each respondent who was missing household income data was attributed the income value of the respondent with income data who is closest (i.e. the "nearest neighbor") along the continuum of predicted final modeled household income values (from step 4). This approach was used to preserve the income distribution structure in the sample.

These imputed data were used in this second study. However, since missing income data were not imputed in the CCHS before 2005, and this study also used data from the 2003 cycle of the CCHS, we imputed missing income data ourselves for the 2003 cycle of the CCHS. Given that we did not have access to the Canadian Census T1 Family File, nor to certain covariate details, such as respondents' health region, we applied an alternative income imputation approach. For 2003 CCHS respondents, missing household income values were imputed based on individuals' age, sex, education, marital status, immigration status, and sampling weight,

using a hot deck imputation approach in Stata 14 (*hotdeckvar* command). In the hot deck imputation method used for this study, missing subject information were imputed stochastically, using data from similar subjects (in terms of the specified covariates) with complete data. An underlying assumption of this imputation was that data were missing at random, conditional on measured covariates.[171] Though error in capturing respondents' true income values is likely, analyses performed with and without independently-imputed income values for the 2003 cycle of the CCHS yielded similar results.

Household income was separated into quartile groupings based on the overall sample's distribution of income: quartile 1 represents lowest income and quartile 4 represents highest income. In the following sections "M2" refers to an indicator variable that compares exposure to the first quartile of household income (Quartile 1) to all other quartile groupings; "M3" represents an indicator variable for the second quartile grouping (Quartile 2); and "M4" represents an indicator variable for the third quartile grouping (Quartile 3).

Rural residence

Rural residence was considered as a potential additional mediator in the association between recent immigration and screening, insofar as recent immigrants are less likely to dwell in more rural areas,[172] and rural residents is a documented determinant of colorectal cancer screening participation.[25,44] As discussed for the first study, CCHS respondents' area of residence is considered "urban" or "rural" based on the population density of the Canadian Census Dissemination Areas in which they live. Dissemination Areas are the smallest geographic unit division for which census data is publicly released in the country. They encompass relatively homogenous and stable populations of between 400 to 700 residents.[145] The urban-rural classification of Dissemination Areas, derived by Statistics Canada, is comprised of seven categories. These are: "Rural," "Urban core," "Urban fringe," "Urban area outside Canadian Metropolitan Areas", "Secondary urban core," or "Mix of urban and rural areas." [144] Statistics Canada considers the first type of areas to be "rural" areas, with the subsequent five types considered as "urban" areas. [144] Statistics Canada assigns urban or rural status to areas labeled "Mix of urban and rural areas" based on the composition of the Census blocks within the each

Dissemination Areas.[144] Typically, urban areas are those that have a population concentration of at least 1,000 residents or of 400 residents per square kilometer.[144] The dichotomous variable of rural residence (versus urban reference) was used to accommodate the mediation analyses discussed below.

3.3.7 Covariate measures

Sociodemographic measures

Sociodemographic covariates used in this study were sex, age, and marital status. Like in the first study, age was dichotomized according to a cut-off of 60 years (comparing those aged 50 to 59 years-old to those 60 to 75 years-old), and marital status was organised into three categories: married or in a common law relationship; divorced, widowed, or separated; and single.

Education

Educational attainment was also treated as a covariate. As in the first study, those who obtained less than high school diploma or its equivalent were compared to those who had a high school diploma or greater (which included both those who did and did not graduate from college).

Exposure to an organised mail-based screening program

As of 2007 in Canada, provinces had begun implementing organised screening programs to promote stool-based screening. An indicator measure for exposure to an organised screening program was included in this study, to account for potential confounding of the associations between recent immigration, access to primary care physicians, and screening. Provincial organised screening programs vary in their design –particularly in their approach of patient registration and screening test distribution and collection. Some programs systematically send out invitation letters to all adults aged 50 to 74 years, with an opportunity to access and return

screening kits via mail in envelopes with pre-paid postage.[48,173] These types of organised "mail-based" programs were introduced in Manitoba (in 2007), Ontario (in 2008), Saskatchewan (in 2009), Nova Scotia (in 2009), and New Brunswick (2014). In contrast, other programs are more "patient-reliant" insofar as they do not send out invitation letters, but rather can require patients to register with the program themselves via their primary care physician, a designated phone line or website, before receiving and returning the test via mail (as seen in Newfoundland and Labrador [introduced in 2010]), or they can require patients to pick-up the screening test themselves at a designated facility (as seen in Alberta [introduced in 2007] and in British Columbia [introduced in 2009]) and/or return the screening kit themselves at a designated facility (as seen in Prince Edward Island [introduced in 2011]).[173] (further details on existing programs are discussed Appendix VII). At the time this study was designed, no study had assessed the effectiveness of these more "patient-reliant" programs in increasing screening participation overall or reducing screening inequalities. Studies reviewed had assessed organised mail-based screening programs, and found them to be associated with small to moderate increases in overall screening participation.[39,40,51,52] Thus, in this study, a covariate was introduced to capture respondents' exposure to an organised mail-based screening program. Individuals living in Manitoba (2007 CCHS cycle onwards), Ontario (2008 CCHS cycle onwards), Saskatchewan (2009 CCHS cycle onwards), Nova Scotia (2009 CCHS cycle onwards) and New Brunswick (2014 CCHS cycle) were considered exposed to an organised mail-based screening programs,[173] while respondents in other "province-years" were not.

3.3.8 Sample weights

As discussed previously, each respondent to the CCHS is attributed a sampling weight according to their contribution to the total population, as well 500 bootstrap weights for the purposes of variance estimation. These weights were not utilized in this second study for both methodological reasons and reasons pertaining to sample size: several analytic methods were used in this study (described in greater detail in section 3.3.9), two of which utilize inverse probability weighting (IPW) methods to condition on the covariates described above, thereby minimizing confounding bias. Sampling weights can be incorporated in IPW approaches, by

multiplying sampling weights and the estimated inverse probability of treatment weights.[174] However, the product of these two weights can yield unreasonably large weights (e.g. one respondent representing thousands of respondents in the analyses).

Indeed, given the small cell sizes for the variables used in the analyses (recall that the sample was stratified by variables of recent immigration status, visible minority status, access to a primary care physician, and screening), certain estimated propensity scores were very small (leading to large inverse probability weights). To avoid excessively large weights, we chose not combined sampling weights with inverse probability weights in the IPW-based methods (described in detail below). To ensure consistency across methods, sampling weights were therefore also excluded from regression-based methods.

3.3.9 Analyses

The aim of this study was to assess whether immigration-based disparities in colorectal cancer screening among adults aged 50-75 years are mediated by access to a primary care physician. To do so, we aimed to estimate 1) the total adjusted association (referred to here as the "total effect") between recent immigration and lifetime colorectal cancer screening, 2) the controlled direct effect of recent immigration on lifetime colorectal cancer screening, and 3) the proportion of the total effect that would be eliminated if all had access to a primary care physician (referred to as the "Proportion Eliminated").

Effect definitions

Here, the total effect can be defined as the total immigration-based disparity in lifetime screening (i.e. prevalence difference or prevalence ratio), assuming all exposure-outcome confounders have been measured, and allowing natural variation in exposure to all potential mediating factors between recent immigrants and individuals born in Canada (i.e. not accounting for physician access, or any other potential mediator).

The controlled direct effect can be defined using the counterfactual or "potential outcomes" framework for causal inference.[120] The latter framework provides a theoretical basis and technical notation to conceptualize causation.[120] It posits that causal inference—or the measurement of a causal effect—would require comparing outcomes that occurred between the true world, where some action, state or exposure took place, and an alternative hypothetical world in which the action, state or exposure had been changed (i.e. the "potential" outcome in the presence or the absence of intervention).[120] In a counterfactual framework,[175] if we assume having measured all mediator-outcome confounders, the controlled direct effect can be defined as the remaining immigration-based disparity in lifetime screening prevalence had all individuals been assigned (possibly counterfactually) a primary care physician. The controlled direct effect estimate is particularly relevant when interested in assessing how a potential intervention on a mediator (here, physician distribution) could influence a known inequality.[176-178]

With the total effect and controlled direct effect, we can estimate the proportion of the total effect that would be eliminated if all had access to a primary care physician (more details on estimation below). If the inequality in access to primary care physicians according to immigration status does explain, at least in part, immigration-based inequalities in screening, we would expect to see a substantial proportion of the inequality be eliminated.

Effect estimation

Multiple approaches have been proposed to estimate direct effects. Some use regression models,[121,122] while other approaches opt instead for the use of inverse probability weighting to estimate marginal associations (i.e. population-average effect). In the latter approaches, respondents are weighted to create synthetic populations that are balanced in terms of the measured covariates, through which contrasts in average outcomes can be estimated.[60] In this study, we used three mediation techniques across which to compare the stability of our findings: (1) a regression-based modeling method (the generalized product method[179]); (2) an inverse probability-weighted marginal structural modeling method;[123] (3) and an inverse probability weighted marginal effect estimation approach.[120]

(1) Generalized product method

The generalized product method[177], proposed by VanderWeele and Vansteelandt,[179] extends Baron and Kenny's product method[121] to allow for effect estimation in the presence of exposure-mediator interaction;[122,180] The original product method proposed by Baron and Kenny was not designed to allow for effect estimation in the presence of exposure-mediator interaction and could therefore yield biased results. If effect modification is present and there is departure from additivity, effect decomposition is no longer valid as the sum of the direct and indirect no longer yield the total effect. Both approaches are described here:

In Baron and Kenny's original method,[121] the total effect is estimated by fitting an outcome model (for Y=1, never have been screened) with the exposure and all covariates (c), but no mediator variable:

$$\log(E[Y|a, c]) = \theta_0 + \theta_1 a_i + \theta' c \qquad [1]$$

The estimate θ_1 from model [1] above represents the total effect. The controlled direct effect is estimated by adding the mediator to the model (m_1) and any other mediators believed to lie on the path between the exposure and outcome (m'):

$$\log(E[Y|a, m,c]) = \Phi_0 + \Phi_1 a + \Phi_2 m_1 + \Phi' m + \Phi' c \qquad [2]$$

Here, the estimate Φ_1 is assumed to represent the controlled direct effect estimate (i.e. the remaining immigration-based disparity in lifetime screening prevalence had all individuals been assigned a primary care physician, $m_1=1$).

In the generalized product method, the total effect is estimated the same way (the estimate θ_1 from model [1] still represents the total effect), but the control direct effect model is tweaked to include a product-term between the exposure (a) and mediator (m_1) (i.e. the am_1 indicator variable:

$$\log(E[Y|a, m_1,m',c']) = \beta_0 + \beta_1 a + \beta_2 m_1 + \beta_3 a m_1 + \beta' m + \beta' c) \qquad [3]$$

The controlled direct effect is interpreted as the following sum: ($\beta_1 + \beta_3 m_1$), where m_1 is set to $m_1=1$ (all have a primary care physician). For these two effects, Poisson models were specified. As for Objective 1, Poisson models were used in lieu of logistic models in order to minimize over-estimation of the associations[160] due to the common outcome.[20] Poisson model estimates are interpreted as screening prevalence ratios (PR). Confidence intervals (95%) for both effects were estimated using a bootstrap variance estimation method (with 500 iterations).[120] Models were repeated for each strata of visible minority status and recent immigration status. Analyses were conducted in R (version 3.4.1).[181]

(2) Inverse probability-weighted marginal structural model method

In the inverse probability-weighted marginal structural model approach, described by VanderWeele,[123] two models are run: one for the total effect, the other for the controlled direct effect. They are the same Poisson regression models specified in the generalized product method:

$$\log(E[Y|a, c]) = \theta_0 + \theta_1 a_i + \theta' c \qquad [1]$$
$$\log(E[Y|a, m_1,m',c']) = \beta_0 + \beta_1 a + \beta_2 m_1 + \beta_3 a m_1 + \beta' m + \beta' c \qquad [3]$$

However, in this approach, models are specified with exposed and unexposed respondents (i.e. recent immigrants and individuals born in Canada) weighted using inverse probability weights. To estimate the total effect, model [1] is specified with inverse probability weights that ensure respondents are balanced in terms of measured covariates [Weight for *a*]. To estimate the controlled direct effect, model [3] is specified with inverse probability weights that ensure respondents are balanced in terms of measured covariates and mediator exposures [Weight for *a* and m_1]. These weights are estimated using a series of propensity score models (summary of weights used are described in **Table 2** below):

The first set of weights [Weight for *a*] are estimated by first specifying two prediction models for the exposure: an empty (intercept only) model and one that includes all covariates:

$$\log(E[a|1]) = \theta_0 \quad [4]$$

$$\log(E[a|c']) = \beta_0 + \beta' c \quad [5]$$

Two sets of propensity scores for a=1 are estimated for each respondent using models [4] and [5]. Propensity scores from model [4] are divided by those from model [5] to yield an inverse probability weight for exposure (a) for each respondent. The second set of weights [Weight for a and m_1] are estimated by specifying a prediction model for mediator m_1 with exposure a, and a model for the for mediator m_1 with exposure a, covariates c, and other mediators m':

$$\log(E[m_1| a]) = \theta_0 + \theta a \quad [6]$$

$$\log(E[m_1| a,c,m']) = \beta_0 + \beta a + \beta' c + \beta' m \quad [7]$$

Two sets of propensity scores for m_1=1 are then estimated using, respectively, models [6] and [7]. Inverse probability weights for m_1 are estimated by dividing propensity scores from model [6] by propensity scores from model [7]. These weights for m_1 are then multiplied with [Weight for a] to create a summary weight [Weight for a and m_1].

Using these weights, the θ_1 estimate from model [1] represents the total effect; and the sum of estimates ($\beta_1 + \beta_3 m_1$) from model [3] represents the controlled direct effect, where m_1 is set to $m_1=1$ (all have a primary care physician). Confidence intervals (95%) for both effects were estimated using a bootstrap variance estimation method (with 500 iterations).[120] Models were repeated for each strata of visible minority status and recent immigration status. Analyses were conducted in R (version 3.4.1).[181]

Table 2: Summary of estimated weights required for total effect and controlled direct effect estimation in an Inverse probability-weighted marginal structural model mediation method

Inverse probability weight	Propensity score (ps) models used for weight estimation	Estimated effect using each weight
Weight for a=1	ps[a=1 ~ 1] / ps[a=1|c]	Total effect
Weight for m_1=1	ps[m_1=1 ~ a] / ps[m_1=1|a,c,m']	

Summary weight for a=1 and m_1 (Weight for a=1 * Weight for m_1=1)	Controlled direct effect

Sensitivity analysis

Beyond the assumption of non-confoundedness of the exposure-outcome and mediator-outcome relationships, effect estimation using inverse probability weighting relies on the assumption of practical positivity (i.e. that propensity scores for the exposure and mediator—both of which are used in constructing the weights—are neither 0 (0% probability) nor 1 (100% probability)). [182] To assess this assumption, we performed stratified, descriptive analyses of propensity scores for the exposure (A) and mediator (M1).[120]

(3) Inverse probability weighted-average marginal effect estimation method

Lastly, an inverse probability weighted-average approach was used. Described in previous work by VanderWeele,[120] this method estimates simple ratios of weighted screening prevalence to estimate total and controlled direct effects. Weighting allows for respondents to be balanced in terms of measured covariates (for total effect estimation), and for both measured covariates and mediator exposures (for controlled direct effect estimation). The models and weights are described here and summarized in Table 3 below.

To estimate the marginal total effect, first a prediction model for the exposure (a) is again specified (model [5]):

$$\log(E[a|c']) = \beta_0 + \beta' c \qquad [5]$$

Using model [5], predicted probabilities (propensity scores) for the exposure (a=1, having recently immigrated) are estimated for each respondent. We label propensity scores for the exposure (a) among recent immigrants (those with values a=1) as scores [A_1], and propensity

scores for the exposure (a) among non-immigrants (those with values a=0) as scores [A_0] (which are equivalent to difference [1– A_1]). Using these propensity scores, inverse probability weights are estimated. Those exposed (a=1) are assigned a weight of [1/[A_1]], and those unexposed (a=0) are assigned a weight of [1/[A_0]]. To estimate the total effect as a prevalence ratio (PR), the prevalence of lifetime screening among recent immigrants (a=1) who are weighted using the weights [1/[A_1]] is divided by the prevalence of lifetime screening among Canadian-born respondents (a=0), who are weighted using the weights [1/[A_0]].

To estimate the marginal controlled direct effect, an additional prediction model is again specified for the mediator (m_1), adjusting for the exposure (a), covariates (c), and other mediators (m'):

$$\log(E[m_1 | a,c,m']) = \beta_0 + \beta a + \beta' c + \beta' m \qquad [7]$$

Using model [7], propensity scores for the mediator (m_1=1) are estimated for all respondents. We label propensity scores for the mediator (m_1=1) among recent immigrants (those with values a=1) as scores [M_1A_1], and propensity scores for the mediator (m_1=1) among individuals born in Canada (those with values a=0) as scores [M_1A_0]. These scores are combined with those from model [5] as follows: recent immigrants (a=1) with a primary care physician (m_1=1) are give weights that represent the inverse of the product between scores [A_1] and [M_1A_1] (i.e. [1/(A_1*M_1A_1)]); Canadian-born respondents (a=0) with a primary care physician (m_1=1) are given weights that represent the inverse of the product between scores [A_0] and [M_1A_0] (i.e. [1/(A_0*M_1A_0)]).

To estimate the controlled direct effect as a prevalence ratio (PR), the prevalence of lifetime screening among recent immigrants (a=1) with a primary care physician (m_1=1), who are weighted using the weights estimated above (i.e. [1/(A_1*M_1A_1)]) is divided by the prevalence of lifetime screening among Canadian-born respondents (a=0) with a primary care physician (m_1=1), who are weighted using their respective weights (i.e. [1/(A_0*M_1A_0)]). In a counterfactual framework, the numerator in this ratio represents the hypothetical screening prevalence that would be expected if all recent immigrants had physicians (Y_{1m}) (where m_1 is set to m_1=1), while

the denominator represents the hypothetical screening prevalence that would be expected if all Canadian-born respondents had physicians (Y_{0m}) (where m_1 is set to m_1=1). The confidence interval (95%) for the total effect ratio and the controlled direct effect ratio are estimated using the bootstrap method (with 500 iterations).[120] Estimation was repeated for each strata of visible minority status and recent immigration status. Analyses were conducted in R (version 3.4.1).[181]

Table 3: Summary of estimated weights required for total effect and controlled direct effect estimation in an Inverse probability weighted-average marginal effect estimation method

Inverse probability weight	Propensity score (ps) models used for weight estimation	Estimated effect using each weight
Weight for a=1	1 / ps[a=1|c]	Total effect
Weight for m_1=1	1 / ps[m_1=1|a,c,m']	Controlled direct effect

Sensitivity analysis

Like with the previous method, the validity of these weighted estimates also relies on the assumption of practical positivity (i.e. that propensity scores for the exposure and mediator—both of which are used in constructing the weights—are neither 0 (0% probability) nor 1 (100% probability)).[182] To assess this assumption, we performed stratified, descriptive analyses of propensity scores for the exposure (A) and mediator (M1).[120]

Proportion eliminated

In all three of these methods, once the total effect and controlled direct effects are estimated, the proportion of the total effect explained by physician access can be calculated on an

excess relative risk scale (i.e. using prevalence ratio [PR] estimates). The formula to estimate the proportion eliminated is as follows[120]:

$$\text{Proportion eliminated} = [PR_{\text{Total Effect}} - PR_{\text{Controlled Direct Effect}}] / [PR_{\text{Total Effect}} - 1]$$

Confidence intervals (95%) for the proportion eliminated are also estimated using the bootstrap method (500 replications).[120] These analyses were also conducted in R (version 3.4.1).[181]

Overall sensitivity analyses

First, the above analyses were repeated with two covariates treated as potential effect modifiers (or moderators): individual-level income and exposure to a systematic organised screening program. Second, since validity of the controlled direct effect estimates (and consequently, of the PE estimates) relies on the assumption of controlled confounding for the exposure-outcome relationship, and the mediator-outcome relationship,[183] we apply formulas derived by VanderWeele (2015)[183] to test the sensitivity of observed controlled direct effect estimates to unmeasured confounding of the mediator-outcome relationship. Under the assumption of no unmeasured confounding for the exposure-outcome relationship or of the exposure-mediator relationship (given covariates), this approach estimates how large the associations between an unmeasured factor and the outcome, and between an unmeasured factor and the mediator, would have to be for the true controlled direct estimates to be null (PR=1) despite non-null estimates.

3.3.10 Power considerations

The ability of the three proposed methods to correctly reject the null hypotheses that no association exists between recent immigration and lifetime screening (total effect); and that no association exists between recent immigration and lifetime screening if all had a primary care physician (controlled direct effect) depends on several factors. First, study power to detect total effects depends on the prevalence of the exposure, the prevalence of screening among those exposed and unexposed, and the total sample size. Analyses of what level of power would be

achieved given sample parameters and various sample sizes were performed based on an approach proposed Hsieh et al. (1998)[184]—results of which are summarized in Appendix IX. Given the sample characteristics and sample size (n=659 visible minority recent immigrants, n=408 white recent immigrants, and n=102,366 white Canadian-born respondents), the available CCHS sample is considered to be sufficiently powered (at 80% power) to detect a minimal total effect of PR=1.08 for lifetime screening between visible minority immigrants and white Canadian-born (true PR≈1.50); and a total effect of PR=1.02 between white recent immigrants and white Canadian-born (true PR≈1.20). Analyses were also performed to assess how large the sample size would have to be to identify various sizes of controlled direct effects, using a formula derived by Vittinghoff et al. (2009).[185] Power to detect controlled direct effects depends on the size of the effect and the sample, the prevalence lifetime screening, the correlation between the exposure (recent immigration) and the mediator (access to a primary care physician), and the variance of the exposure.[185] Summarized in Appendix IX, results of these analyses suggest that a CCHS sample of approximately 100,000 respondents in each stratified analysis is sufficiently powered (80%) to detect at minimum a main effects coefficient of PR=1.25 for visible minority recent immigrants (observed PR≈3.05), and an PR=1.35 for white recent immigrants (observed PR=1.47).

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3.4 OBJECTIVE 3

The third objective of this thesis was to quantify the impact of two types of organized colorectal cancer screening programs—programs that send out invitation letters and screening kits systematically to all age-eligible adults, and allow mail-based returns of kits (which will be referred to as "systematic" programs) and programs that send invitation letters but rely on individuals to request screening kits and return kits in person (which will be referred to as "patient-reliant" programs)—on screening participation overall, and on screening disparities (by income, education, rurality, access to primary care physicians). The programs assessed were systematic programs in Saskatchewan and Nova Scotia, and a patient-reliant program in Prince Edward Island. Additional organised screening programs have also been implemented in provinces of Alberta and British Columbia. However, data were not available to include the latter provinces in these analyses.

3.4.10 Analyses

Descriptive analyses

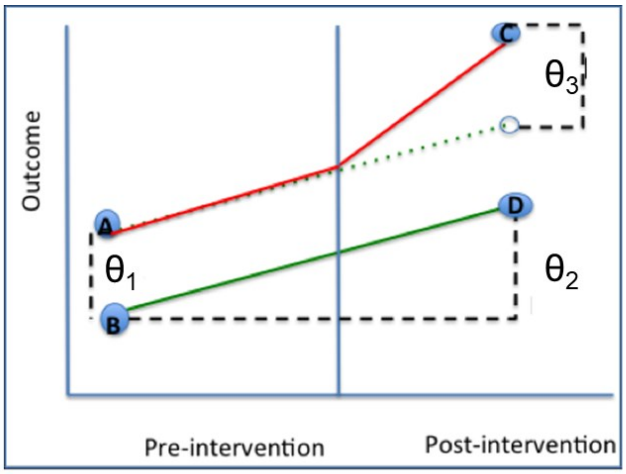
Descriptive statistics were calculated for the demographic, socioeconomic, and screening characteristics of treated and comparison groups. Covariates used for these analyses were individual-level age, sex, marital status, immigration status, access to a primary care physician, education, income, and rural residence. Analyses were also performed to assess pre-intervention screening trends in treated and comparison provinces. Descriptive analyses of screening prevalence according to CCHS years were performed using chi-squared statistics, followed by Poisson regression models adjusted for year, treatment group, and the product of both terms (*year*treated*).

Difference-in-Differences analyses

To apply the Difference-in-Differences framework, five multivariate Poisson regression models were specified. Poisson models were used in lieu of logistic models in order to minimize

over-estimation of the associations[160] due to the common nature of non-recent screening .[20] One outcome model was adjusted for the treatment indicator variables and covariates:

$$\log(E[Y|\ treated,\ post,\ covariates]) = \theta_0 + \theta_1(treated) + \theta_2(post) + \theta_3(treated*post) + \theta'(covariates) \quad [8]$$



log(E[Y| treated, post, covariates])= θ_0+ θ_1(treated) + θ_2(post) + θ_3(treated*post) + θ'(covariates)

Coefficient	Interpretation
θ_0	Baseline average in screening prevalence
θ_1	Difference between treated and control provinces pre-intervention
θ_2	Time trend in control province
θ_3	Differences in changes in screening over time

Figure 4: Interpretation of Difference-in-Differences modeling output. Source: Image adapted from Columbia University, *Difference-in-Difference Estimation*, New York, Accessed February 2018, https://tinyurl.com/y9yjnd7f.

The other four models adjusted treatment indicator variables, covariates, and each of the four social stratification indicator (*sstrata*) product terms (for income, education, rurality, and access to a primary care physician). This approach is known as the Difference-in-Differences-in-Differences method[186]:

$$\log(E[Y|\ treated,\ post,\ covariates]) = \beta_0 + \beta_1(treated) + \beta_2(post) + \beta_3(treated*post) + \beta_4(sstrata) + \beta_5(sstrata\ *treated) + \beta_6(sstrata\ *post) + \beta_7(sstrata\ *treated*post) + \beta'(covariates) \quad [9]$$

Estimates from these models can be interpreted as screening prevalence ratios (PR). Using predicted probabilities from these Poisson models (using Stata 14's *margins* command[171]), covariate-adjusted prevalence differences (PD) were also estimated. On the additive scale, model estimates can be interpreted as follows: the θ_3 coefficient indicates the overall effect of the program (as described in Figure 4[187]). In inequality indicator models, the β_7 coefficient indicates the overall effect of the program on the identified screening disparity inequality indicator. Analyses were repeated for each treatment province (individually, and pooling Saskatchewan and Nova Scotia), for each outcome (lifetime and recent stool-based screening, lifetime and recent endoscopic screening, and flu vaccination). The 95% confidence intervals for estimates were estimated using 500 bootstrap replications. Analyses were performed using Stata, version 14.[171] Additionally, to assess the sensitivity of findings to potential bias in variance estimation caused by autocorrelation of respondents within provinces, analyses were also repeated using the same macro-based generalized estimating equation (GEE) analysis[155] described in section 3.2.6 above. Through this macro, GEE identity-link Poisson models were specified, with an assumed exchangeable covariance structure for respondents living within the same province. These sensitivity analyses were conducted using SAS 9.4.[161]

3.4.1 Design

The establishment of these programs represents a policy change in the Canadian landscape that allows researchers to obtain exogenous variation in a main explanatory variable (here, exposure to an organised screening program).[188] The implementation of these programs can be considered "natural experiments" insofar as the precise location and timing of their establishment (2009 in Saskatchewan and Nova Scotia, 2011 in Prince Edward Island) is considered to be

random. Without their implementation one would not have expected to see a drastic shift in screening participation trends around those years of implementation.

Given the natural experiments that these programs represent, a quasi-experimental analysis design was used. Quasi-experimental design refers to the application of experimental analyses to data that do not meet the full requirements of a randomized controlled trial data (i.e. full randomization of respondents to treatment or control conditions).[189] Here, the Difference-in-Differences design framework was used.[186] In this framework, screening outcomes in "treated" provinces are compared to those of provinces without organized screening programs ("comparison" provinces). Assuming similar pre-intervention population-level characteristics and screening trends between treated and comparison provinces, any differences in before-after differences in screening outcomes between the two populations are assumed to be attributable to program implementation.[39,98]

3.4.2 Study population

Like in the second manuscript, this study utilizes data from the 2003, 2005, 2007-2014 cycles of the CCHS. The population of interest for this study were 50 to 75-year-old respondents from the CCHS who no known familial or medical risk factors of colorectal cancer (i.e., those at "average risk"[5]—approximately 80% of the respondents aged 50 to 75 in CCHS cycles 2003 to 2014), and who were either residing in one of the "treated" provinces before or after intervention (i.e., Saskatchewan, Nova Scotia, or Prince Edward Island) or in one of the "comparison" provinces before or after intervention (i.e., New Brunswick, Newfoundland and Labrador). These comparison provinces were chosen based on data availability and parallel screening trends pre-intervention (as will be discussed below). Respondents from the other provinces and territories were excluded.

3.4.3 Direct acyclic graph (DAG) of study measures

Drawing from the thesis' conceptual framework (Chapter 2: Figure 1) and from existing literature, the assumed associations between relevant factors in the association between exposure

to an organised screening program and colorectal cancer screening are described in the Directed Acyclic Graph (DAG) below (Figure 5). Age, sex, marital status, immigration status, access to a primary care physician, education, income, and rural residence are assumed to be potential confounders of the association between exposure to an organised screening program and screening. Additionally, access to a primary care physician, education, income, and rural residence are assumed to potentially act as modifiers of the association between organised screening program exposure and screening. The latter four factors are therefore used to assess the effect of screening programs on social disparities in screening.

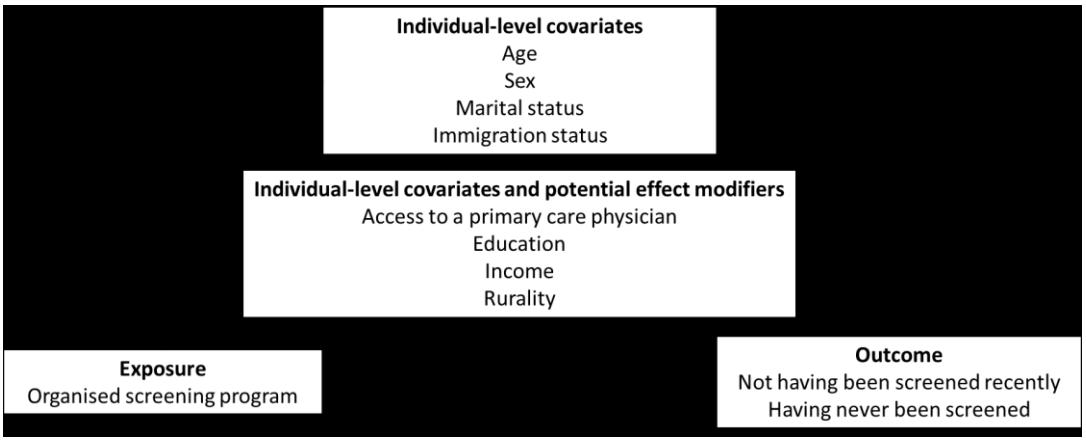


Figure 5: Directed Acyclic Graph (DAG) of the assumed directionality of associations between exposure to an organised screening program, social and demographic characteristics, and colorectal cancer screening.

3.4.4 Outcome measures

CCHS respondents were asked if they had ever received a fecal-occult blood test, a colonoscopy, or sigmoidoscopy in their lifetime, and if so, when. The primary outcome measure studied was stool-based screening in the previous two years (versus over two years or never). Two more conservative screening outcome categorizations were to construct secondary outcomes, across which to assess the stability of program effects: lifetime stool-based screening (ever versus never) and stool-based screening in the previous year (versus over one year or never). Observing screening in the previous year ensured that respondents in the year of, or year following program implementation, were not reporting screening that occurred before program

implementation. Lastly, to complement analyses on stool-based screening, we also assessed the tertiary outcomes of lifetime (ever vs. never) and non-recent (>5 years) endoscopic screening. Though programs were not designed to influence endoscopic screening participation, it is plausible that programs influence uptake of colonoscopies or sigmoidoscopies.

3.4.5 Exposure measures

The exposure of interest in this study was living in a province with an organised screening program. The specific programs assessed were Prince Edward Island's patient-reliant program (first introduced in 2011), and Saskatchewan and Nova Scotia's systematic screening programs (first introduced in 2009).

Within a Difference-in-Differences framework, three exposure measures were operationalized to quantify the impact of these programs:[98] (1) an indicator variable for residence in a "treated" province (respondents were assigned the value *treated*=1 if they lived in the province were the program would be or was implemented, or *treated=0* if they lived in a province with no program, i.e. the comparison provinces); (2) an indicator variable for the CCHS years after program intervention (respondents were assigned the value *post*=0 if they responded to the CCHS in years before the program was implemented, or *post=1* for the year of the intervention onwards); and (3) an indicator variable for residence in a province with a program, after the program was implemented. The latter is the equivalent to a product term between the first two indicators *(treated*post)*. Provinces considered "treated" were Saskatchewan, Nova Scotia, and Prince Edward Island. The year of initial implementation was 2009 for the first two provinces, and 2011 for Prince Edward Island.

Selection of comparison provinces

Untreated "comparison" provinces for this study were selected based on three factors[98,190]: They were required to (1) have available colorectal cancer screening outcome data for at least two cycles in the pre- and post-intervention periods. Since CCHS questionnaire items on colorectal cancer screening are considered "optional" content in the CCHS, the availability of

CCHS data colorectal cancer screening varies across provinces and survey cycles. The choice of opting-in on the collection on colorectal cancer screening data at every survey cycle is made by provincial and territorial stakeholders in coordination with health regions, based on their needs.[139] Gaps in colorectal cancer screening data therefore exist from year to year of CCHS data (described in Appendix X). Second, they were required to (2) have parallel screening trends in the pre-intervention period to the treated populations. Underpinning this requirement of analysis using the Difference-in-Differences framework is the assumption that in the absence of treatment, the difference in outcomes (here screening prevalence) between treated and comparison groups would stay constant over time.[98] Departures from expected parallel trends in the treated population versus comparison population (i.e. a difference in the pre-intervention and post-intervention differences) represent the effect of the intervention. Figure 6 below, from the Columbia University Mailman School of Public Health,[187] graphically describes these differences. Lastly, they were required to (3) have not been exposed to an organised screening program themselves in the periods specified. Using these three criteria, eligible comparison populations for the evaluation of programs in Saskatchewan and Nova Scotia were pooled respondents from New Brunswick and Newfoundland and Labrador, whereas Prince Edward Island's comparison population were solely respondents from New Brunswick.

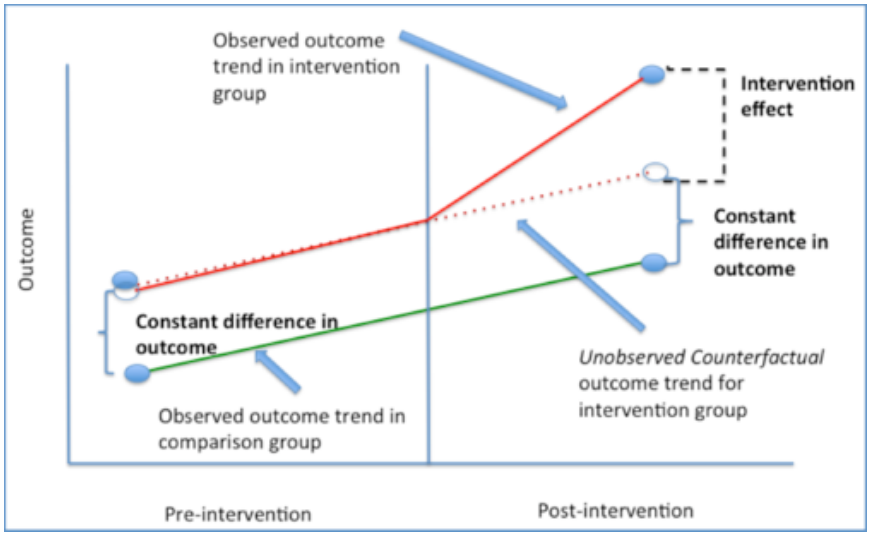


Figure 6: Graphical explanation of Difference-in-Difference estimation. Image source: Difference-in-Difference Estimation, Columbia University, New York, Accessed February 2018, https://tinyurl.com/y9yjnd7f.

3.4.6 Markers of social stratification

To assess program impacts on screening inequalities, four markers of social stratification were used to capture social disparities in screening: access to a primary care physician, educational attainment, individual-level income, and rural residence. These factors were treated both as covariates and as potential effect modifiers of the association between systematic and patient-reliant organised screening programs and screening participation.

Access to a primary care physician

Respondents were considered to not have a primary care physician if they answered "No" to the question "Do you have a regular medical doctor?" To assess program impacts on screening inequalities by access to a primary care physician, four (4) indicator variable were operationalized: a term to indicate lack of a primary care physician (*sstrata);* a product term between indicators for treatment province and access to a primary care physician (*treated* sstrata*), a product term between indicators for time period and access to a primary care physician (*post* sstrata*), and a product term between indicators for time period, treatment province, and access to a primary care physician (*treated*post* sstrata*).

Educational attainment

Like in the previous two studies, those who obtained less than high school diploma or its equivalent were compared to those who had a high school diploma or greater (which included both those who did and did not graduate from college). To assess program impacts on screening inequalities by educational attainment, four (4) indicator variables were operationalized: a term to indicate lower educational attainment (*sstrata);* a product term between indicators for treatment province and educational attainment (*treated* sstrata*), a product term between indicators for time period and educational attainment (*post* sstrata*), and a product term between indicators for time period, treatment province, and educational attainment (*treated*post* sstrata*).

Income

As in the previous two studies, a measure of individual-level income was used, drawing on respondent's reported household income from all sources, before taxes and deductions, in the previous 12 months (stated in Canadian Dollars, CAD). The imputed income values produced by Statistics Canada for CCHS cycles from 2005 onwards were used. Income values imputed for the 2003 cycle of the CCHS for the second manuscript were again used in this study. These imputed values were based on individuals' age, sex, education, marital status, immigration status, and sampling weight. In this third study, categories of absolute income values in Canadian dollars (CAD) were used instead of quartile groupings. As respondents were not treated as a single population, but rather, were grouped by province, the categorization in absolute Canadian dollars were used to facilitate comparisons across provinces. A dichotomous variable of household income of less than 30,000 CAD versus 30,000 CAD and above was used to assess screening program impacts among lower-income Canadians. To assess program impacts on screening inequalities by individual-level income, four (4) indicator variables were operationalized: a term to indicate lower income (<30,000 CAD) (*sstrata);* a product term between indicators for treatment province and income (*treated* sstrata*), a product term between

indicators for time period income (*post* sstrata*), and a product term between indicators for time period, treatment province, and income (*treated*post*sstrata*).

Rural residence

As in the second study, a dichotomous variable of rural residence (versus urban reference) was used. CCHS respondents' area of residence is considered "urban" or "rural" based on the population density of the Canadian Census Dissemination Areas in which they live. Urban areas are those that have a population concentration of at least 1,000 residents or of 400 residents per square kilometer.[144] To assess program impacts on screening inequalities by rural residence, four (4) indicator variables were operationalized: a term to indicate rural residence (*sstrata);* a product term between indicators for treatment province and rural residence (*treated*sstrata*), a product term between indicators for time period and rural residence (*post*sstrata*), and a product term between indicators for time period, treatment province, and rural residence (*treated*post* sstrata)*.

3.4.7 Covariate measures

In addition to education, income, rural residence, and access to a primary care physician, the following covariate measures were also included in the analyses:

Sociodemographic measures

Sociodemographic covariates used in this study were sex, age, and marital status. Like in the first two studies, age was dichotomized according to a cut-off of 60 years (comparing those aged 50 to 59 years-old to those 60 to 75 years-old), and marital status was organised into three categories: married or in a common law relationship; divorced, widowed, or separated; and single.

Immigration status

Immigration status was treated as a covariate in this study. Respondents were considered to be immigrants to Canada if they stated a country other than "Canada" when asked "In what country were you born?" and answered "No" to the question "Were you born a Canadian citizen?" Due to the small number of immigrants residing in the provinces assessed in this study (Saskatchewan, Nova Scotia, Prince Edward Island, New Brunswick, and Newfoundland), use of additional characteristics such as region of origin or visible minority status were not possible in this study.

3.4.8 Falsification measures

To assess whether any observed effect could be due to chance or other driving factors, [127,128] analyses were also performed using the falsification outcome of reported flu vaccination in the past year (more details below, in section 3.3.10). In the CCHS, respondents were asked "Have you ever had a seasonal flu shot, excluding the H1N1 flu shot? [Yes, No, Refuse to answer, Don't know]" and "When did you have your last seasonal flu shot? [Less than 1 year ago, 1 year to less than 2 years ago, 2 years ago or more, Refuse to answer, Do not know]". Respondents were considered to have received a flu shot in the past year if they answered "Yes" to the first question and "Less than 1 year ago" to the second question. A non-null association between program implementation and vaccination could indicate that observed changes in screening may be due to other systematic changes in health care services delivery and utilization in Canada.[39]

3.4.9 Sample weights

As discussed previously, each respondent to the CCHS is attributed a sampling weight according to their contribution to the total population, as well 500 bootstrap weights for the purposes of variance estimation.[133,152,153] Both sampling and bootstrap weights were used this study.

3.4.11 Power considerations

The ability of the latter analyses to correctly reject the null hypotheses that no association exists between patient or systematic screening programs and changes in screening outcomes, depends on the number of respondents in treated and comparison provinces, both pre- and post-intervention, and on the prevalence of screening outcomes.[191] Applying formulas proposed by Bloom (2006) and VanderWeele (2012),[192] we estimate that given the sample characteristics and sample size (approximately N=15,000 to 20,000 total, depending on the provinces studies), the available CCHS sample is considered to be sufficiently powered to detect changes in prevalence differences (due to program implementation) of 3- to 5-percentage-points (i.e. effects of PD = 0.03 to 0.05). A summary of sample sizes needed to detect program effects is described in Appendix IX.

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3.5 Ethical procedures

The ethics, feasibility and potential unique contributions of this thesis project were evaluated and approved by the Canadian Research Data Centre Network (CRDCN) (documentation provided in Appendix XI). Ethics approval for this project was also received from the Centre du recherche du Centre hospitalier de l'Université de Montréal (CRCHUM) on May 20, 2016 (see Appendix XI). The principal area of ethical concern for this thesis was the protection the confidentiality of CCHS data. To protect respondents' confidentiality, Statistics Canada removes all personal identifiers from the dataset (i.e. name, address, social insurance number), and our team respected strict data access procedures (as stipulated in the Canada's Statistics Act). The analyses presented in this thesis were conducted at the Quebec Inter-university Centre for Social Statistics (QICSS) (3535-420 Queen-Mary road, Montreal, Quebec, H3V 1H8), which is part of the Canadian Research Data Centre Network (CRDCN). Exported results were vetted by Statistics Canada Analyst Franck Larouche (franck.larouche@ciqss.org) to ensure respondents' confidentiality was not compromised.

CHAPTER 4: MANUSCRIPT 1

Area-level income and colorectal cancer screening in Canada: Evidence to inform future surveillance

Area-level income and colorectal cancer screening in Canada: Evidence to inform future surveillance

Running Title:
Area-level income and colorectal cancer screening

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Authors contributions:

Alexandra Blair conceptualised the manuscript, conducted the data analysis, wrote the first draft of the manuscript reacted to and integrated co-authors comments.
Lise Gauvin contributed to the conceptualisation of the manuscript, and to writing and reviewing the manuscript.
Samiratou Ouédraogo contributed to data analysis, particularly the implementation of the proposed SAS macro for generalized estimating equations, and also contributed to the review of the manuscript.
Geetanjali D. Datta contributed to the conceptualisation of the manuscript and data analysis and contributed to writing and reviewing the manuscript.

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Conflict of interest: None to declare

Abbreviations: DA, Dissemination Area; CCHS, Canadian Community Health Survey; CI, Confidence Interval; CRC, colorectal cancer; EMM, effect measure modification; FIT, fecal immunochemical test; FOBT, fecal occult blood test; GEE, generalised estimating equations; PD, prevalence difference; PR, prevalence ratio.

Keywords: Cancer Prevention; Screening, Inequalities, Epidemiology, Public Health, Neighborhood and place.

Counts:
Abstract: 260 words
Main text, including tables and figures: 4778 words
Tables: 2
Supplementary materials: 2 eTables

4.1 ABSTRACT

Background: Participation in colorectal cancer screening remains low even in countries with universal health coverage. Area-level determinants of low screening participation in Canada remain poorly understood.

Methods: We assessed the association between area-level income and two indicators of colorectal cancer screening (never having been screened, not having been screened recently) by linking Census-derived local area-level income data with self-reported screening data from urban-dwelling respondents to the Canadian Community Health Survey (aged 50-75 years, cycles 2005 and 2007, N=18,362) who had no personal or family history of colorectal cancer. Generalized estimating equation Poisson models estimated the prevalence ratios (PR) and differences (PD) of having never been screened and having not been screened recently, adjusting for individual-level income, education, marital status, having a regular physician, age, and sex.

Results About 53% of the study population had never been screened. Among those ever screened, 35% had been screened recently. Adjusting for covariates, lower area-level income was associated with having never been screened (covariate-adjusted PR for Quartiles 1-3, respectively: (Q1) PR=1.24, 95% CI: 1.16, 1.34 [PD=7%, 95% CI 2%-10%]; (Q2) PR=1.25, 95% CI: 1.15, 1.33 [PD=5%, 95% CI: 2%-8%]; (Q3) PR=1.15, 95% CI: 1.08, 1.23 [PD=4%, 95% CI 1%-7%]). Among those who had been screened in their lifetime, area-level income was not associated with having not been screened recently.

Conclusions: Lower area-level income is associated with never having been screened for colorectal cancer even after adjusting for individual-level SES. These findings highlight the potential importance of socioeconomic contexts for colorectal cancer screening initiation, and merits attention both in future research and surveillance efforts.

4.2 BACKGROUND

Colorectal cancer is currently the third most common cause of cancer death in Canada, yet only 20% to 30% of average-risk adults (i.e. those with no known familial or medical risk factors) have participated in preventive colorectal cancer screening— either via stool test in the previous two years or endoscopic testing in the previous five or ten years (for sigmoidoscopies and colonoscopies, respectively) (1, 2). This represents a much lower screening participation rate than that observed for breast cancer (63% participation) or for cervical cancer (79% participation) in the country despite universal health care coverage (3).

In trying to understand what factors operate to keep population-level colorectal cancer screening participation so low, extant Canadian literature has identified several determinants of colorectal cancer screening. These include: social and demographic factors, such as age, marital status, visible minority or immigration status, educational attainment, household income, and area of residence (i.e. rural versus urban) (4, 5); health service-related factors, such as having access to regular physician or primary care services and receiving a screening recommendation from a health care provider (6, 7); and psychological factors, such as fear, embarrassment, or anxiety about test result or procedures (especially related to the invasive nature and intensive preparation required for endoscopic procedures)(8).

Missing from this list of determinants, however, are potential factors that operate beyond the individual-level. Indeed, the environments in which people live are known to affect many individual health behaviours, independent of (or above and beyond) individual-level characteristics (9). Canadian studies have yet to examine the association of community- and local area-level factors with colorectal cancer screening participation—as has been done in other countries (10-13). Important studies in Ontario have set the groundwork in this area, observing associations between area-level income and colorectal screening uptake (14-17). However, due to limitations in data availability, these studies did not examine associations independent of individual-level confounding factors such as income. Outside of Canada, independent associations have been observed between colorectal cancer screening participation and exposure to area-level primary care provider density and educational attainment, (13) income, (18)

perceived social and physical disorder (10), and neighbourhood satisfaction (11). It is possible that these same independent associations exist in Canada but have yet to be shown. If underlying area-based disparities in screening do exist, this information will be relevant for future cancer prevention and control. A better understanding of the association between area-based predictors and screening could be of relevance for Canadian provinces that have implemented or are planning to implement organised colorectal cancer screening programs, particularly for guiding surveillance efforts of potential differential program impacts across socioeconomic area profiles or identifying geographic targets of program adjustments.

In this study, we examined the association between area-level income and colorectal cancer screening as a predictor above and beyond individual factors. Intersecting ecological, materialist and psychosocial theories (12) suggest that area-level income, a correlate of broader area-level material and social deprivation (19), may influence screening likelihood through pathways of weakened social ties and resource scarcity (9,20). Low area-level income is often associated, for example, with lowered social support, lower ability to cope with stress, as well as potential barriers to screening such as lower infrastructural and health-related resources. (12, 21)

We aimed to assess the association between area-level income and screening among average-risk individuals that existed before the implementation of organised colorectal cancer screening programs in Canada (i.e. before 2007, at the latest), in order to assess baseline inequalities in screening pre-interventions. We focused on two colorectal cancer screening uptake outcomes: 1) never having been screened and 2) not having been screened recently (neither via stool-based test in the previous 2 years nor via endoscopy in the previous 5 years). These two outcomes enable the assessment of area-level income's association with two distinct screening-related events: initial screening participation and continued screening uptake. Divergence of predictors can inform public health intervention targeted either to those who have never been screened, or those who have, but are not up-to-date in their screening.

4.3 METHODS

4.3.1 Data sources and sample

We used individual-level data from years 2005 and 2007 of the Canadian Community Health Survey (CCHS) and area-level income data from the 2006 Canadian Census (22). The CCHS is a nationally-representative multi-year cross-sectional survey of individuals across Canada, with response rates in 2005 and 2007 of 79% and 78%, respectively (23). Based on the Canadian Census, the CCHS covers approximately 97% of the Canadian population (23). CCHS and Canadian Census data were linked using CCHS respondents' 2006 Canadian Census Dissemination Area codes.

The study's target population was urban-dwelling adults aged 50-75 years without known familial or medical risk factors—which typically include having a first-degree relative with or having a personal history of colorectal cancer or inflammatory bowel disease (2). Thus, excluded from this study were respondents who reported screening due to "family history of colorectal cancer", "follow-up of a problem", and "follow-up of colorectal cancer treatment" (23). Persons reporting screening due to "age", "race", or as "part of regular check-up/routine screening" were included. Applying these criteria, we analysed data on 18,362 CCHS respondents.

4.3.2 Measures

Dependent variables

The outcomes of interest were 1) having never been screened, and 2) not having been screened recently for colorectal cancer. Respondents were considered to never have been screened if they responded "No" to questions of whether they had ever had a fecal occult blood test or endoscopy (colonoscopy or sigmoidoscopy). Respondents were considered to not have been screened recently if they had been screened in their lifetime, but neither had received a stool test in the previous 2 years, nor received any form of endoscopy in the previous 5 years (a conservative time cut-off used because the CCHS questionnaire does not distinguish between types of endoscopy used).

Independent variable

The independent measure was dissemination area (DA) level income, categorized into quartile groupings (quartile 1 represented lowest income). Marked by their small population size (400 to 700 persons per DA) and homogeneity (20), Canadian census DAs which are the smallest geographic unit division in the country, capture the immediate area-level socioeconomic resources available to residents.

Covariates

Covariates included age, marital status, immigration status, educational attainment, household income, and access to a primary care physician. All covariates were measured at the individual level. Age was dichotomized as 50-59 years or 60-75 years. The cut-off of 60 years was used to compare screening in younger age-eligible adults to screening in older adults (namely those who were more likely to be retired). The average year of retirement in Canada in 60 years (25). An important moment in the lifecourse, retirement marks a period of potential increase in discretionary time, which is a determinant of colorectal screening (8). Marital status was defined using three categories: being married or in common-law relationship; being divorced, widowed, separated; or single. The immigration status measure compared persons who had immigrated to Canada from the United States, Europe or Oceania, and persons who had immigrated from Central and South America, Africa, or Asia, to those who were Canadian-born. Country groupings were designed to roughly capture potential differences in socio-cultural experiences of health care and colorectal screening environments (including policies, infrastructure) pre-immigration—with immigrants from the first group's "Western" nations assumed to be more likely to have been exposed to health care systems and colorectal cancer screening policies similar to those in Canadian provinces and territories (26,27). Educational attainment was dichotomized as having obtained less than high school graduation, or having a high school graduation and above (including college attendance). Household income was separated into quartile groupings based on the overall sample's distribution of income.

4.3.3 Statistical analyses

Descriptive statistics were calculated to compare demographic, socioeconomic, and screening characteristics across categories of area-level income. To accommodate the hierarchical data structure of the CCHS (i.e. on average 6 [minimum 1 & maximum of 68] individuals are nested within each areal unit and are therefore more likely to be correlated), and the need to incorporate both sampling and bootstrap weights provided by Statistics Canada (500 weights for each participant), a macro-based analysis proposed by SAS Corporation was applied (28). This macro (28) looped through a generalized estimating equation (GEE) log-link Poisson model (with an exchangeable covariance structure) 500 times—each time using a new, unique bootstrap weight to construct robust 95% confidence intervals for the exposure and covariates' prevalence ratio (PR) estimates. Given that the screening outcomes of this study are known to be common in Canada (approximately 80% were not screened recently in 2012) (3), we used Poisson models rather than logistic models to minimize over-estimation of the associations (29). To complement the measure of prevalence ratios (PR) we also estimated prevalence differences (PD) which refer to the difference in adjusted prevalence (%) of non-recent and never screening. Additionally, we assessed potential effect measure modification (EMM) of the absolute and relative associations by immigration status, physician access, and household income, and tested the sensitivity of principal findings to unmeasured confounding using Ding and VanderWeele's Bounding Factor approach (30). A sensitivity analysis was also conducted using a 10-year cut-off for endoscopic screening (since colonoscopies are recommended to be repeated every 10 years (2)), which yielded similar results (results not shown). All analyses were conducted using SAS 9.4 (31).

4.3.4 Ethics

This study received ethical approval from the Comité d'éthique de la recherche of the Centre Hospitalier de l'Université de Montréal.

4.4 RESULTS

4.4.1 Sample characteristics

Overall, 53% of the study population had never been screened, 12% had been screened in their lifetime but not recently, and 35% had been screened recently. We observed that persons more likely to have never been screened for colorectal cancer were: i) younger adults; ii) persons who were neither married nor in a common-law relationship; iii) persons who had immigrated to Canada from countries in South and Central America, Africa and Asia, iv) persons who had lower school educational attainment; v) those who did not have a primary care physician, and vi) were in the three poorest quartile groups of both individual- and area-level income (Table 1). Among those who had been screened in their lifetime, those not screened recently were more likely to be persons i) who were older, ii) who were born in Canada, and iii) who did not have a regular physician (Table 1).

Table 1: Prevalence of having never been screened, having ever been screened but not recently, and having been screened recently as a function of demographic and socioeconomic characteristics of adults aged 50 through 75 years and participating in the 2005 and 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342)

	Overall	Proportion never screened (n=10,206)		Proportion ever screened, but not recently screened (n=2,359)		Proportion ever screened, screened recently (n=5,797)	
	%[b]	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI
Overall	100	53.3	(52.4, 54.7)	11.7	(11.0, 12.4)	34.8	(33.6, 36.0)
Age							
50-59 years	53.1	60.0	(58.2, 61.8)	9.7	(8.8, 10.8)	30.2	(28.5, 32.0)
60-75 years	46.9	46.2	(44.6, 47.7)	13.9	(12.9, 15.0)	40.0	(38.3, 41.5)
Sex							
Female	50.7	53.3	(52.6, 55.0)	11.6	(10.7, 12.5)	35.2	(33.5, 36.8)
Male	49.3	53.8	(52.0, 55.5)	11.8	(10.7, 13.0)	34.4	(32.7, 36.2)
Marital Status[a]							
Married/com-law	76.0	52.6	(51.2, 53.9)	11.7	(10.9, 12.6)	35.7	(34.4, 37.1)
Div/wid/sep	17.8	55.9	(53.6-58.2)	11.8	(10.5, 13.1)	32.3	(30.1, 34.6)
Single	6.2	58.6	(55.2, 62.0)	11.1	(9.1, 13.6)	30.2	(27.0, 33.6)
Immigration[a]							
Canadian-born	62.1	52.1	(50.8, 53.3)	13.0	(12.2, 13.9)	34.9	(33.7, 36.2)
Immigrant (Europe, US, Oceania)	22.0	51.5	(48.6, 54.4)	11.1	(9.5, 13.0)	37.4	(34.5, 40.4)
Immigrant (Asia, Africa, S-C. Amer.)	15.9	62.8	(58.7, 66.6)	7.2	(5.5, 9.4)	30.3	(26.4, 33.9)
Education[a]							
HS Graduate	83.0	52.6	(51.3, 53.9)	11.7	(10.9, 12.5)	35.7	(34.4, 37.0)
< HS Degree	17.0	57.9	(52.4, 54.7)	11.8	(10.2, 13.7)	30.3	(27.8, 32.9)
Physician Access[a]							
Yes	94.0	52.5	(51.3, 53.6)	11.7	(11.0, 12.5)	35.9	(34.7, 37.1)
No	6.0	70.8	(66.4, 74.8)	11.9	(9.3, 15.3)	17.4	(14.1, 21.2)
Individual Income							
Quartile 1 (lowest)	17.1	56.7	(54.4, 58.8)	12.5	(10.8, 14.4)	30.9	(28.9, 33.0)
Quartile 2	21.6	55.5	(53.2, 57.8)	11.5	(10.3, 12.9)	33.0	(30.9, 35.2)
Quartile 3	26.7	54.0	(51.7, 56.3)	10.8	(9.6, 12.6)	35.2	(32.9, 37.6)
Quartile 4 (highest)	34.6	50.4	(48.2, 52.6)	12.1	(10.7, 13.6)	37.5	(33.6, 35.9)
Area Income							
Quartile 1 (lowest)	20.5	60.3	(57.7, 62.9)	10.7	(9.4, 12.0)	29.0	(26.7, 31.5)
Quartile 2	22.6	58.5	(55.9, 61.0)	11.3	(9.9, 12.8)	30.3	(27.9, 32.7)
Quartile 3	24.8	53.8	(51.6, 56.0)	11.5	(10.1, 13.0)	34.7	(32.6, 36.8)
Quartile 4 (highest)	32.1	45.5	(43.2, 47.8)	12.8	(11.4, 14.4)	41.7	(39.4, 44.1)

[a] Marital Status: "Com-law" indicates common law marital status; "Div" indicates divorced marital status;"Wid" indicates widowed marital status; "Sep" indicates separated marital status; Immigration: "US" indicates United States of America ; "S-C Amer" indicates South and Central America; Education: "HS" indicates High School; "Physician access" indicates having a primary care physician. [b] These are column percentages. [c] These are row percentages.

4.4.2 Association between area-level income and having never been screened

Adjusting for covariates, an association was observed between lower area-level income and having never been screened (Table 2). The prevalence of having never been screened followed a gradient according to income quartile: covariate-adjusted prevalence differences were 12% (95% CI 8%, 15%), 11% (95% CI 8%, 14%), and 7% (95% CI 3%, 10%) between the poorest areas (quartiles 1 through 3, respectively) and the wealthiest areas (quartile 4) (Table 2). The adjusted prevalence difference for having never been screened between the highest and lowest levels of area-level income (12%) was slightly larger than the prevalence difference between those with the highest and lowest levels of individual-level income (7%, 95% CI, 2%, 10%) (Table 2). Lastly, individuals who were born in Africa, Asia, or South or Central America were also more likely to have never been screened (Table 2).4.4.3 Association between area-level income and not having been screened recently

No association was observed between area-level income and not having been screened recently among only those who had been screened in their lifetime (Table 2). Instead, the strongest predictors of not having been screened recently were not having a regular physician (15% difference in recent screening prevalence between those with and without a regular physician (95% CI 6% to 23%)) and being born Canada (Table 2). Among those who had ever been screened, immigrants to Canada were more likely to have been screened recently than those born in the country (covariate-adjusted prevalence differences ranged from 5% to 8% according to region of origin) (Table 2).

4.4.3 Sensitivity analyses

The direction of associations between predictors and screening outcomes were similar when analyses were stratified by individual-level income (Supplement's eTable 1). Analyses of potential unmeasured confounding indicate that the size of effect of any unmeasured factor, or matrix of factors, would have to range between PR=1.4 and PR=1.6 to explain away the observed associations of area-level income and never having been screening (Supplement's eTable 2). Unmeasured factors would therefore have to show stronger associations with the

exposure and outcome than, for example, not having a primary care physician (for which the observed PR was 1.31).

Table 2: Results of GEE Poisson regression analyses examining associations between area-level income and never having been screened, and not having been screened recently (among those who had been screened in their lifetime), expressed as prevalence ratios (PR) and differences (PD) among adults aged 50-75 years of the 2005 and 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342)

Covariates	Never screened			Not screened recently		
	Bivariate analyses PR (95% CI)[a]	Adjusted PR (95% CI) [b]	Adjusted **PD** (95% CI) [c]	Bivariate analyses PR (95% CI)[a]	Adjusted PR (95% CI) [b]	Adjusted **PD** (95% CI) [c]
Age						
50-59	1	1	0	1	1	0
60-75	0.77 (0.73,0.80)	0.73 (0.70-0.77)	-0.16 (-0.14, -0.19)	1.06 (0.93, 1.21)	1.04 (0.91, 1.19)	0.01 (-0.02, 0.04)
Sex						
Female	1	1	0	1	1	0
Male	1.01 (0.96,1.06)	1.03 (0.98, 1.08)	0.01 (-0.01, 0.04)	1.04 (0.92, 1.17)	1.04 (0.92, 1.18)	0.01 (-0.02, 0.05)
Marital Status[d]						
Married/com-law	1	1	0	1	1	0
Div/wid/sep	1.06 (1.01, 1.11)	1.04 (0.99, 1.10)	0.03 (-0.01, 0.06)	1.07 (0.95, 1.22)	1.02 (0.89, 1.18)	0.01 (-0.03, 0.04)
Single	1.11 (1.05, 1.19)	1.02 (0.96, 1.09)	0.01 (-0.02, 0.05)	1.09 (0.89, 1.34)	1.03 (0.83, 1.26)	0.0 (-0.05, 0.06)
Immigration[d]						
Canadian-born	1	1	0	1	1	0
Imm. (Eur., US, Oc.)	0.99 (0.93, 1.06)	1.04 (0.98, 1.11)	0.02 (-0.01, 0.05)	0.85 (0.72, 1.00)	0.85 (0.72, 1.00)	-0.05 (-0.08, -0.01)
Imm. (Asi., Afr., S/C Am.)	1.21 (1.13, 1.30)	1.18 (1.10, 1.26)	0.09 (0.05, 0.14)	0.71 (0.54, 0.95)	0.72 (0.54, 0.95)	-0.08 (-0.13, -0.02)
Education[d]						
HS Graduate	1	1	0	1	1	0
< HS Degree	1.10 (1.04-1.16)	1.11 (1.04, 1.18)	0.05 (0.02, 0.8)	1.14 (0.98, 1.33)	1.09 (0.92, 1.27)	0.03 (-0.02, 0.07)
Physician Access[d]						
Yes	1	1	0	1	1	0
No	1.35 (1.27, 1.44)	1.31 (1.23, 1.38)	0.17 (0.12, 0.21)	1.65 (1.32, 2.06)	1.58 (1.27, 1.97)	0.15 (0.06, 0.23)
Individual Income						
Quartile 1 (lowest)	1.12 (1.06, 1.18)	1.12 (1.05, 1.21)	0.07 (0.02, 0.10)	1.18 (0.99, 1.40)	1.08 (0.86, 1.35)	0.03 (-0.04, 0.09)
Quartile 2	1.10 (1.03, 1.17)	1.11 (1.04, 1.18)	0.05 (0.02, 0.08)	1.06 (0.90, 1.23)	1.00 (0.84, 1.19)	0.0 (-0.05, 0.05)
Quartile 3	1.07 (1.01, 1.14)	1.08 (1.01, 1.14)	0.04 (0.01, 0.07)	0.96 (0.81, 1.13)	0.93 (0.79, 1.10)	-0.02 (-0.06, 0.02)
Quartile 4 (highest)	1	1	0	1	1	0
Area Income						
Quartile 1 (lowest)	1.32 (1.24, 1.42)	1.24 (1.16-1.34)	0.12 (0.08, 0.15)	1.16 (0.99, 1.36)	1.11 (0.94, 1.30)	0.02 (-0.02, 0.06)
Quartile 2	1.29 (1.20, 1.38)	1.25 (1.15, 1.33)	0.11 (0.08, 0.14)	1.16 (0.98, 1.38)	1.13 (0.95, 1.36)	0.03 (-0.01, 0.07)
Quartile 3	1.19 (1.11, 1.27)	1.15 (1.08, 1.23)	0.07 (0.03, 0.10)	1.10 (0.93, 1.30)	1.07 (0.90, 1.27)	0.02 (-0.02, 0.06)
Quartile 4 (highest)	1	1	0	1	1	0

[a] These PRs are yielded by bivariate models containing the outcome and each covariate. [b] Adjusted for all covariates. [c] Adjusted for all covariates; reference category for PDs is always 0 (no difference), given these associations are expressed on the additive rather than multiplicative (ratio) scale. [d] Marital Status: "Com-law" indicates common law status; "Div" indicates divorced status;"Wid" indicates widowed status; "Sep" indicates separated status; "Imm." indicates immigrant status: regions of immigration include the United States, Europe (Eur.), Oceania (Oc.); Asia (Asi), Africa (Afr.), South and Central (S./C.) America (Am.); "Physician access" indicates having a primary care physician.

4.5 DISCUSSION

This study examined the association between local area-level income and both never having been screened and not having been screened recently, while adjusting for known individual predictors, in a sample of urban-dwelling Canadians without any known familial or medical risk factors for colorectal cancer. Lower area-level income was associated with having never been screened. This result remained statistically significant after adjusting for individual-level covariates, including individual-level income, and appeared robust to unmeasured confounding. Among those who had been screened in their lifetime, we did not observe a statistically significant association between area-level income and recent screening.

The observation that approximately 35% of respondents were screened recently is slightly higher than estimates from previous studies, which used more recent data (3). This is likely due to our combination of endoscopic and stool-based screening, whereas previous prevalence estimates were based solely on stool-based screening. The observed association between area-level income and the outcome of never having been screened is aligned with the findings of one other study (18). Though, unlike this present work, the study used screening information on adults aged 50 year or older, regardless of risk status, it found the odds of having never received endoscopic (OR=1.10, 95% CI: 1.01,1.19) or stool-based screening (OR=1.19, 95% CI: 1.12, 1.27) increased with every 5% increase in the proportion of residents per census tract living below the US federal poverty line. The authors hypothesized that area-level deprivation could be influencing screening likelihood through pathways such as lower access to medical infrastructure and social capital. (18) They recommend that area-level poverty merit attention in future research and policy planning but note that targeting only high-poverty areas may miss low-income populations living in more affluent areas who are also in need of additional resources to overcome screening barriers. Further, in the broader context of cancer prevention across other cancer sites—our finding is also aligned with previous findings of an association between area-level income and never having received a mammography, or cervical cancer screening (32).

To our knowledge, there are no prior studies against which to compare the null association between area-level income and having not been screened recently, specifically among those who had been screened in their lifetime. Most existing studies assessed the outcome of having not been screened recently, regardless of lifetime screening uptake (i.e. among both those who had and had not been screened in their lifetime). Using data on adult populations aged 50 years or older, regardless of risk status, these previous studies find significant associations between area-level income and recent screening (33, 34). We too observed a significant, though attenuated, association between area-level income and not having been screened recently when all respondents are included (data not shown), regardless of whether they had been screened in their lifetime.

Future studies of determinants of colorectal cancer screening may benefit from distinguishing between those who had not been screened recently but had been screened in their lifetime, and those who had not been screened recently or at any point in their lifetime, for several reasons. First, the outcome of having never been screened is particularly relevant in the Canadian context, where most age-eligible adults have never been screened and are therefore at elevated risk of being diagnosed at a more advanced stage (35). Second, it is possible that those who have never been screened and those who have been screened, but not recently, have two distinct risk factor profiles—knowledge of which can benefit future public health interventions. Studies have observed, for example, that individuals who have pursued screening at least once in their lifetime may have overcome initial logistic and psychological barriers to screening (36) (i.e. fear, lack of discretionary time, resources, or awareness of screening tests (6, 8)), but may face new barriers for re-screening, such as having experienced a negative experience at initial screening (i.e. having received an inconclusive test result) or perceiving screening services to be of inadequate quality (36). It is possible that area-level income exposure is less relevant to these new additional barriers. Minimizing barriers to re-screening (versus initiation) may require distinct types of interventions (i.e. improved screening instructions or quality control measures). Third, it is possible that previously observed area-level associations between income and recent screening are driven mainly by the large proportions of persons who have never been screened. This would mean that area-level income is potentially a less relevant predictor for continued screening participation than it is for screening initiation. This distinction may be relevant for

provinces that have implemented or are planning to implement organised colorectal cancer screening programs; surveillance of program effects on screening initiation according to area-level income is warranted. Where programs fail to reduce area-level screening disparities in screening initiation, program modifications or additional targeted interventions may be necessary.

There are two plausible explanations for the finding of a direct association between area-level income and lifetime screening. First, it is possible that the observed association between area-level income and lifetime screening may be an artefact of reverse causation (37). Individuals who have less intention to pursue screening may be more likely to move to, or stay, in areas where health-related resources, including screening, are not available. The cross-sectional design of this study does not allow for ruling out this possibility. However, that associations were consistent across individual-level income and education groups offers some, albeit incomplete evidence against the reverse-causation hypothesis. Further, our findings are aligned with those of a longitudinal study of area-level deprivation on screening behaviour in the United States (38) which found a negative association between individuals' baseline exposure to area-level poverty and lower probability of any endoscopic screening four years later, in 36 US states. Our findings are therefore in line with alternative theoretical explanations. Specifically, intersecting ecological, materialist and psychosocial theories suggest that area-level income can have a direct influence on screening uptake through several social, physical, and economic pathways. Low-income areas are believed to expose residents to a multitude of concurrent barriers to screening uptake, including physical barriers, unreachable or inadequate resources, social stressors, and lowered social support (12). These concurrent exposures are thought to shape health beliefs and practices and limit health service utilization. Further, since lower-income areas are known to shape people's abilities to cope with stress (21), they may weaken residents' abilities to manage concerns and discomfort about the test and test results or fear of pain or injury from the test procedures—leading to lower screening uptake (8). Our use of the smallest possible area-level census unit (the Dissemination Area)—which captures the immediate social environment around one's residence—rather than a larger geographic delineation (e.g. broader administrative health regions)—make these psychosocial hypotheses

more plausible, insofar as social norms and social capital shared between residents may be more likely to be captured at a smaller, more homogenous area-level unit (39).

The present findings have several implications for public health. Foremost, low screening participation overall requires attention. That most people who have not been screened recently have in fact never been screened in their lifetime is relevant for cancer prevention in Canada and abroad. Secondly, the association between income at the dissemination area—a geographic unit that captures the immediate area-level socioeconomic resources available to residents—and never having been screened has implications for public health planning and surveillance. As of 2015, all Canadian provinces except Quebec have implemented province-wide organized colorectal cancer screening programs, which are thought to modify the pathways through which colorectal cancer screening services are accessed. In Ontario, initial pre-post comparisons in stool screening, unadjusted for individual-level socioeconomic factors, following the implementation of the province's screening program suggest only modest decreases in area-level income disparities have been observed (40). Continued surveillance of the programs' impact on area-level screening disparities can inform if complimentary targeted interventions might be necessary to reach all segments of society. Potential targeted interventions include the use of nurse navigators (41), the addition of instructional and/or reminder calls to usual invitation letters and written informational packages (42), and peer-education programs (43). Insofar as low area-level income may influence residents' access to resources and exposure to social stressors, these types of targeted interventions in low-income areas (within community or clinical settings) may enable residents to overcome known barriers of screening initiation. However, as noted in previous studies, (18) additional considerations may be needed to reach socioeconomically vulnerable individuals living in more affluent areas.

The study's findings are bound by certain limitations. Namely, the cross-sectional nature of CCHS data prevented us from assessing any potential lags in effect between area-level exposures and screening outcomes or drawing conclusions on the causal relationship between area-level income and screening. Future longitudinal studies are needed to address these concerns. Second, since the CCHS questionnaire made no distinction of the endoscopic screening modality used, we were unable to apply the appropriate timeframe cut-offs for

sigmoidoscopies and colonoscopies—which are recommended to be received every 5 and 10 years, respectively. The definition of non-recent screening using a 5-year cut-off was therefore potentially conservative for those using colonoscopies. However, when a 10-year cut-off was applied, similar results for lifetime and non-recent screening were observed. Third, we cannot discount the possibility of residual confounding. However, our sensitivity analyses suggest that an unmeasured factor would have to be strongly associated with the area-level income and lifetime screening (as strong as not having a regular physician) to bring the lowest bound of the 95% confidence interval to cross the null. Fourth, all data were self-reported. On average, respondents tend to over-report preventive cancer screening (i.e. previous two-year FOBT sensitivity is 77.4% and specificity is 89.8%, and record-to-record ratio is 1.18 (95% CI 1.16, 1.20)) (44, 45), which suggests that screening gaps may be underestimated by the CCHS. Although no studies to our knowledge have assessed differences in self-reported colorectal cancer screening by socioeconomic status, evidence for other cancer sites suggest that self-reported data may also lead to underestimation of socioeconomic disparities in screening (46).

4.6 CONCLUSION

This study shows a gradient in never screening according to local area-income in a system with universal healthcare coverage. This finding highlights the potential influence of social and environmental contexts on colorectal cancer screening uptake above and beyond individual-level factors. The role of socioeconomic contexts on screening behaviour merits attention both in future research and surveillance. Persistent area-level screening disparities in screening initiation may indicate a need for program modifications or additional targeted interventions.

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4.8 SUPPLEMENTARY MATERIALS

Supplementary file titles

eTable 1: Adjusted associations between area-level income and never screening, stratified by individual-level income quartiles, expressed as prevalence ratios (PR) among adults aged 50 through 75 years and participating in the 2005 and 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342).

eTable 2: Estimate of the maximum size of an unmeasured[a] factor or matrix of factors' association with area-level income and never screening to bring observed point estimates and lower confidence bounds to cross the null (1). Observed adjusted prevalence ratio (PR) estimates are yielded from GEE Poisson models, performed among adults aged 50 through 75 in the 2005, 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342).

eTable 1 Adjusted associations between area-level income and all covariates and having never been screened, stratified by individual-level income quartiles, expressed as prevalence ratios (PR) among adults aged 50 through 75 years and participating in the 2005 and 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342)

Covariates	**Overall** Adjusted PR (95% CI)[a,b]	**Quartile 1** Adjusted PR (95% CI) [b]	**Quartile 2** Adjusted PR (95% CI) [b]	**Quartile 3** Adjusted PR (95% CI)[b]	**Quartile 4** Adjusted PR (95% CI) [b]
Age					
50-59 years	1	1	1	1	1
60-75 years	0.73 (0.70-0.77)	0.84 (0.77, 0.92)	0.67 (0.58, 0.77)	0.67 (0.62, 0.74)	0.79 (0.71, 0.88)
Sex					
Female	1	1	1	1	1
Male	1.03 (0.98, 1.08)	1.00 (0.93, 1.11)	1.05 (0.98, 1.14)	1.08 (0.99, 1.17)	0.99 (0.90, 1.08)
Marital Status[c]					
Married/com-law	1	1	1	1	1
Div/wid/sep	1.04 (0.99, 1.10)	1.09 (1.00, 1.18)	1.02 (0.93, 1.11)	1.11 (0.99, 1.25)	0.94 (0.79, 1.12)
Single	1.02 (0.96, 1.09)	1.10 (0.98, 1.23)	1.01 (0.89, 1.14)	1.04 (0.92, 1.18)	0.87 (0.68, 1.12)
Immigration[c]					
Canadian-born	1	1	1	1	1
Immigrant (Eur., US, Oceania)	1.04 (0.98, 1.11)	1.11 (1.00, 1.24)	1.05 (0.94, 1.16)	1.01 (0.90, 1.12)	1.00 (0.88, 1.14)
Immigrant (Asia, Africa, S./C. Amer.)	1.18 (1.10, 1.26)	1.18 (1.03, 1.36)	1.15 (1.02, 1.31)	1.02 (0.87, 1.19)	1.29 (1.14, 1.46)
Education[c]					
HS Graduate	1	1	1	1	1
< HS Degree	1.11 (1.04, 1.18)	1.05 (0.96, 1.15)	1.14 (1.04, 1.25)	1.06 (0.90, 1.22)	1.30 (1.11, 1.52)
Regular MD[c]					
Yes	1	1	1	1	1
No	1.31 (1.23, 1.38)	1.25 (1.13, 1.37)	1.30 (1.13, 1.50)	1.33 (1.19, 1.48)	1.34 (1.17, 1.53)
Area Income					
Quartile 1	1.24 (1.16-1.34)	1.21 (1.04, 1.41)	1.11 (0.98, 1.25)	1.20 (1.05, 1.36)	1.27 (1.09,1.48)
Quartile 2	1.25 (1.15, 1.33)	1.14 (0.97, 1.32)	1.03 (0.92, 1.17)	1.25 (1.11, 1.42)	1.33 (1.19, 1.50)
Quartile 3	1.16 (1.08, 1.15)	1.03 (0.87, 1.21)	1.04 (0.94, 1.17)	1.09 (0.97, 1.22)	1.22 (1.08, 1.38)
Quartile 4	1	1	1	1	1

[a] This model was also adjusted for individual-level income (PRs not shown). Full model output was described previously in Table 2. [b] These prevalence ratios (PRs) are adjusted for all covariates. [c] Marital Status: "Com-law" indicates common law marital status; "Div" indicates divorced marital status; "Wid" indicates widowed marital status; "Sep" indicates separated marital status; Regions of immigration include the United States, Europe (Eur.), Oceania; Asia, Africa, South and Central (S./C.) America; Regular "MD" indicates regular physician.

eTable 2 Estimate of the maximum size of an unmeasured[a] factor or matrix of factors' association with area-level income and never screening to bring observed point estimates and lower confidence bounds to cross the null (1). Observed adjusted prevalence ratio (PR) estimates are yielded from GEE Poisson models, performed among adults aged 50 through 75 in the 2005, 2007 waves of the Canadian Community Health Survey (N=18,362; Weighted N = 4,838,342)

Area-level income	Observed adjusted PR for lifetime never screening (95% CI) [c]	Max value of unmeasured PR[b, d] = [PRobserved + √ (PRobserved (PRobserved -1))] to explain away:	
		Point Estimate	Lower Confidence Bound
Quartile 1	1.24 (1.16-1.34)	1.79	1.59
Quartile 2	1.25 (1.15, 1.33)	1.81	1.57
Quartile 3	1.16 (1.08, 1.15)	1.59	1.37
Quartile 4	1		

[a] Applying Ding & VanderWeele's Bounding Factor formula (from Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology (Cambridge, Mass.). 2016;27(3):368.)

[b] Assuming true PR is ≥1

[c] Adjusted point estimates and confidence intervals are from Table II.

[d] This approach aims to describe how large the association would have to be between an unmeasured factor or matrix of factors (U) and both area-level income (A) (PR_{AU}), and the screening outcome (Y) (PR_{UY}), to bring the observed point estimate (PR_{obs}) and its 95% confidence bound closest to 1 to cross the null. The formula, $RR_{obs}+\sqrt{(}RR_{obs.}*(RR_{obs.}-1))$, yields the maximum value of PR_{AU} and PR_{UY} —the associations between the unmeasured factor or matrix of factors and both area-level income and the independent variable.

CHAPTER 5: MANUSCRIPT 2

The role of access to a primary care physician in mediating immigration-based disparities in colorectal cancer screening: Application of multiple mediation methods

The role of access to a primary care physician in mediating immigration-based disparities in colorectal cancer screening: Application of multiple mediation methods

Running Title:
Mediation of immigration-based disparities in screening

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Alexandra Blair conceptualised the manuscript, conducted the data analysis, wrote the first draft of the manuscript and reacted to and integrated co-authors comments.
Lise Gauvin contributed to the conceptualisation of the manuscript, and to writing and reviewing the manuscript.
Mireille Schnitzer contributed to data analysis, particularly the implementation of inverse probability weighted mediation analyses, and contributed to the review of the manuscript.
Geetanjali D. Datta contributed to the conceptualisation of the manuscript and data analysis, and to the writing and reviewing of the manuscript.

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Abbreviations: CCHS, Canadian Community Health Survey; CI, Confidence Interval; EMM, effect measure modification; CDE, controlled direct effect; CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test; GEE, generalised estimating equations; IPW, Inverse probability weight; PD, prevalence difference; PE, proportion eliminated; PR, prevalence ratio; TE, total effect.

Keywords: Prevention; Gastrointestinal cancers/Colorectal cancer; Biostatistics; Behavioral prevention research; Health inequalities; Immigrant health

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5.1 ABSTRACT

Background: Colorectal cancer screening participation is lower among recent immigrants than among Canadian-born individuals. We assessed whether this immigration-based screening disparity is mediated by access to primary care physicians (PCP).

Methods: Pooling years 2003-2014 of the Canadian Community Health Survey, lifetime screening in respondents aged 50-75 years who immigrated in the previous 10 years (n=1,067) was compared to Canadian-born respondents (N=102, 366). Regression- and inverse probability weighting-based methods were used to estimate the Total Effect (TE) and Controlled Direct Effect (CDE) of recent immigration on never having received either a stool- or endoscopic-based screening test. The proportion of the TE that would be eliminated if all had a PCP was computed using these estimates (Proportion Eliminated (PE) = [TE-CDE]/[TE-1]). Analyses were stratified by visible minority status, and adjusted for income, rurality, age, sex, marital status, education, and exposure to a provincially organized colorectal cancer screening program.

Results: The prevalence of never having been screened was 71% and 57% in visible minority and white recent immigrants, respectively, and 46% in white Canadian-born respondents. If all had regular PCPs, there would be no reduction in the screening inequality between white recent immigrants and Canadian-born (null PE), and the inequality between visible minority immigrants and white Canadian-born may increase by 6% to 13%.

Conclusions: Ensuring all have regular PCPs may lead to greater gains in screening among those born in Canada than among recent immigrants.

Impact: Improving access to PCPs may increase screening overall, but not reduce immigration-based disparities in colorectal cancer screening. Alternative interventions to reduce this disparity should be explored.

5.2 INTRODUCTION

In Canada, as in other developed nations,[1, 2] immigrants are less likely than Canadian-born residents to have ever been screened for colorectal cancer,[3] which is currently the third most common cause of cancer death in the country.[4] The gap in lifetime screening between those born in Canada and those born abroad is of approximately 10%.[5] Since having never been screened is associated with later-stage at diagnosis and higher levels of colorectal cancer mortality,[6] immigrants are likely to bear a disproportionate amount of the burden of colorectal cancer, in part because they are under-screened. Immigration-based screening disparities beg two questions: how do these disparities come to exist; and what interventions can be leveraged to reduce them?

Known social determinants of colorectal cancer screening include lack of free time, [7] lack of high school graduation, [8] lower income,[3] rural residence,[9] and not being exposed to an organized screening program.[10] Beyond these determinants, one factor that is hypothesized to drive immigration-based inequalities in colorectal cancer screening is the difficulty that many recent immigrants face in accessing primary health care services. In Canada, though immigrants granted permanent residency are entitled to universal health care coverage, linguistic, cultural and system-based barriers can make accessing health resources difficult. [11, 12] For example, recent immigrants are less likely than non-immigrants to have a primary care physician (PCP). [13] Since individuals without PCPs are less likely to be screened,[3] the disparity in access to PCPs may explain, at least in part, this disparity in colorectal cancer screening.

Though improving regular PCP access has been identified as a potential area of intervention to increase screening among recent immigrants, this potential mediating pathway of the association between recent immigration and colorectal cancer screening has yet to be formally empirically assessed. The aim of this study was therefore to assess if having a PCP mediates the disparity in lifetime colorectal cancer screening between recent immigrants and non-immigrants in Canada, and if so, assess what proportion of the disparity would be eliminated if all had a regular PCP (referred to as the Proportion Eliminated or "PE"). Since recent immigrants' cancer screening habits and beliefs, and overall interactions with the health care

system, can vary across racial and ethnic identities, [14, 15] we wished to assess this potential mediating pathway across visible minority and white sub-populations. We did so using multiple techniques to compare the stability of findings.

5.3 MATERIALS AND METHODS

5.3.1 Data and target population

Data from years 2003, 2005, 2007-2014 of the population-based, cross-sectional Canadian Community Health Study (CCHS) were used. [16] The CCHS questionnaire was administered in English and French (with the possibility of completing the interview in an alternative language when necessary) via computer-assisted interviewing, either in-person or by telephone (40% and 60% of interviews, respectively [17]). Response rates ranged from 80.7% in 2003 [18] to 65.6% in 2014 [17], with sampling weights adjusted for non-response. The study's target population was adults aged 50-75 years, with no known risk factors or symptoms of colorectal cancer. [19]

Excluded from this study were respondents who reported screening due to "family history of colorectal cancer," "follow-up of a problem", and "follow-up of colorectal cancer treatment." [16, 19]. The study focused on two groups of respondents: those who were either white and Canadian-born, and those who had immigrated to Canada recently (≤10 years) and were either white or of visible minorities. The study sample was restricted to these groups for two reasons. First, longer-term immigrants (>10 years since arrival) were excluded given their similar overall prevalence of never having been screened for colorectal cancer (45.6%, 95% CI: 44.4%, 47.1%) as Canadian-born respondents (46.3%, 95% CI: 45.8, 46.8%). The application of mediation analysis to explain differences in screening between longer-term immigrants and Canadian-born respondents was therefore not pertinent, as no distinct inequality was present. Second, screening among white recent immigrants and visible minority recent immigrants was compared to screening among white Canadian-born respondents to isolate associations for joint exposure of visible minority status and recent immigration (i.e. through the contrast of screening among visible minority recent immigrants versus white, Canadian-born respondents) and single exposure of recent immigration (i.e. through the contrast of screening among white recent

immigrants versus white, Canadian-born respondents). Differences in these the size of these two inequalities are assumed to offer an indication of the effect-modifying potential of visible minority status lived by recent immigrants.

5.3.2 Measures

Figure 1 describes the hypothesized relations between the following measures (additional theory and literature on which are described in detail in the Supplement's eMethods 1):

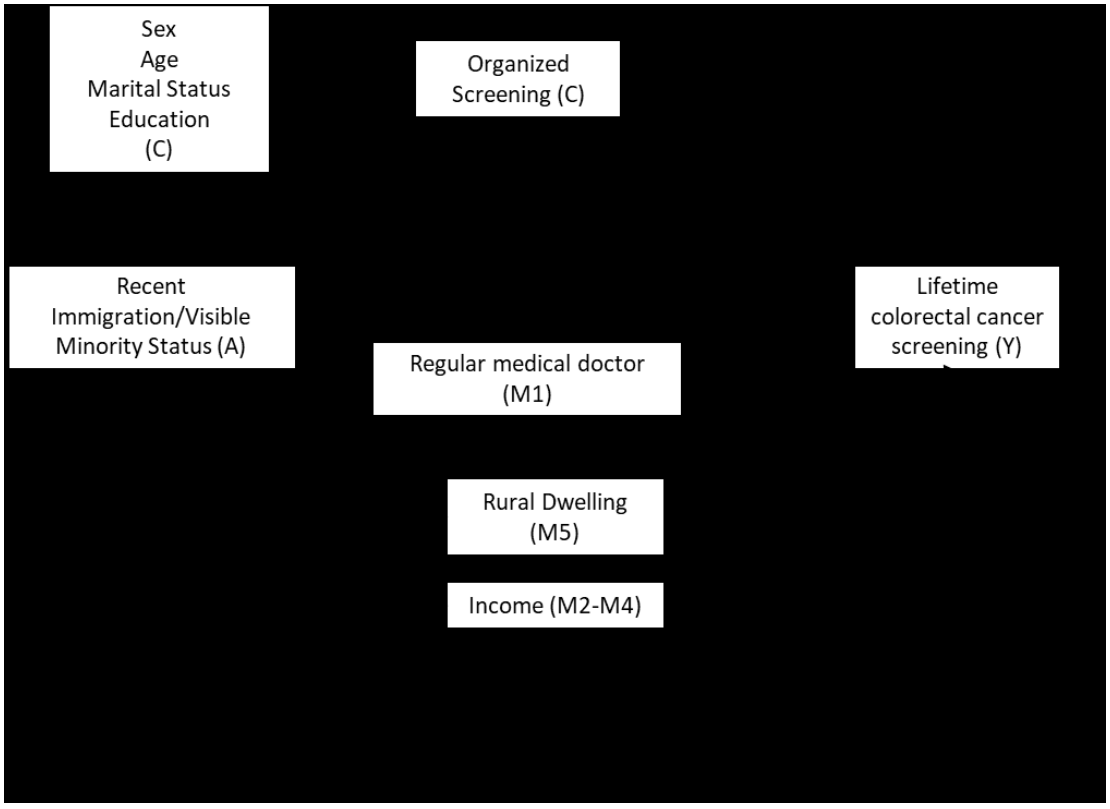

Figure 1: Directed Acyclic Graph (DAG) of the assumed direction of associations between study measures. One-way arrows indicate assumed direction of associations between the exposure of the study (A, recent immigration/visible minority status), the principal mediator (M1, access to a primary care physician), the outcome (Y, lifetime colorectal cancer screening), other assumed mediators (M2-M5) and covariates (C).

Outcome measure

The CCHS questionnaire describes stool-tests and endoscopic examination (sigmoidoscopy, colonoscopy) and asks: "Have you ever had this test/either of these exams?" For immigrants, the question did not differentiate whether tests were conducted before or after arrival to Canada. Respondents were considered to have never been screened (Y=1) if they reported to have never had any of these tests. We focused on lifetime screening as most Canadians have in fact never been screened in their lifetime [5] and since having never been screened is associated with later-stage cancer at diagnosis and higher risk of mortality. [6]

Exposure measure

The exposure of interest (A) was recent immigration (A=1 for those who reported immigrating to Canada in the previous 10 years). A 10-year cut-off was used to identify non-recent immigrant, as it reflects the observed period it takes, on average, for new residents to feel a sense of familiarity in the Canadian setting, and to report similar income earnings as average Canadian residents. [20] To account for the intersecting experiences of recent immigration and racialization, [21] recent immigrants and non-immigrants were stratified by visible minority status (yes or no). The CCHS' derived variable for visible minority status captures whether respondents' self-reported cultural and racial background is other than "White". [22] The construct of "visible minority status" was used in this study as a proxy for racialized status and the potential marginalization it entails. [23] Screening among white recent immigrants and visible minority recent immigrants was compared to screening among white Canadian-born respondents to isolate associations for joint exposure (visible minority status, recent immigration) and single exposure (recent immigration).

Mediator measures

The principal mediator of interest was access to a PCP. Respondents were considered to not have a PCP if they answered "No" to the question "Do you have a regular medical doctor?" And, as it is convention to consider other potential mediating factors in the analysis of direct and

indirect effects, [24] we identified two factors in the literature to be treated as additional potential mediators in the analyses: household income and area of residence. The full mediation analyses (i.e. the estimation of the TE, CDE, and PE) described below were not run for these additional mediators. Rather, the identification of additional potential mediating factors among the covariates of the study is recommended insofar as these factors must be treated differently in the estimation of the TE, compared to the estimation of the CDE for the primary mediator of interest. These potential additional mediators were excluded from TE analyses, insofar as they were not assumed to confound the association between recent immigration and screening. In contrast, they were included as potential confounders of the principal mediator-outcome association in CDE analyses, given that they were assumed to determine both likelihood of access to a primary care physician and screening (Figure 1). Household income was categorized as quartile groupings (highest income [Quartile 4] as reference). Since missing income data were not imputed in the CCHS before 2005, income for CCHS 2003 was imputed based on individuals' age, sex, education, marital status, immigration status, and sampling weight, using hot deck imputation in Stata 14 (hotdeckvar). [25] Area of residence was dichotomized (urban vs. rural). Urban classification in the CCHS is based on census population concentration (n≥1,000 inhabitants) and density (n≥400/km2). It includes urban core, urban fringe, secondary urban core, and suburban areas. [22]

Covariate measures

Covariates included were sex, age (50-59 years; 60-75 years), marital status (single; divorced, widowed, or separated; married or in a common-law relationship), educational attainment, and exposure to a provincial organized mail-based colorectal cancer screening program. Since lack of high school graduation is an important predictor of non-recent screening participation across white and visible minority groups at other cancer sites [8] and has previously been associated with lower likelihood of colorectal screening (with non-differential effect sizes for higher education groups, i.e., high school graduates, postsecondary attendees) [26], those who had not completed high school were compared to those who had a high school diploma or more formal education (including college attendance). Residents of Manitoba from 2007, Ontario from 2008, Saskatchewan from 2009, Nova Scotia from 2009, and New

Brunswick from 2014 were considered exposed to a mail-based organized colorectal cancer screening program, [27] designed to promote screening. Exposure to these programs was included as a confounder (i.e. as a potential determinant of PCP access, screening likelihood, and how immigration is experienced) and effect modifier (i.e. as a moderating factor of the associations between recent immigration and PCP access, and between PCP access and screening).

5.3.3 Analysis

Estimating the proportion of the disparity would be eliminated if all had a regular PCP (the Proportion Eliminated or "PE"), requires an estimation of 1) the total adjusted association (referred to as the total effect or "TE") between recent immigration and lifetime colorectal screening, and 2) the direct association between recent immigration and lifetime colorectal screening if all had a PCP (referred to as the controlled direct effect "CDE"). In a counterfactual framework,[28] if we assume having measured all mediator-outcome confounders, the CDE can be defined as the remaining immigration-based disparity in lifetime screening prevalence had all individuals been assigned (possibly counterfactually) a regular PCP.[29, 30] Measuring the CDE is particularly relevant when interested in assessing how a potential intervention on the mediator (here, assigning all a PCP) could influence a known inequality.[29, 30] If the inequality in access to regular PCPs according to immigration status does explain, at least in part, immigration-based inequalities in screening, we would expect to see a proportion of the inequality eliminated.

Multiple approaches have been proposed to estimate the TE and CDE. Some use regression modeling,[18, 30] whereas others combine regression modeling with inverse probability weighting techniques,[31] or use a purely inverse probability weighting approach.[24] The aim of using inverse probability weights is to create synthetic populations that are balanced in terms of the measured covariates, through which contrasts in average outcomes can be estimated.[24] In this study, we applied three methods (summarized in detail in other texts [29-31] and Table 1)—which, taken together, enable an assessment of the robustness of the findings.

First, we used a regression-based product method (also referred to as the generalized product method [17]) proposed by VanderWeele and Vansteelandt, [30] which extends Baron and Kenny's product method [18] to allow for effect estimation in the presence of exposure-mediator interaction [Method 1]. This method requires the specification of two Poisson regression models for the screening outcome—one with, the other without, the mediator measure and its product term with the exposure (these are the CDE, and TE models, respectively). Second, we used an inverse probability-weighted marginal structural model approach [Method 2], described by VanderWeele, [30] in which TE and CDE models (as in Method 1) are weighted using inverse probability weights for the exposure and mediator. These weights are constructed using propensity scores (predicted probabilities) for the exposure and mediator, given covariates and other mediator values, which are estimated using logistic models (details in Table 1 and the Supplement's eMethod 2). Lastly, we used an inverse probability weighted approach for marginal effect estimation [Method 3], described by VanderWeele, [24] in which screening prevalence is weighted (as in Method 2), and simple ratios of the average screening prevalence between the exposed and unexposed (for TE estimation), and between the exposed with a PCP and unexposed with a PCP (for CDE estimation) are computed. Inverse probability weights used in this method are also constructed using propensity scores for the exposure and mediator, estimated using logistic models (details in Table 1 and Supplement's eMethod 2). Estimates from IPW methods 2 and 3 can be interpreted as the average associations in the population, whereas method 1 associations are conditional on the strata of the variables in the models. With the TE and CDE, the proportion of the total effect explained by PCP access (PE) was estimated on an excess relative risk scale (using prevalence ratio [PR] estimates) as follows: $(PR^{TE} - PR^{CDE}) / (PR^{TE} - 1)$. [24]] Confidence intervals (95%) for CDE, TE, and PE were estimated using the bootstrap method (500 replications). [24] Though sampling weights are available in the CCHS, they were not use in this study in order to avoid unreasonably large weights in the inverse probability weighted analyses (e.g. where one respondent could represent thousands of respondents due to multiplied sampling and inverse probability weights [32]). To ensure consistency across methods, sampling weights were therefore also excluded from regression-based methods. Analyses were conducted in R (version 3.4.1). [33]

Assumptions and sensitivity analyses

The analyses described above rely on two assumptions, the validity of which was tested using sensitivity analyses. First, the validity of the CDE estimates (and consequently, of the PE estimates) relies on the assumption of controlled confounding for the mediator-outcome relationship. [34] We apply formulas derived by VanderWeele (2015) [35] to test the sensitivity of observed CDE estimates to unmeasured confounding of the mediator-outcome relationship. This approach estimates how large associations would have to be between an unmeasured factor and both the mediator and outcome for the true CDE estimates to be null (PR=1) despite non-null estimates, or to be equivalent or smaller to the observed TEs (yielding null or positive PEs).

Secondly, estimating CDE requires both theoretical positivity of the mediator (i.e. that all respondents have a non-null probability of PCP access) and—when using inverse probability weighting—practical positivity for the exposure and mediator (i.e. that propensity scores for these factors are neither 0 nor 1 [0% or 100% probability]).[36] To assess this, we performed stratified, descriptive analyses of propensity scores for the exposure and mediator.[24]

The study protocol was approved by the Ethical Review Board of the Centre de Recherche du Centre Hospitalier de l'Université de Montréal.

Table 1: Summary of models required for the estimation of the controlled direct effect (CDE) and total effect (TE), in the three methods used in the study

Method	Controlled direct effect (CDE)	Total effect (TE)
(1) Generalized Product Method	**Outcome model** $\log(E[Y\|a,m\ c] = \theta_0 + \theta_1 A_i + \theta_2 M1 + \theta_3 AM1 + \theta' M_i + \theta' c$ CDE indicated by $(\theta_1 + \theta_3 m)$, where m was set to $m=1$; all have physicians	**Outcome model** $\log(E[Y\|a,m\ c] = \theta_0 + \theta_1 A_i + \theta' M_i + \theta' c$ TE indicated by (θ_1)
(2) Inverse probability weighting (IPW) Marginal Structural Model approach	**Propensity score models** Logistic model for A=1 ~ 1 (p_A) Logistic model for A=1 with C_i (p_A1) Logistic model for M1=1 with A (p_M) Logistic model for M1=1 with A,C_i, all M_i (p_M1) **Weights for A** If A=1: p_A/p_A1 If A=0: p_A/(1-p_A1) **Weights for M1** If M1=1: p_M/p_M1 If M1=0: p_M/(1-p_M1) **Outcome model** Where all are weighted using product of weights for A and for M1: $\log(E[Y\|a,m\ c] = \theta_0 + \theta_1 A_i + \theta_2 M1 + \theta_3 AM1 + \theta' M_i + \theta' c$ CDE indicated by $(\theta_1 + \theta_3 m)$, where m was set to $m=1$; all have physicians	**Propensity score models** Logistic model for A=1 ~ 1 (p_A) Logistic model for A=1 with C_i (p_A1) **Weights for A** If A=1: p_A/p_A1 If A=0: p_A/(1-p_A1) **Outcome model** Where all are weighted using weights for A: $\log(E[Y\|a,m\ c] = \theta_0 + \theta_1 A_i + \theta' M_i + \theta' c$ TE indicated by (θ_1)
(3) Inverse probability weighted (IPW) Average Marginal Effect approach	**Propensity score models** Logistic model for A=1 with C_i (p_A1) Logistic model for M1=1 with A, C_i, all M_i (p_M1) **Weights for A** If A=1: 1 /p_A1 If A=0: 1/(1-p_A1) **Weights for M1** If M1=1: 1/p_M1 If M1=0: 1/(1-p_M1) **Estimation** CDE is estimated by the ratio of weighted (using product of weights for A and M1) screening prevalence in those with A=1 and M1=1 over those with A=0 and M1=1: $Y_{A=1,\ M1=1,\ weighted} / Y_{A=0,\ M1=1,\ weighted}$	**Propensity score model** Logistic model for A=1 with C_i **Weights for A** If A=1: 1/p_A1 If A=0: 1/(1-p_A1) **Estimation** TE is estimated by the ratio of weighted screening prevalence in those with A=1 over those with A=0: $Y_{A=1,\ weighted} / Y_{A=0,\ weighted}$

[a] A= exposure (recent immigration). M1=mediator (not having a primary care physician). M_i describes the additional mediators, here M2-M4 are quartile groupings 1,2,3 of household income, and M5 stands for rural residence. C_i represent covariates, which include sex, age, marital status, education, and exposure to an organized screening program.

5.4 RESULTS

5.4.1 Sample characteristics

Of the total sample (102,366 of whom were white Canadian-born respondents, 659 were recent-immigrants of visible minorities, and 408 of whom were white recent-immigrants), 47% had never been screened in their lifetime and 9% did not have a PCP (Table 2). The prevalence of never having been screened was 71% and 57% in visible minority and white recent immigrants, respectively, and 46% in white Canadian-born respondents (Table 2). Approximately 9% of white Canadian-born respondents did not have a PCP, compared to 18% among both visible minority and white recent immigrants, respectively (Table 2). Overall, the proportion of those who had never been screened was higher among those who were younger than 60 years, not partnered, had lower income (quartiles 1 and 2), had not obtained a high school diploma, did not have a PCP, resided in rural settings, and were not exposed to a provincial organized mail-based screening program (Table 2).

5.4.2 Associations between exposure, mediator, and outcome

Adjusting for all factors, recent immigrants and Canadian-born respondents differed in relation to age, sex, marital status, and exposure to organised screening programs. However, the direction of these associations was at times heterogeneous across the visible minority status contrasts. Though all recent immigrants tended to be younger and more likely to be married than their Canadian-born peers, white recent immigrants were less likely to be exposed to organised screening programs compared to white Canadian-born respondents (PR=0.88) (whereas visible minority recent immigrants were more likely to live in provinces with organised mail-based screening programs; PR=1.23) (Table 3). Further, though no statistically significant sex-differences were observed between white recent immigrants and white Canadian-born respondents, a larger proportion of visible minority respondents identified as male (PR=1.16) compared to respondents in the white Canadian-born sample (Table 3).

Overall, associations were observed between immigration status, having a regular PCP, and screening. Associations were again heterogenous across the visible minority status contrasts. Adjusting for all factors, recent immigrants were less likely to have a PCP (Table 3). However, the inequality in access to a regular PCP was larger between white recent immigrants and white Canadian-born respondents (PR=2.86) than it was between visible minority recent immigrants and white Canadian-born respondents (PR=1.40) (Table 3).

Recent immigrants were more likely to have never been screened compared to white Canadian-born respondents (Table 4). Adjusting for all factors, the inequality in the prevalence of having never been screened was larger between visible minority recent immigrants and white Canadian-respondents (PR=1.16) than between white recent immigrants and white Canadian-born respondents (PR=1.01) (Table 4).

Lastly, associations between having a regular PCP and screening were heterogeneous across strata of immigration status. Expressed as prevalence differences (PD), the adjusted difference in screening between those with and without a PCP was larger among white Canadian-born respondents (PD = 19% [95% CI 17% to 20%], i.e. prevalence of approximately 44% among those with a PCP, 68% among those without) than among white immigrants (PD=4% [95% CI -15% to 24%], i.e. prevalence of approximately 54% among those with a PCP, 58% among those without) or among visible minority immigrants (PD=8% [95% CI -10% to 27%], i.e. prevalence of approximately 71% among those with a PCP, 79% among those without) (data not in table).

Table 2: Prevalence of having never been screened and not having a primary care physician across demographic, social, and economic population characteristics among respondents aged 50-75 years to the 2003-2014 waves of the Canadian Community Health Survey (n=659 visible minority recent-immigrants, n=408 white recent-immigrants, n=102,366 white Canadian-born respondents)

Characteristics	Overall	% Without a Primary care physician (95% CI)	% Never Screened (95% CI)
	100	9.3	47.0
Recent immigration			
No	99.2	9.0 (8.7, 9.4)	46.3 (45.8, 46.8)
Yes	0.9	18.2 (13.8, 23.7)	67.9 (62.6, 72.7)
Visible minority status			
No	93.6	9.0 (8.7, 9.3)	46.3 (45.7, 46.8)
Yes	6.4	14.4 (12.0. 17.2)	57.6 (54.7, 60.5)
Immigration/visible minority			
Recent Immigrant, Visible Minority (n=659)	0.61	18.4 (13.0, 25.4)	71.0 (65.0, 76.3)
Recent Immigrant, White (n=408)	0.38	17.6 (13.0, 23.4)	56.8 (46.5, 66.4)
Canadian-born, Visible Minority (n=5241)	4.82	11.7 (10.4, 13.2)	48.9 (46.0, 51.7)
Canadian-born, White (n=102,366)	94.20	8.9 (8.6, 9.3)	46.2 (45.7, 46.7)
Sex			
Men	49.9	11.1 (10.5, 11.6)	47.1 (46.2, 47.9)
Women	50.1	7.6 (7.2, 8.0)	46.9 (46.2, 47.6)
Age (years)			
50-59	52.8	11.3 (10.5, 12.0)	54.9 (54.0, 55.8)
60-75	47.2	7.2 (6.8, 7.6)	38.1 (37.5, 38.8)
Marital status			
Married/Common Law	73.6	7.8 (7.4, 8.2)	45.4 (44.7, 46.0)
Divorced/Widowed/Separated	18.6	11.3 (10.5, 12.0)	49.5 (48.3, 50.8)
Single	7.8	19.8 (18.4, 21.3)	47.0 (46.5, 47.6)
Education			
≥High School	80.5	9.1 (8.0, 9.5)	45.8 (45.2, 46.5)
<High School	19.5	10.2 (9.6, 10.9)	51.9 (50.8, 53.0)
Organized mail-based program			
Yes	39.6	7.4 (6.9, 8.0)	35.2 (34.2, 36.1)
No	60.4	10.6 (10.2, 11.1)	55.8 (54.1, 55.4)
Primary care physician			
Yes	90.7		44.7 (44.1, 45.2)
No	9.3		69.8 (67.9, 71.6)
Income quartiles			
Quartile 1	19.0	12.0 (11.2, 12.8)	51.6 (50.6, 52.7)
Quartile 2	20.4	9.6 (8.9, 10.4)	45.0 (43.9, 46.1)
Quartile 3	30.4	9.1 (8.4, 9.8)	46.3 (45.2, 47.5)
Quartile 4	30.2	7.7 (7.2, 8.3)	46.1 (45.0, 47.2)
Rural			
Yes	25.9	9.3 (8.8, 9.9)	49.2 (45.6, 46.9)
No	74.1	9.3 (8.9, 9.8)	46.3 (45.6, 46.9)

Table 3: Covariate-adjusted models for recent immigration (A) and not having a primary care physician (M1), stratified by visible minority status (n=659 visible minority, n=408 white), with white Canadian-born respondents (n=102,366) as reference category, in the Canadian Community Health Survey 2003-2014

	Stratified, covariate-adjusted models for recent immigration (A)		**Stratified, covariate-adjusted models for not having a primary care physician (M1)**	
	Visible minority recent immigrants vs. White Canadian-born	White recent immigrants vs. White Canadian-born	Visible minority recent immigrants vs. White Canadian-born	White recent immigrants vs. White Canadian-born
Characteristics	Recent immigration PR[b] (95% CI)	Recent immigration PR[b] (95% CI)	Not having a primary care physician PR[b] (95% CI)	Not having a primary care physician PR[b] (95% CI)
Recent immigration [a]				
Yes			1.40 (1.14, 1.82)	2.86 (2.22, 3.63)
No			1	1
Sex				
Men	1.16 (1.07, 1.26)	0.91 (0.82, 1.00)	1.58 (1.54, 1.61)	1.57 (1.54, 1.61)
Women	1	1	1	1
Age				
50-59	2.15 (1.98, 2.32)	1.52 (1.38, 1.69)	1.65 (1.61, 1.68)	1.65 (1.61, 1.68)
60-75	1	1	1	1
Marital Status[a]				
Mar./Com. Law	1	1	1	1
Div./Widow.	0.63 (0.57, 0.70)	0.63 (0.55, 0.72)	1.55 (1.51, 1.60)	1.56 (1.50, 1.60)
Single	0.41 (0.35, 0.49)	0.40 (0.32, 0.50)	2.41 (2.34, 2.49)	2.42 (2.36, 2.47)
Education				
≥High School	1	1	1	1
<High School	1.06 (0.97, 1.17)	0.25 (0.20, 0.30)	1.13 (1.10, 1.15)	1.13 (1.10, 1.16)
Organized mail-based program				
Yes	1	1	1	1
No	1.23 (1.13, 1.33)	0.88 (0.79, 0.97)	1.25 (1.22, 1.28)	1.25 (1.22, 1.28)
Income Quartiles				
Quartile 1			1.13 (1.09, 1.17)	1.13 (1.09, 1.17)
Quartile 2			1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Quartile 3			1.01 (0.97, 1.04)	1.01 (0.98, 1.04)
Quartile 4 (highest)			1	1
Rural				
Yes			1.19 (1.17, 1.22)	1.19 (1.17, 1.22)
No			1	1

[a] "Mar" indicates married; "Com. Law" indicates Common law relationship status; "Div." indicates divorced, "Widow." indicates widowed. [b] Stratified PR values represent stratified prevalence risk ratios estimated via Poisson log-linear regression models. Models were adjusted for age, sex, marital status, educational attainment, exposure to a provincial organized screening program, income quartile, rural residence

Table 4: Covariate-adjusted models for having never been screened (Y), stratified by visible minority status (n=659 visible minority, n=408 white), with white Canadian-born respondents (n=102,366) as reference category, in the Canadian Community Health Survey 2003-2014

	Stratified, covariate-adjusted models for having never been screened (Y)	
	Visible minority recent immigrants vs. White Canadian-born	White recent immigrants vs. White Canadian-born
Characteristics	Having never been screened PR_{11}[b] (95% CI)	Having never been screened PR_{10}[b] (95% CI)
Recent Immigration (A)[a]		
Yes	1.16 (0.92, 1.41)	1.01 (0.75, 1.27)
No	1	1
Primary care physician (M1)		
Yes	1	1
No	1.41 (1.36, 1.44)	1.42 (1.36, 1.47)
Product terms		
A*M1	1.33 (1.07, 1.60)	1.23 (0.93, 1.53)
Sex		
Men	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
Women	1	1
Age		
50-59	1.40 (1.39, 1.42)	1.41 (1.39, 1.42)
60-75	1	1
Marital Status[a]		
Mar./Com. Law	1	1
Div./Widow.	1.08 (1.06, 1.11)	1.08 (1.06, 1.11)
Single	1.12 (1.09, 1.15)	1.12 (1.09, 1.15)
Education		
≥High School	1	1
<High School	1.13 (1.11, 1.15)	1.13 (1.11, 1.15)
Organized mail-based program		
Yes	1	1
No	1.66 (1.64, 1.68)	1.66 (1.64, 1.68)
Income Quartiles		
Quartile 1	1.04 (1.02, 1.07)	1.04 (1.02, 1.07)
Quartile 2	0.96 (0.93, 0.98)	0.96 (0.93, 0.99)
Quartile 3	0.94 (0.92, 0.97)	0.94 (0.91, 0.97)
Quartile 4 (highest)	1	1
Rural		
Yes	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)
No	1	1

[a] "Mar" indicates married; "Com. Law" indicates Common law relationship status; "Div." indicates divorced, "Widow." Indicates widowed. [b] PR values represent stratified prevalence ratios estimated via Poisson log-linear regression models. Models were adjusted for age, sex, marital status, educational attainment, exposure to a provincial organized screening program, income quartile, rural residence and product terms.

Table 5: Estimated total effect of recent immigration (exposure) on lifetime screening, and controlled direct effect when access to a primary care physician (mediator) is held fixed, stratified by visible minority status (n=659 visible minority, n=408 white), with white Canadian-born respondents (n=102,366) as reference category, in the Canadian Community Health Survey 2003-2014

Population Strata	Approach	Total Effect (TE) PR (95% CI)	Controlled Direct Effect (CDE) PR (95% CI)	Proportion Eliminated (PE) $(PR^{TE} - PR^{CDE}) / (PR^{TE} - 1)$ % (95% CI)
Visible minority recent immigrants vs. White Canadian-born	(1) Generalized Product Method approach[a]	1.51 (1.28, 1.65)	1.56 (1.48, 1.63)	-9% (-15%, -4%)
	(2) IPW Marginal Structural Model approach[b]	1.54 (1.41, 1.69)	1.58 (1.50, 1.68)	-6% (-12%, -2%)
	(3) IPW Average Marginal Effect approach[c]	1.53 (1.44, 1.61)	1.60 (1.51, 1.70)	-13% (-20%, -6%)
White recent immigrants vs. White Canadian-born	(1) Generalized Product Method approach[a]	1.24 (1.08, 1.40)	1.24 (1.12, 1.35)	-2% (-29%, 24%)
	(2) IPW Marginal Structural Model approach[b]	1.31 (1.15, 1.48)	1.32 (1.18, 1.47)	1% (-21%, 24%)
	(3) IPW Average Marginal Effect approach[c]	1.25 (1.13, 1.37)	1.27 (1.12, 1.42)	-10% (-51%, 36%)

NOTE: IPW = Inverse probability weighted, PR= Prevalence Ratio.

[a] The generalized product method, proposed by VanderWeele and Vansteeladnt (2009), extends Baron and Kenny's (1986) product method to allow for effect estimation in the presence of exposure-mediator interaction. Note that when exposure-mediator interaction is not accounted for, effects were the following for visible minority recent immigrants (ref. White, Canadian-born): TE = 1.51 (1.38, 1.66), the CDE = 1.49 (1.42, 1.56), and the PE = 3.8% (1%, 7%); and for white recent immigrants (ref. white Canadian-born) they were TE=1.24 (1.08, 1.40), CDE= 1.18 (1.08, 1.29), PE = 26% (15%, 43%).

[b] The inverse probability-weighted marginal structural model approach, proposed by VanderWeele (2009), fits inverse-probability-weighted TE and CDE models (on outcome Y) such that the exposed and unexposed are balanced in terms of measured covariates (for CDE, TE estimation) and primary care physician values (for CDE estimation).

[c] The IPW Average Marginal Effect approach estimates CDE by computing the ratio between i) the average prevalence of lifetime screening in recent immigrants with physicians (who are weighted to be balanced in terms of measured covariates and mediators with those born in Canada) and ii) the average prevalence of lifetime screening in Canadian-born respondents with physicians (who are weighted to be balanced in terms of measured covariates and mediators with recent immigrants). Similarly, the TE is estimated by computing ratio between i) the average prevalence of lifetime screening in recent immigrants (weighted to be balanced in terms of measured covariates with those born in Canada) and ii) the average prevalence of lifetime screening in Canadian-born respondents (weighted to be balanced in terms of measured covariates).

5.4.3 TE, CDE, and PE estimates

The TE, CDE, and PE estimates were largely consistent across all three mediation methods (Table 5). Large CDE estimates (between PR=1.56 and 1.60 for visible minority recent immigrants, and between PR=1.24 to 1.27 for white recent immigrants, depending on the method used) suggest that even if inequalities in access to a PCP were eliminated, a large disparity in lifetime screening would remain for recent immigrants across visible minority status. Most CDE estimates were larger than TE estimates, yielding null PE estimates for white recent immigrants, and negative PE estimates (i.e. exacerbated inequalities under mediator intervention) for visible minority recent immigrants (between -6% and -13%, depending on the method used) (Table 2).

5.4.4 Results of sensitivity analyses

First, we found that the associations between the unmeasured factor and both the mediator and outcome would have to be at minimum PR = 2.5 for visible minority recent immigrants, and PR=1.8 for white recent immigrants for the true CDE estimates to be null (PR=1) despite non-null estimates; and would have to be at minimum PR=1.3 and PR=1.1 for visible minority and white recent immigrants, respectively, for true CDE estimates to be equivalent or smaller than observed TE estimates (yielding null or positive PE values) (Supplement's eTable 1 and eTable 2). These are larger estimates than those observed for low education and not being exposed to an organized mail-based screening program (Table 2, Table 3). Nonetheless, the potential for unmeasured confounding remains. Second, analyses of propensity scores indicate good covariate balance between exposed and unexposed respondents after weighting, and of practical positivity for access to a PCP (Supplement's eTable 3, eTable 4). However, the requirement of practical positivity for recent immigration may be violated (i.e. propensity scores—even when truncated at the 10th percentile—were close to 0). Lack of practical positivity may lead to potential instability of the weighting methods. Lastly, results were largely consistent when accounting for effect modification by exposure to an organized mail-based screening program, with slightly attenuated direct effects (Supplement's eTable 5).

5.5 DISCUSSION

The aim of this study was to assess whether having a PCP mediates the disparity in lifetime colorectal cancer screening between recent immigrants and non-immigrants in Canada. In this sample, in which nearly half (47%) have never been screened, we observed large controlled direct effects between recent immigration and screening, as well as proportions eliminated that were either null or negative—indicating that improving access to PCPs may not reduce observed immigration-based screening inequalities. As the screening disparity between those with and without a PCP is larger among white Canadian-born respondents (PD=19%) than among recent immigrants (PD=8% and 4% among visible and white minority recent immigrants, respectively), having a PCP lead to larger increases in screening among Canadian-born individuals than among recent immigrants, thereby leaving the disparity untouched or exacerbated.

The observed associations between recent immigration and lifetime screening are consistent with those observed previously in Canada and North America. [1] These associations may be explained by recent immigrants' more limited knowledge of and trust in the efficacy of the screening tests and the medical system, discomfort with the test itself, or lower perceived susceptibility to cancer. [1, 37] Differences in effect sizes between white and visible minority recent immigrants may be explained by differences in ethno-cultural feelings of fatalism and helplessness with regards to colorectal cancer diagnosis and mortality[14] or in the acceptability of screening tests.[15] On a more distal level, systemic discrimination,[38] barriers to health care, and social stressors such as inadequate housing and precarious employment[39] are thought to explain, in part, why persons who immigrate to Canada —who, upon arrival are disproportionately healthy—see their health experience a decline in health over time, eventually converging with Canadian-born residents their age.[11] These distal factors may also explain why such strong associations are observed between recent immigration and screening. However, it should be noted that Canada's immigrant and visible minority populations are highly heterogenous, and explanations for the observed findings may not hold across all sub-groups.

Though having a regular PCP is an important enabling determinant of screening participation overall, [1] our findings suggest increasing access to PCPs may lead to greater gains in screening for Canadian-born individuals than for recent immigrants. Several factors may explain this observation. First, recent immigrants may not systematically receive screening recommendations from their PCPs—as is observed for patients of visible minorities or lower socioeconomic status in Canada.[40] Recent immigrants to Canada have also reported gaps in the cultural competency of health care providers, specifically with regards to cultural understandings of health and health care,[41] and to language and communication.[42] These limitations of the Canadian health care system, in conjunction with general logistic and psychological barriers to colorectal cancer screening (such as unreachable or inadequate resources, lower social support, fear, embarrassment or anxiety of the test, its required preparation—especially for endoscopic procedures—or of its result[43]) may explain why simply having a regular PCP may not be sufficient to ensure screening uptake. We recommend that future studies explore alternative areas of intervention to both reduce these inequalities and increase screening uptake overall.

The implication of these findings is that improving individuals' access to regular PCPs may improve screening participation overall (namely through large gains among Canadian-born individuals) but fail to reduce screening disparities according to recent immigration. We recommend that future studies explore alternative areas of intervention to both reduce these inequalities and increase screening uptake overall.

These findings are bound by certain limitations. First, the broad categories of white versus visible minority immigrants may obscure sub-group heterogeneity in the associations measured, as has been observed in previous studies [44]. These findings should therefore be interpreted as the average mediating role of PCPs in white and visible minority immigrants. Similarly, the variable of "exposure to an organised mail-based screening program" did not account for potential heterogeneity in program effects across time, including lagged programs effects. Associations for the latter variable must therefore be interpreted as the average effect of exposure to an organised mail-based screening program across time. Second, the cross-sectional data used required additional assumptions of the temporal ordering of associations between recent immigration, access to PCPs, screening, and other social factors. We assumed it unlikely

that having access to Canadian physicians would occur before immigration to Canada. However, the temporal ordering of physician access and screening experience may be more ambiguous. Further, certain other factors in the study, such as income, are likely time-dependent [45], and could be treated as such in future analyses. Replication of these analyses using longitudinal data will likely be beneficial. Third, although we stated effect estimates in the causal language used in epidemiologic research, the validity of these assertions relies on the satisfaction of the causal assumptions underpinning each method. [24] Sensitivity analyses suggest that some residual confounding is likely present. Among the unmeasured factors in this study (and indeed, in the CCHS) are concordance of individuals' and PCPs' gender identity or economic, linguistic, ethnic, or cultural background [46, 47]. Future mediation studies may benefit from incorporating the latter measures, as well as exploring downstream mediators such as knowledge and cultural beliefs around cancer or cancer prevention, and the frequency or recency of PCP visits. Fourth, as no sampling weights were used in this study, the findings of this study are representative of the CCHS sample but may be less representative of the entire Canadian population. Given that extant studies using weighted CCHS sample aged 50 to 75 years report higher prevalence of having never been screened than the prevalence observed in this study (i.e. 53% never screened compared to the 47% reported here [48]), it may be that the unweighted sample of this study is a population that is slightly more likely to be screened compared to the true Canadian average. Lastly, since self-reported screening data tend to over-estimate recent screening (i.e. previous two year fecal occult blood test (FOBT) sensitivity is 77.4% and specificity is 89.8%), [49] and studies at other cancer sites have observed differential self-reported screening according to racial and ethnic subpopulations,[49] it is possible that the screening gaps between immigrants and non-immigrants observed in this study may be underestimated.

5.6 CONCLUSION

In sum, almost half of adults aged 50 to 75 years in Canada have never been screened for colorectal cancer, and the prevalence of having never been screened is even higher for recent immigrants. Interventions to promote screening for all are therefore needed. This study suggests

that increasing all individuals' access to regular PCPs may increase screening overall, but not eliminate immigration-based disparities in colorectal cancer screening. Other levers will be necessary to decrease these inequalities.

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5.9 SUPPLEMENTARY MATERIALS

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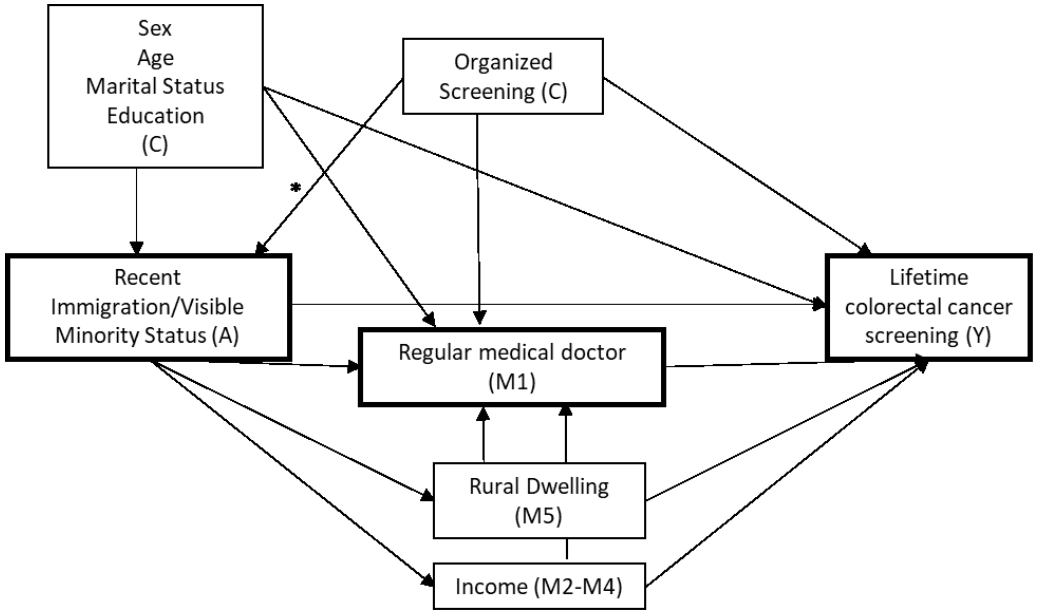
eMethods 1: Theory and conceptual framework

Described in the study's directed acyclic graph (DAG) (Figure 1) are the assumed associations between the exposure (recent immigration– stratified by visible minority status), the mediator (having access to a primary care physician), the outcome (lifetime colorectal cancer screening), covariates (sex, age, marital status, education, exposure to an organised mail-based screening program) and other potential mediators (living in rural areas, and income).



*** The arrow from exposure to an organized screening program to recent immigration (A) reflects the assumptions that 1) recent immigration entails a set of experiences, some of which are mutable and can vary according to the country of arrival's integration policies, and 2) organized screening programs (which represent a provincial investment in health promotion and health service accessibility—or least, the promotion of service and screening awareness) could shape recent immigrants' experiences in navigating a new health system.**

Figure 1: Directed Acyclic Graph (DAG) of the assumed direction of associations between study measures. One-way arrows indicate assumed direction of associations between the exposure of the study (A, recent immigration/visible minority status), the principal mediator (M1, access to a primary care physician), the outcome (Y, lifetime colorectal cancer screening), other assumed mediators (M2-M5) and covariates (C).

The assumed direction of these associations is informed by Intersectional Theory,[i] the Social Determinants of Health framework,[ii] Andersen[iii] and Gelberg's[iv] Health Services Behavioral Models, and Ager and Strang's Core Domains of [Immigrant] Integration framework.[v] These theories and frameworks suggest that screening is a socially-patterned behaviour. They also suggest that recent immigration entails a set of experiences, some of which are mutable and vary according to the country of arrival's integration policies. Here, integration is defined according to the degree of a country's social, structural, and institutional openness to immigrants.[vi]

Assumed mediators explained

Despite the numerous strengths of the Canadian integration system,[vii] immigrants are often disproportionately burdened by discrimination,[viii] stressors such as inadequate housing and precarious employment, and barriers to health care.[ix] This is why factors such as access to a primary care physician (M1), and income (M2-M4) are placed downstream from recent immigration. The third mediator, area of residence (rural vs. urban) (M5) is also considered to be downstream from recent immigration insofar as most recent immigrants settle in cities

Assumed confounding covariates explained

Sex, age, marital status, and education are all considered potential confounding factors in the associations between immigration, physician access, and screening. These factors are

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[i] Bauer GR. Incorporating intersectionality theory into population health research methodology: Challenges and the potential to advance health equity. *Soc Sci & Med* 2014;110:10-17.
[ii] Solar O, Irwin A. A conceptual framework for action on the social determinants of health. 2007.
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[iv] Gelberg L, Andersen RM, Leake BD. The Behavioral Model for Vulnerable Populations: application to medical care use and outcomes for homeless people. *Health services research*. 2000; 34(6):1273.
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[vii] Dewing M. Canadian Multiculturalism. Ottawa, Canada: Social Affairs Division, Government of Canada;2009.
[viii] De Maio FG, Kemp E. The deterioration of health status among immigrants to Canada. *Global P Health*. 2010;5(5):462-478.
[ix] Guruge S, Birpreet B, Samuels-Dennis JA. Health Status and Health Determinants of Older Immigrant Women in Canada: A Scoping Review. *J Aging research*. 2015:393761.

believed to precede immigration status insofar as they are often criteria upon which permission to enter the country is granted. They are also documented predictors of screening uptake.[x]

Further, exposure to an organised mail-based screening program is also believed to be a potential confounding factor of the latter relationships, insofar as these programs represent provincial investments in health promotion and health service awareness and accessibility. We hypothesize that these forms of investments may affect immigrants' experience in navigating their new health system, and therefore their potential integration in Canadian society (i.e. it affects what it means to be exposed to the experience of recent immigration).

[x] **References**: Sewitch MJ, Fournier C, Ciampi A, Dyachenko A. Adherence to colorectal cancer screening guidelines in Canada. BMC gastroenterology. 2007; 7:39; Vernon SW. Participation in Colorectal Cancer Screening: A Review. *J National Cancer Institute*. 1997;89(19):1406-1422; Natale-Pereira A, Marks J, Vega M, Mouzon D, Hudson SV, Salas-Lopez D. Barriers and facilitators for colorectal cancer screening practices in the Latino community: perspectives from community leaders. *Cancer control*. 2008;15(2):157-165.; Ramji F, Cotterchio M, Manno M, Rabeneck L, Gallinger S. Association between subject factors and colorectal cancer screening participation in Ontario, Canada. *Cancer detection and prevention*. 2005;29(3):221-226.; Crouse A, Sadrzadeh SM, de Koning L, Naugler C. Sociodemographic correlates of fecal immunotesting for colorectal cancer screening. *Clinical biochemistry*. 2015;48(3):105-109; von Euler-Chelpin M, Brasso K, Lynge E. Determinants of participation in colorectal cancer screening with faecal occult blood testing. *J Public Health*, 2009; Wools A, Dapper EA, Leeuw JR. Colorectal cancer screening participation: a systematic review. *Eur J public health*. 2015; Almadi MA, Mosli MH, Bohlega MS, et al. Effect of public knowledge, attitudes, and behavior on willingness to undergo colorectal cancer screening using the health belief model. *Saudi journal of gastroenterology*. 2015;21(2):71-77.

eMethods 2: Inverse probability weight estimation

Below is a description of how inverse probability weights are estimated for two distinct methods of mediation analysis: 1) an Inverse probability weighting (IPW) Marginal Structural Model approach; and 2) Inverse probability weighted (IPW) Average Marginal Effect approach

Inverse probability weighting (IPW) Marginal Structural Model approach [Method 2]

In this approach, four prediction models are specified: an empty (intercept only) model for exposure A [Model 1]; a model for A that includes all covariates C [Model 2]; a model for mediator M1 with exposure A [Model 3]; and a model for the mediator M1 that includes the exposure A, the covariates, and other mediators [Model 4]. Inverse probability weights are estimated for each respondent by diving the propensity scores obtained using Model 1 by propensity scores obtained using Model 2 [Weight for A]; and by diving the propensity scores obtained using Model 3 by propensity scores obtained using Model 4 [Weight for M1]. For CDE estimation, weights for A and weights for M1 are multiplied to form a summary weight [Summary weight for A and M1]. For TE estimation, solely weights for A are used.

Inverse probability weighted (IPW) Average Marginal Effect approach [Method 3]

In this method, two prediction models are specified: a model for A that includes all covariates C [Model 1], and a model for M1 that includes the exposure A, all other mediators (M2-M5), and covariates [Model 2]. Propensity scores for A=1 are estimated for each respondent using Model 1 (p_A1). These propensity scores were truncated at the 10^{th} percentile to limit violation of the assumption of practical positivity, since many score values approached zero. Propensity scores for M1=1 are estimated (p_M1) for recent immigrants (A=1) using Model 2 (scores M1A1). Propensity scores for M1=1 are also estimated for Canadian-born respondents (A=0) (scores M1A0). These propensity scores (scores A1, A0, M1A1, M1A0) are then used to estimate inverse probability weights. For CDE estimation, recent immigrants (A=1) with a primary care physician (M1=1) are given weights that represent the inverse of the product between scores for A1 and scores M1A1 [1/(A1*M1A1)]; Canadian-born respondents (A=0) with a physician (M1=1) are given weights that represent the inverse of the product between scores for A0 and scores M1A0 [1/(A0*M1A0)]. For TE estimation, inverse probability weights for A=1 are used.

Supplementary Tables

eTable 1 Estimate of the maximum size of an unmeasured factor's association with the mediator and the outcome to be for the true controlled direct estimates to be null (PR=1) despite non-null estimates or to be equivalent or smaller than the observed TE (PR=1.51), among visible minority recent immigrants and White Canadian-born respondents. Observed CDE estimates were yielded via inverse probability weighting and 500 bootstrap replications in the Canadian Community Health Survey 2003-2014

Expected CDE if observed smallest CDE (PR = 1.56) divided by bounding formula *((γ λ) / (γ + λ – 1))* [a]

						γ						
λ	**1.01**	**1.05**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**2**	**2.5**	**3**	**4**	**5**
1.01	1.56	1.56	1.56	1.56	1.56	1.56	1.55	1.55	1.55	1.55	1.55	1.55
1.05	1.56	1.56	1.55	1.55	1.54	1.54	1.54	1.52	1.52	1.51	1.50	1.50
1.1	1.56	1.55	1.55	1.54	1.53	1.52	1.51	1.49	1.47	1.47	1.45	1.45
1.2	1.56	1.55	1.54	1.52	1.50	1.49	1.47	1.43	1.40	1.39	1.37	1.35
1.3	1.56	1.54	1.53	1.50	1.48	1.46	1.44	1.38	1.34	1.32	1.29	1.27
1.4	1.56	1.54	1.52	1.49	1.46	1.43	1.41	1.34	1.29	1.26	1.23	1.20
1.5	1.55	1.54	1.51	1.47	1.44	1.41	1.39	1.30	1.25	1.21	1.17	1.14
2	1.55	1.52	1.49	1.43	1.38	1.34	1.30	1.17	1.09	1.04	0.98	0.94
2.5	1.55	1.52	1.47	1.40	1.34	1.29	1.25	1.09	1.00	0.94	0.86	0.81
3	1.55	1.51	1.47	1.39	1.32	1.26	1.21	1.04	0.94	0.87	0.78	0.73
4	1.55	1.50	1.45	1.37	1.29	1.23	1.17	0.98	0.86	0.78	0.68	0.62
5	1.55	1.50	1.45	1.35	1.27	1.20	1.14	0.94	0.81	0.73	0.62	0.56

[a] Formula described in: VanderWeele, T.J., 2016. Mediation Analysis: A Practitioner's Guide. Annual Review of Public Health 37:17-32; where γ denotes the maximum risk ratio relating an unmeasured factor with the outcome among the exposed subjects across strata of the mediator, conditional on covariates, and λ denotes the maximum risk ratio relating an unmeasured factor and the exposure across different conditional levels of the mediator (combinations of λ and γ that would indicate true effects to be null; PR=1—smallest combination encircled)

eTable 2 Estimate of the maximum size of an unmeasured[a] factor's association with the mediator and the outcome to be for the true controlled direct estimates to be null (PR=1) despite non-null estimates or to be smaller than the observed TE (PR=1.24), among White recent immigrants and White Canadian-born respondents. Observed CDE estimates were yielded via inverse probability weighting and 500 bootstrap replications in the Canadian Community Health Survey 2003-2014

Expected CDE if observed smallest CDE (PR = 1.24) divided by bounding formula *((γ λ) / (γ + λ – 1))* [a]													
							γ						
λ	**1.01**	**1.05**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.8**	**2**	**2.5**	**3**	**4**	**5**
1.01	1.24	1.24	1.24	1.24	1.24	1.24	1.24	1.23	1.23	1.23	1.23	1.23	1.23
1.05	1.24	1.24	1.23	1.23	1.23	1.22	1.22	1.21	1.21	1.20	1.20	1.20	1.19
1.1	1.24	1.23	1.23	1.22	1.21	1.21	1.20	1.19	1.18	1.17	1.16	1.16	1.15
1.2	1.24	1.23	1.22	1.21	1.19	1.18	1.17	1.15	1.14	1.12	1.10	1.09	1.07
1.3	1.24	1.23	1.21	1.19	1.17	1.16	1.14	1.11	1.10	1.07	1.05	1.03	1.01
1.4	1.24	1.22	1.21	1.18	1.16	1.14	1.12	1.08	1.06	1.03	1.00	0.97	0.96
1.5	1.24	1.22	1.20	1.17	1.14	1.12	1.10	1.06	1.03	0.99	0.96	0.93	0.91
1.8	1.23	1.21	1.19	1.15	1.11	1.08	1.06	1.00	0.96	0.91	0.87	0.83	0.80
2	1.23	1.21	1.18	1.14	1.10	1.06	1.03	0.96	0.93	0.87	0.83	0.78	0.74
2.5	1.23	1.20	1.17	1.12	1.07	1.03	0.99	0.91	0.87	0.79	0.74	0.68	0.64
3	1.23	1.20	1.16	1.10	1.05	1.00	0.96	0.87	0.83	0.74	0.69	0.62	0.58
4	1.23	1.20	1.16	1.09	1.03	0.97	0.93	0.83	0.78	0.68	0.62	0.54	0.50
5	1.23	1.19	1.15	1.07	1.01	0.96	0.91	0.80	0.74	0.64	0.58	0.50	0.45

[a] Formula described in: VanderWeele, T.J., 2016. Mediation Analysis: A Practitioner's Guide. Annual Review of Public Health 37:17-32; where γ denotes the maximum risk ratio relating an unmeasured factor with the outcome among the exposed subjects across strata of the mediator, conditional on covariates, and λ denotes the maximum risk ratio relating an unmeasured factor and the exposure across different conditional levels of the mediator (combinations of λ and γ that would indicate true effects to be null; PR=1—smallest combination encircled).

eTable 3: Propensity scores and inverse probability weights estimated for the inverse probability weighting (IPW) Marginal Structural Model approach (Method 2)

		Visible minority recent immigrants vs. White Canadian-born	**White recent immigrants vs. White Canadian-born**	
Model description	**Strata**	**Predicted probability (propensity score)** Minimum, Mean, Maximum		
Model for A=1 ~ 1	A=0	0.01	0.004	
Model for A=1 ~ 1	A=1	0.01	0.004	
Model for A=1| c_i	A=0	0.002, 0.01, 0.01	0.0004, 0.004, 0.01	
Model for A=1| c_i	A=1	0.002, 0.01, 0.01	0.001, 0.005, 0.01	
Model for M=1 ~ a	M1=0	0.88, 0.91, 0.91	0.79, 0.91, 0.91	
Model for M=1 ~ a	M1=1	0.88, 0.91, 0.91	0.79, 0.91, 0.91	
Model for M=1| a, c_i , m_i	M1=0	0.67, 0.89, 0.96	0.47, 0.89, 0.96	
Model for M=1| a, c_i , m_i	M1=1	0.67, 0.91, 0.96	0.50, 0.91, 0.96	
Weights	**Strata**	**Inverse probability weight** Minimum, Mean, Maximum		**Estimated effect**
Weight for A=1	A=0	0.45, 1.27, 3.62	0.50, 1.72, 9.52	TE, CDE
Weight for A=1	A=1	0.45, 1.01, 3.62	0.50, 0.94, 4.85	TE, CDE
Weight for M1=1	M1=0	0.92, 1.03, 1.31	0.88, 1.03, 1.68	CDE
Weight for M1=1	M1=1	0.92, 1.00, 1.31	0.88, 1.00, 1.58	CDE
Summary weight (Weight for A=1 * Weight for M1=1)	A=0	0.46, 1.28, 3.78	0.48, 1.75, 10.98	CDE
Summary weight (Weight for A=1 * Weight for M1=1)	A=1	0.46, 1.01, 3.76	0.46, 1.00, 4.65	CDE
Summary weight (Weight for A=1 * Weight for M1=1)	M1=0	0.46, 1.33, 3.78	0.47, 2.00, 10.98	CDE
Summary weight (Weight for A=1 * Weight for M1=1)	M1=1	0.46, 1.27, 3.78	0.47, 2.00, 10.98	CDE

eTable 4: Propensity scores and inverse probability weights estimated for the inverse probability weighted (IPW) Average Marginal Effect approach (Method 3)

		Visible minority recent immigrants vs. White Canadian-born	**White recent immigrants vs. White Canadian-born**	
Model description	**Strata**	**Predicted probability (propensity score)** Minimum, Mean, Maximum		
Model for A=1| c_i	A=0	0.003, 0.006, 0.01	0.001, 0.004, 0.01	
Model for A=1| c_i	A=1	0.003, 0.008, 0.01	0.001, 0.005, 0.01	
Model for M=1| a, c_i , m_i	M1=0	0.61, 0.91, 0.96	0.44, 0.74, 0.90	
Model for M=1| a, c_i , m_i	M1=1	0.61, 0.84, 0.95	0.44, 0.78, 0.90	
Weights	**Strata**	**Inverse probability weight** Minimum, Mean, Maximum		**Estimated effect**
Weight for A=1	A=0	71.12, 154.7, 347.1	125.9, 244.5, 957.8	TE
Weight for A=1	A=1	71.12, 192.6, 347.1	125.9, 385.8, 957.8	TE
Summary weight (Weight for A=1 * Weight for M1=1)	A=0, M1=1	1.04, 1.11, 1.45	1.04, 1.10, 1.45	CDE
Summary weight (Weight for A=1 * Weight for M1=1)	A=1, M1=1	82.5, 1.76, 437	146.8, 506.6, 1314	CDE

eTable 5: Estimated total effect of recent immigration (exposure) on lifetime screening, and controlled direct effect when access to a primary care physician (mediator) is held fixed, and stratified by visible minority status (n=659 visible minority, n=408 white), with white Canadian-born respondents (n=102,366) as reference category, in the Canadian Community Health Survey 2003-2014 – not accounting for and accounting for potential effect measure modification by exposure to an organised mail-based screening program, using a generalized product method approach[a]

Population Strata	Approach	**Total Effect (TE)** PR (95% CI)	**Controlled Direct Effect (CDE)** PR (95% CI)	**Proportion Eliminated (PE)** $(PR^{TE} - PR^{CDE}) / (PR^{TE} - 1)$ % (95% CI)
Visible minority recent immigrants vs. White Canadian-born	**Without** accounting for potential effect measure modification by exposure to an organised mail-based screening program	1.51 (1.28, 1.65)	1.56 (1.48, 1.63)	-9% (-15%, -4%)
	Accounting for potential effect measure modification by exposure to an organised mail-based screening program[b]	1.41 (1.34, 1.47)	1.46 (1.38, 1.54)	-14% (-21%, -8%)
	Without accounting for potential effect measure modification by exposure to an organised screening program	1.24 (1.08, 1.40)	1.24 (1.12, 1.35)	-2% (-29%, 24%)
	Accounting for potential effect measure modification by exposure to an organised mail-based screening program[b]	1.13 (1.02, 1.23)	1.15 (1.03, 1.29)	-16% (-123%, 51%)

NOTE: PR= Prevalence Ratio.

[a] The generalized product method, proposed by VanderWeele and Vansteelandt (2009), extends Baron and Kenny's (1986) product method to allow for effect estimation in the presence of exposure-mediator interaction.

[b] Effect measure modification was estimated using product terms between immigration experience, access to a primary care physician, and exposure to a mail-out based provincial organised screening program.

CHAPTER 6: MANUSCRIPT 3

Impact of organized colorectal cancer screening programs on screening and screening inequalities: A study of systematic- and patient-reliant programs in Canada

Impact of organized colorectal cancer screening programs on screening and screening inequalities: A study of systematic- and patient-reliant programs in Canada

Running Title:
Evaluation of organised screening programs

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Alexandra Blair conceptualised the manuscript, conducted the data analysis, wrote the first draft of the manuscript and integrated co-authors comments in subsequent versions.

Lise Gauvin contributed to the conceptualisation of the manuscript, and to writing and reviewing the manuscript.

Erin Strumpf contributed to the conceptualisation of the study and the reviewing of the manuscript.

Geetanjali D. Datta contributed to the conceptualisation of the manuscript and data analysis, and to the writing and reviewing of the manuscript.

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Conflict of interest: None to declare

Keywords: Colorectal cancer, Screening, FOBT, FIT, Endoscopy, Social Determinants of Health, Health Inequalities, Policy Evaluation, Quasi-experimental Design, Adults, Canada.

Abbreviations: CAD, Canadian dollars; CCHS, Canadian Community Health Survey; CI, Confidence Interval; CRC, colorectal cancer; DD, Difference-in-Differences, DDD, Difference-in-Differences-in-Differences; FIT, fecal immunochemical test; FOBT, fecal occult blood test; IPW, Inverse probability weight; NB, New Brunswick; NFLD, Newfoundland; NS, Nova Scotia; PD, prevalence difference; PEI, Prince Edward Island; PR, prevalence ratio; SASK, Saskatchewan.

Counts

Abstract: 302 words

Main text, including tables and figures: 4543 words

Tables: 1

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Supplementary materials: 3 eFigures, 5 eTables

6.1 ABSTRACT

Background: Varying organized colorectal cancer screening programs have been implemented in selected Canadian provinces but have yet to be evaluated.

Objective: We examined the effects of patient-reliant and systematic organised colorectal cancer screening programs on colorectal cancer screening uptake and on screening inequalities by income, education, rural residence, and access to a primary care physician.

Methods: Lifetime and recent (< 1, <2 years) stool-based and recent endoscopic (<5 years) screening were assessed among Canadian Community Health Survey respondents (cycles 2003-2014), aged 50-75 years, with no family history or symptoms of colorectal cancer. We used Poisson regression and Difference-in-Differences models to estimate the effects of Saskatchewan and Nova Scotia's systematic programs (where all age-eligible residents receive screening kits via mail), and of Prince Edward Island's patient-reliant program (where respondents receive screening kits via mail following their request to a physician, phoneline or website), with New Brunswick and Newfoundland as comparison populations.

Results: Overall, systematic and patient-reliant programs were associated with a 4- [95% CI: 1%, 7%] and a 12-percentage point [95% CI: 2%, 8%] increase in recent (<2 years) stool-based screening, respectively. By the third-year post-implementation, both program types were associated with an approximate 10% increase in recent stool-based screening. Systematic programs did not appear to affect endoscopic screening, or stool-based screening disparities. The patient-reliant program was associated with no significant effect on recent stool-based screening among those who did not have a physician, and an 11% [95% 5%, 17%] increase in uptake among those with a physician—leading to an increased inequality in uptake according to physician access.

Interpretation: Both program types increase screening overall, with similar effect sizes observed by the third-year post-implementation. However, those that rely on patients' screening request may increase disparities according to physician access. Evaluation of potential complementary targeted interventions in patient-reliant settings appears warranted.

6.2 BACKGROUND

As in several other developed nations, (1, 2) organised screening programs have been implemented in nine of Canada's ten provinces. These programs are designed to promote regular stool-based screening for colorectal cancer, Canada's third most common cause of cancer death.(3) Stool-based screening every two years is recommended for adults aged 50 to 74 years to identify early signs of polyp growth and reduce the risk of colorectal cancer mortality.(4-7) Organised colorectal cancer screening programs are designed to increase awareness, access, and uptake of stool-based screening tests (e.g., Fecal Occult Blood Tests (FOBT), or Fecal Immunochemical Test (FIT))—especially given the many known risk factors for low colorectal cancer screening participation). Documented risk factors include lack of knowledge of where or how to access screening services, (7) lack of discretionary time, (8-10) fear, embarrassment or anxiety towards the test, its required preparation or its result ,(8)not having completed a high school diploma, (11) having lower income, (12-14) living in rural or remote settings,(15, 16) and not having a primary care physician.(12, 13, 16-18)

Canadian organised colorectal cancer screening programs can be categorised in relation to their level of reliance on potential participants' initiative in registering for the program and accessing and returning screening kits. Some programs send out invitation letters systematically to all adults aged 50 to 74 years and allow screening kits to be accessed and returned via mail using pre-paid postage. (19, 20) These can be referred to as "systematic" mail-based programs. Other programs are more "patient-reliant" insofar as they can require participants to request screening kits, or to return kits in person to designated facilities. (19) The effectiveness of various types of screening programs in promoting screening uptake remains under-studied in Canada. Only organised screening programs in Ontario (where invitations letters are mailed to age-eligible adults, and screening kits can be requested and returned via mail) and in Manitoba (where screening kits are mailed to all age-eligible adults and can be returned via mail) have been assessed. (21, 22) Both showed promising results with screening participation increased by respectively 6-percentage points (16% to 22% from 2003 to 2009) and 14-percentage points (43% to 57%, from 2007 to 2012) across Ontario and in Manitoba's capital city Winnipeg,

respectively. (21, 22) Programs in other provinces have yet to be assessed using rigorous evaluation methods.

Further, no study has assessed how screening programs that vary according to their reliance on patient initiative potentially differ in their effects on social inequalities in screening.(7, 12-16, 23) Between 2001 and 2008, observed screening disparities in Canada include an 50% difference in recent stool-based screening between men with and without a high school diploma, and between those who did and did not receive a screening recommendation from a primary care physician,(18) as well as an 18% difference in lifetime stool-based screening between low and high income groups, and a 4% difference in recent stool-based screening between those living in urban and rural areas.(24) Patient-reliant and systematic screening programs may lead to decreases, increases, or no change in inequalities (25-28) according to these markers of social stratification.

This study aimed to assess how "systematic" mail-based and more "patient-reliant" screening programs affect 1) average, population-level lifetime and non-recent stool-based screening, as well as 2) screening inequalities according to individual-level income, education, access to a primary care physician, and rural residence. This study examined systematic mail-based screening programs in the provinces of Saskatchewan and Nova Scotia (both initiated in 2009)—where screening kits are mailed to all age-eligible adults and can be returned via mail—and the more "patient-reliant" screening program in the province of Prince Edward Island (PEI) (initiated in 2011)—where residents register for the program through their physician, the designated phone line or website, after which they can receive a screening kit in person or via mail, and return screening kits in-person to designated facilities. (19) The latter program will hereafter be referred to as the "patient-reliant" program, where as the former programs will be referred to as the "systematic" screening program. Provincial populations of New Brunswick and Newfoundland were utilised as comparison groups. Though provinces of British Columbia and Alberta also implemented programs in this study's time frame, data were not available for inclusion in analyses.

6.3 METHODS

6.3.1 Data and Target Population

Data from years 2003 to 2014 of the Canadian Community Health Study (CCHS) were used. CCHS response rates ranged from 80.7% in 2003,(29) to 65.6% in 2014.(30) Excluded from the CCHS' sampling frame are persons living on First Nations reserves, full-time members of the Canadian Forces, and those living in institutions in Nunavik and in the Cree Territory of James Bay.(31) The CCHS sample covers 97% of the Canadian population recorded in the Canadian Census.(31) The study's target population was adults aged 50 to 75 years, with available information on colorectal cancer screening and no family history or current symptoms of colorectal cancer (i.e. who were considered to be at "average risk" of colorectal cancer).(4) Excluded from this study were participants who reported screening due to "family history of colorectal cancer," "follow-up of a problem," and "follow-up of colorectal cancer treatment."(32)

6.3.2 Design

To examine the impact of provincial screening programs, the Difference-in-Differences (DiD) method was applied. (33) In this framework, changes in screening outcomes in the intervention provinces can be compared to those of provinces without organized screening programs ("comparison" provinces). Time-invariant differences between the two groups, both observed and unobserved, are controlled for, as are temporal trends in the outcome shared by both groups. If pre-intervention screening trends between intervention and comparison provinces are parallel and the timing of implementation of the interventions are not the result of pre-intervention outcomes, any differential changes in screening outcomes between the two populations before versus after the intervention are considered attributable to program implementation (as illustrated in the Supplement's eFigure 1). (21, 34) The application of DiD here relies on the key assumption that, conditional on measured confounders, time-invariant differences between the groups, and shared temporal trends in the outcome, the specific location and timing of these interventions are "as good as random". In other words, the change in

outcomes in the control group is a valid counterfactual for the treatment group and no other changes that would affect the two groups differently occur around the same time as the intervention. (34,35,36, 37) The operationalized measures and models for DiD analysis are described below.

6.3.3 Measures

Outcome measures

CCHS respondents were asked if they had ever received a FOBT, a colonoscopy, or sigmoidoscopy in their lifetime, and if so, when. The primary outcome studied was stool-based screening in the previous two years (versus over two years or never). Two alternative screening outcome categorizations were used across which to assess the stability of program effects. First, we applied the outcome of lifetime stool-based screening (ever versus never). Applying the latter measure, we expect to see more conservative program effects, insofar as changes in the prevalence lifetime screening requires screening uptake among individuals who have never been screened. Second, we used a measure of stool-based screening in the previous year (versus over one year or never). Using a variable of screening in the previous year ensured that respondents in the year of, or year following program implementation, were not reporting screening that occurred before program implementation.

To complement analyses on stool-based screening, we also assessed the outcomes of lifetime and recent (>5 years) endoscopic screening. Though programs were not designed to influence endoscopic screening participation, it is plausible that their uptake may be affected.

Exposure measures

Respondents' exposure to a screening program depended on their province of residence and the CCHS cycle to which they participated. The provinces that were considered to have received the "intervention" of an organised screening program were Saskatchewan (N=6,589), Nova Scotia (N=4,662), Prince Edward Island (N=3,116). The intervention year was 2009 for the

first two provinces, and 2011 for Prince Edward Island. Respondents from New Brunswick (N=5,515) and Newfoundland (N=4,065) were selected as the comparison group for the assessment of programs in Saskatchewan and Nova Scotia, and respondents from New Brunswick were selected as the comparison group for the evaluation of Prince Edward Island's program. These comparison groups were chosen for having both data availability for pre- and post-intervention periods (38) (Supplement's eTable 1) and pre-intervention screening trends that were parallel to those in the intervention groups (Supplement's eFigure 2, eFigure 3). (34)

Covariates

Covariates included were sex, age (50-59 years or 60-75 years), marital status (single, or divorced, widowed, or separated, or married or in a common-law relationship), educational attainment (less than high school graduation or high school graduation and above, including college attendance), access to a primary care physician (yes or no), rural residence (yes or no), and household income. Household income was separated into four income categories (less than 30,000 CAD, 30,000-50,000 CAD, 50,000-80,000 CAD, 80,000 CAD and above). Since missing income data were not imputed in the CCHS before 2005, income for CCHS 2003 was imputed based on individuals' age, sex, education, marital status, immigration status, and sampling weight, using hot deck imputation in Stata 14. (39)

Markers of social stratification

Social inequalities in screening were measured according to four markers of social stratification: rural residence, not having a primary care physician, not having received a high school diploma, and earning less than 30,000 CAD (versus 30,000 CAD and above).

6.3.4 Analysis

First, descriptive analyses of the pre-intervention characteristics of intervention and comparison groups were performed using chi-squared statistics. To test the validity of the pre-intervention parallel trends assumption, pre-intervention screening prevalence trend lines in

intervention and comparison populations were first visually inspected. Analyses of trends were then performed using Poisson regression models adjusted for year, intervention group, and the product of both terms (*year*intervention*). Analyses were repeated for colorectal cancer screening outcomes.

Second, the DiD framework was applied via five multivariate Poisson regression models, weighted using the CCHS' sampling weights. Model [1] was adjusted for the indicator variables for the intervention group (*intervention*), post-intervention period (*post*), the product between both terms, and covariates. Models [2] to [5] were each specified with additional indicator variables for the product terms between the marker of social stratification (*sstrata*), intervention group, and post-intervention period to account for effect measure modification (EMM) across social strata (33):

$$\text{(DiD) } Y_i = \theta_0 + \theta_1(\textit{intervention})_i + \theta_2(\textit{post})_i + \theta_3(\textit{intervention*post})_i + \theta'(\textit{covariates})_i \quad [1]$$

$$\text{(DiD with EMM) } Y_i = \beta_0 + \beta_1(\textit{intervention})_i + \beta_2(\textit{post})_i + \beta_3(\textit{intervention*post})_i + \beta_4(\textit{sstrata})_i + \beta_5(\textit{sstrata * intervention})_i + \beta_6(\textit{sstrata *post})_i + \beta_7(\textit{sstrata * intervention*post})_i + \beta'(\textit{covariates})_i \quad [2\text{-}5]$$

Using predicted probabilities from these Poisson models (using Stata's *margins* command), we estimated adjusted prevalence risk differences (PD). From these models, θ3 indicates the overall effect of the program, and β7 indicates the effect of the program on the measured inequality. Analyses were repeated for each outcome and intervention group, and 95% confidence intervals were estimated using 500 bootstrap replications. Analyses were performed using Stata, version 14. (39) Additionally, sensitivity analyses of statistically significant effect estimates were conducted to account for potential auto-correlation within provinces that may lead to an underestimation of the variance of program effects. These DiD analyses were performed using generalized estimating equation (GEE) identity-link Poisson models, with exchangeable covariance structure assumed for respondents living within the same province. Given the significant computational time required, the numerous models assessed, and the knowledge that these calculations would serve only to widen observed confidence intervals, we did not conduct these analyses for estimates that were not found to be significant in the main models. These models were applied in SAS 9.4. (40)

Sensitivity analyses

In addition to the main analyses, we performed two sensitivity analyses. First, to assess whether any observed effect could be due to chance or other driving factors, (41, 42) we performed pre-intervention parallel trend analyses as well as DiD analyses with the "falsification" outcome of reported influenza vaccination in the previous year (yes or no). A non-null association between program implementation and vaccination could indicate that observed changes in screening may be due to other systematic changes in health care services delivery and utilization in Canada.(21) Second, since effects of the programs on screening uptake may be detectable only several years after program implementation, an overall average "post-period" effect estimate will may be biased downward. We applied DiD models with indicator variables for two post-intervention periods (1 to 2 years, and 3 to 4 years post-intervention).

6.4 RESULTS

6.4.1 Pre-intervention sample characteristics

Systematic screening provinces

Pre-intervention, residents of the intervention provinces (Nova Scotia, Saskatchewan) were more likely to have a partner, live in rural areas, report higher income, and have completed a high school diploma, than respondents of the comparison provinces (New Brunswick, Newfoundland) (Table 1). DiD models were adjusted for these factors, however, to ensure unbiased effect estimates. Nova Scotia reported similar stool-based screening as the comparison group, whereas residents of Saskatchewan were slightly more likely to be screened recently (Table 1). Nonetheless, overall pre-intervention trends in lifetime, past year- and past two-year stool-based screening were parallel ($p<0.05$) between intervention and comparison provinces (eFigure 2) (difference in previous two-year screening slopes PD=0.0, 95% CI: -0.02, 0.01). Lastly, pre-intervention social inequalities in stool-based screening were small or null, save for a

13% difference in prevalence of recent (<2 year) stool screening between those with and without a physician in Saskatchewan (18% versus 5% screened, respectively) (eTable 2).

Patient-reliant screening province

Pre-intervention, residents in the intervention province (PEI) were less likely to have completed a high school diploma or have access to a physician than residents in the comparison province (New Brunswick) (Table 1). PEI residents reported less stool-based screening in the previous one and two years, whereas lifetime stool-based screening was similar in both groups. Overall, pre-intervention trends in lifetime and recent (<1, <2 years) stool-based screening between the two groups were parallel (eFigure 3) (difference in previous two-year screening slopes PD=0.0, 95% CI: -0.01, 0.01). Pre-intervention social inequalities in stool-based screening were again small or null, save for an 11% difference in prevalence of previous two-years stool-based screening between those with and without a physician in PEI (22% and 11% screened, respectively), and 9% difference between these two groups in the comparison provinces (14% and 5% screened, respectively) (eTable 3).

6.4.2 Program effects

Systematic screening programs

With regards to stool-based screening, systematic screening programs were associated with a 4-percentage point increase in recent (< 2 years) stool-based screening (95% CI: 1%, 7%) (Figure 1). Program effects varied over time, with no statistically significant effect in the first two years (2009-2010; PD=1%, 95% CI: -2%, 5%), and an 11% increase by the third- and fourth-years post-intervention (2011-2012; 95% CI: 4%, 14%) post-intervention (Figure 3). The overall increase of recent stool-based screening was of 3- and 5-percentage points in Saskatchewan and Nova Scotia, respectively (eTable 4, eTable 5). When pooled, systematic screening programs did not appear to affect any of the stool-based screening inequalities (Figure 1). When stratified, however, Saskatchewan's program was associated with a reduced disparity

in lifetime and recent (<2 year) stool-based according to physician access, and a reduced disparity in recent screening according to educational attainment (eTable 4).

With regards to endoscopic screening, both Saskatchewan and Nova Scotia's programs did not appear to impact overall lifetime or recent (≤ 5 years) screening (Figure 1). However, these pooled systematic screening programs were associated with an increase in recent (<5 years) endoscopic screening among those without a physician (PD = 7%, 95% CI: 3%, 12%), relative to those who had a physician (PD= -3%, 95% CI: -6%, 0.4%) (Figure 1).

Patient-reliant screening program

PEI's patient-reliant screening program was associated with a 12-percentage-point increase in lifetime stool-based screening (95% CI: 6%, 18%), and a 10-percentage-point increase in recent (< 2 years) stool-based screening (95% CI: 4%, 15%) (Table 2). Program effects were similar over time, with an average 7-percentage-point increase in recent screening in the first two years (2011-2012; 95% CI: 0.4%, 14%), and an 11-percentage point increase in third- and fourth-years post-intervention (2013-2014; 95% CI: 4%, 19%) (Figure 3). All stool-based screening disparities remained unaffected, except for those according to physician access (Figure 2). The program increased recent (<2 years) stool-based screening among those who had a physician (PD = 11%, 95% CI: 5%, 17%), but did not appear to affect screening in those without a physician (PD= -6%, 95% CI: -19%, 7%)—leading to a 17-percentage point decrease (95% CI: -32%, -3%) in screening among those without a physician, relative to those who had a physician. Lastly, the program did not appear to affect overall lifetime or recent (< 5 years) endoscopic screening, nor social disparities in endoscopic-based screening (Figure 2)

Sensitivity analyses results

All pre-intervention influenza vaccination trends were parallel (all decreasing) except for those between PEI and New Brunswick (Slope PD=0.03, 95% CI: 0.001, 0.07). However, none of the observed program effects on screening (described above) were mirrored in changes in

vaccination (Figure 1, Figure 2). Lastly, analyses repeated using GEE models yielded similar results.

Table 1: Crude descriptive statistics of residents of intervention provinces (Saskatchewan, Nova Scotia, Prince Edward Island) and comparison provinces (New Brunswick, Newfoundland), pre-intervention (pre-2009 for Saskatchewan, Nova Scotia; pre-2011 for Prince Edward Island) [a]

	Systematic mail-out based programs			**Comparison**	**Patient-reliant program**	**Comparison**
Characteristics	Sask. & Nova Scotia (N=5,658) % (95% CI)	Saskatchewan (N=3,371) % (95% CI)	Nova Scotia (N=2,287) % (95% CI)	N.B. & NFLD. (N=5,818) % (95% CI)	PEI (N=1,836) % (95% CI)	New Brunswick (N=3,871) % (95% CI)
Never received stool-test	73.4 (71.6, 75.0) *	75.3 (74.0, 76.5) *	76.5 (73.7, 79.1)	78.2 (76.7, 79.6)	70.4 (67.7, 72.9)	73.5 (71.5, 75.5)
No stool test in past year	91.0 (89.5, 91.6) *	90.0 (88.6, 91.3) *	91.3 (89.2, 93.0)	93.3 (92.4, 94.1)	85.1 (82.8, 87.1) *	91.8 (90.5, 92.9)
No stool test in past 2 years	85.1 (83.7, 86.4)	83.2 (81.2, 85.1) *	87.2 (85.0, 89.2)	89.5 (88.4, 90.6)	79.0 (76.6, 81.3) *	86.9 (85.4, 88.2)
Sex						
Men	50.3 (48.9, 51.6)	51.3 (49.6, 52.9)	52.1 (50.0, 54.3)	50.3 (49.1, 51.5)	51.8 (49.5, 54.1)	49.3 (47.7, 50.9)
Women	49.7 (48.4, 51.1)	48.7 (47.1, 50.4)	47.9 (45.7, 50.1)	49.7 (48.5, 51.0)	48.2 (45.9, 50.5)	50.7 (49.1, 52.3)
Age						
50-59 years	54.0 (52.6, 55.7)	55.1 (53.1, 57.2)	53.1 (50.6, 55.5)	53.4 (51.9, 55.0)	51.4 (48.6, 54.1)	53.4 (51.9, 55.5)
60-75 years	45.8 (44.3, 47.4)	44.9 (42.9, 46.9)	46.6 (45.5, 49.4)	46.6 (45.0, 48.1)	48.7 (45.9, 51.4)	46.3 (44.5, 48.1)
Marital Status						
Mar./Com. Law.[b]	76.5 (75.0, 77.9)*	77.0 (75.1, 78.9)	75.6 (63.5, 78.1)*	79.2 (78.0, 80.5)	75.9 (73.3, 78.2)	78.1 (76.4)
Divorced/Widowed	17.3 (16.1, 18.7)*	16.9 (15.4, 18.5)	17.9 (15.8, 20.2)*	15.5 (14.4, 16.6)	16.5 (14.5, 18.7)	15.9 (14.5, 17.3)
Single	6.2 (5.3, 7.1)*	6.1 (5.1, 7.3)	6.2 (5.0, 7.8)*	5.3 (4.7, 6.0)	7.6 (6.3, 9.1)	6.1 (5.2, 7.0)
Education						
≥High School	73.7 (72.1, 75.3)*	74.2 (72.2, 76.1)*	73.1 (70.5, 75.6)*	66.7 (65.1, 68.3)	69.7 (67.0, 72.3)*	75.0 (73.1, 76.8)
<High School	26.3 (24.7, 27.9)*	25.8 (23.9, 27.8)*	26.9 (24.4, 29.5)*	33.3 (31.7, 34.9)	30.3 (27.7, 33.0)*	25.0 (23.2, 26.9)
Income (CAD)[b]						
<30,000	18.9 (17.7, 20.2)*	20.4 (18.8, 22.1)*	17.1 (15.1, 19.3)*	26.1 (24.8, 27.6)	16.1 (14.1, 18.3)	17.0 (15.7, 18.4)
30,000-50,000	15.1 (13.8, 16.6)*	14.1 (12.5, 16.0)*	16.2 (14.2, 18.5)*	17.2 (15.9, 18.6)	16.6 (14.5, 19.1)	16.7 (15.1, 18.3)
50,000-80,000	16.4 (15.1, 17.9)*	16,4 (14.6, 18.3)*	16.5 (14.4, 18.7)*	13.5 (12.4, 14.7)	17.2 (14.9, 19.8)	16.5 (15.0, 18.2)
> 80,000	49.6 (47.6, 51.2)*	49.1 (46.6, 51.6)*	50.2 (47.2, 53.3)*	43.2 (41.4, 45.0)	50.4 (46.7, 53.3)	49.8 (47.6, 52.0)
Rural						
Yes	59.8 (57.6, 61.9)*	35.0 (32.3, 37.8)*	46.4 (42.9, 49.9)	45.2 (43.5, 47.4)	49.0 (45.1, 52.9)	49.7 (47.0, 52.4)
No	40.3 (38.1, 42.4)*	65.0 (62.3, 67.7)*	53.6 (50.1, 57.1)	54.8 (52.7, 57.9)	51.0 (47.1, 54.9)	50.3 (47.6, 53.0)
Physician access[b]						
Yes	92.5 (91.5 93.5)	89.3 (87.6, 90.8)*	96.1 (95.2, 97.2)*	91.4 (90.4, 92.3)	91.1 (89.2, 92.7)*	93.8 (92.6, 94.7)
No	7.5 (6.5, 8.6)	10.7 (9.2, 12.4)*	3.7 (2.8, 4.8)*	8.6 (7.7, 9.6)	8.9 (7.3, 10.8)*	6.24 (5.3, 7.4)

NOTE: Sask.=Saskatchewan. N.B.=New Brunswick, NFLD.=Newfoundland. PEI=Prince Edward Island. CI=Confidence Interval. [a] The pre-intervention period for Saskatchewan and Nova Scotia included all CCHS years before 2009; whereas the pre-intervention period of Prince Edward Island was 2011. [b] Mar" indicates married; "Com. Law" indicates Common law relationship status; "Div." indicates divorced, "Widow." indicates widowed; "CAD" indicates Canadian Dollars; "Physician access" indicates access to a primary care physician. *Significantly different from comparison ($p<0.05$)

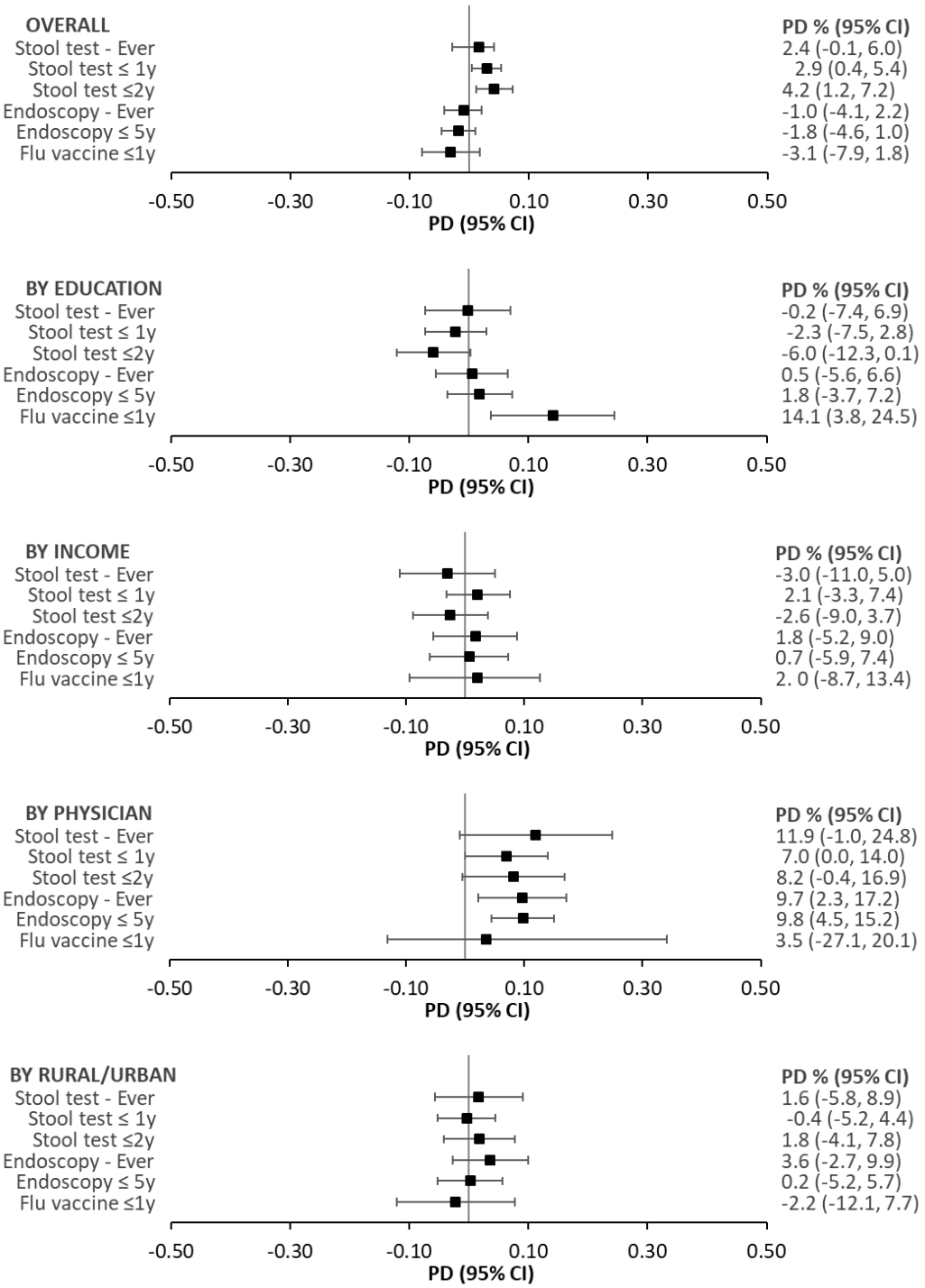


Figure 1 Results of covariate-adjusted difference-in-differences analyses examining the effects of systematic screening programs (Saskatchewan & Nova Scotia pooled (N=11,251) vs. New Brunswick & Newfoundland as comparison provinces; N=9,580) on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

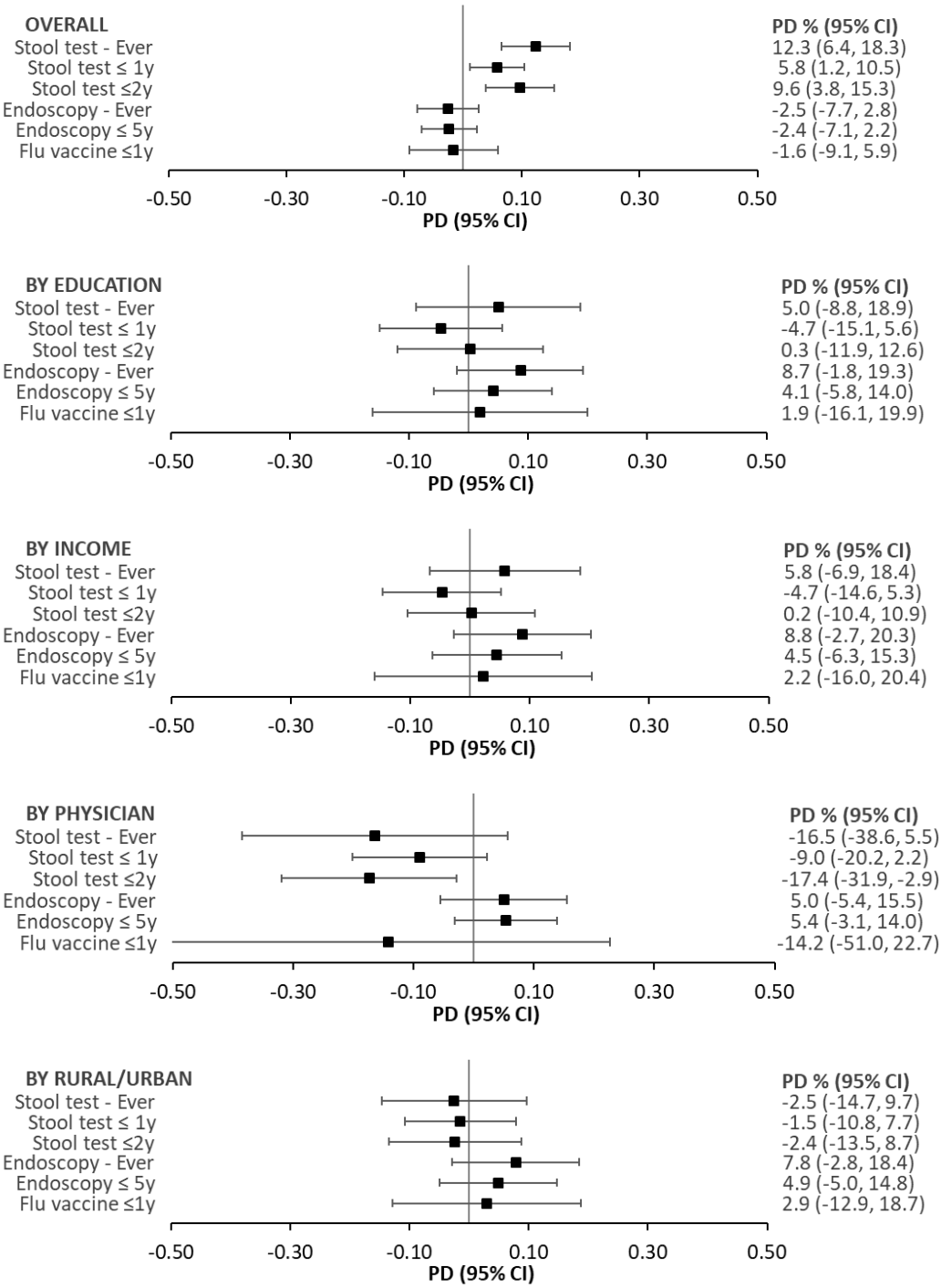
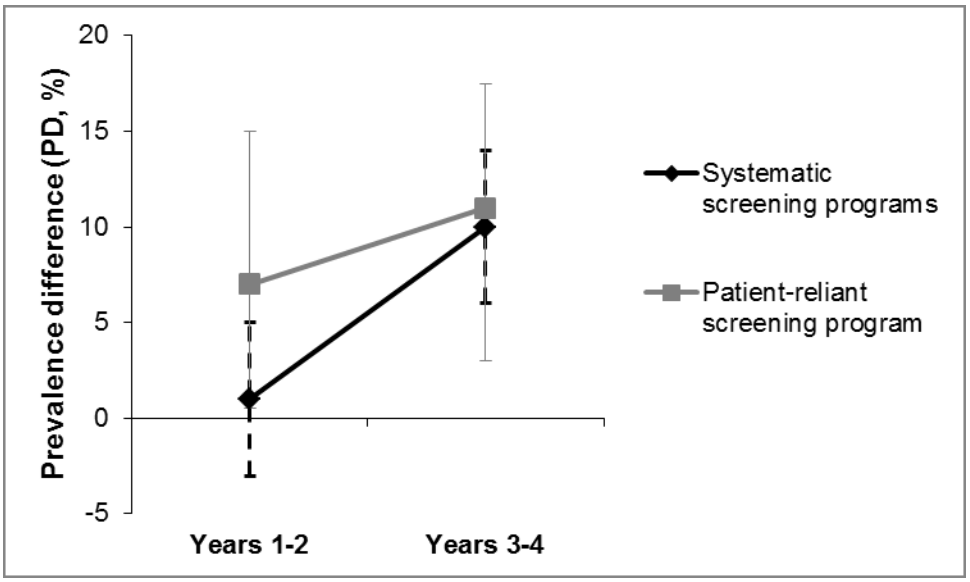


Figure 2 Results of difference-in-differences analyses examining the effects of a patient-reliant program in Prince Edward Island (N=3,116) (vs. New Brunswick (N=5,515) as comparison), on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

Figure 3 Covariate-adjusted difference in recent (≤2 years) stool-based screening prevalence between provinces with a systematic screening program (Saskatchewan and Nova Scotia) and controls, and between a patient-reliant screening province (Prince Edward Island) and controls, according to time since intervention.



6.5 DISCUSSION

The overall aims of this study were to assess how systematic and patient-reliant screening programs affect colorectal cancer screening participation overall, and screening inequalities. Both types of programs were associated with overall increases in recent (< 2 years) stool-based screening. Looking at the post-period as a whole, the patient-reliant program was associated with a higher overall effect than the systematic programs. However, the systematic program's effects appeared to be lagged; when looking exclusively at program effects by the third to fourth year after implementation, both types were associated with similar effect sizes. With regards to screening inequalities, most were small before programs were implemented, and appeared unaffected by either type of program. However, both Saskatchewan and Nova Scotia's systematic screening programs were associated with a decrease in the inequality in recent (< 5 years) endoscopic screening between those with and without a physician, and Saskatchewan's program was associated with a decrease in the inequality in both lifetime and recent (<2 year) stool-based screening according to access to a physician. In contrast, PEI's patient-reliant program was associated with an increase in screening inequalities according to physician access. These heterogeneous effects through time and across social groups may be important for jurisdictions to consider when planning the implementation of a colorectal screening program and weighing program options. Though the systematic screening programs assessed here took up to three years to reach the effect sizes of patient-reliant programs, they did not appear to be associated with the increased screening disparities observed in patient-reliant program settings.

The observed increases in recent (<2 years) stool-based screening following program implementation are consistent with those previously observed in the literature, both in Canada (21, 22) and abroad.(2, 43) Despite these positive gains, by the end of the study period none of the studied provinces met the proposed Canadian target of 60% prevalence of recent screening.(44) Further, the finding that most socioeconomic differences in screening remained following program implementation is consistent with findings from France and England.(1, 2, 45) A cross-sectional study in a French region exposed to a pilot of the country's organised screening program observed a 6% gap in recent stool-based screening between the highest and lowest area-level deprivation quintile groups in the first year of the program's

implementation.(45) In England, in the first year of their program's implementation, a 14% gap in recent-stool based screening was observed between adults living in the highest and lowest deprivation areas (Quintile 1 [lowest deprivation]=62% screened; Q5=48% screened) (2). Two years later, despite gains in uptake among all groups, the gap between the highest and lowest quintile groups had grown slightly to 16%, due to the higher uptake among the least deprived areas (Q1=67% screened; Q5=51%). This gap persisted two years later in 2010 (Q1=72%, Q5=56%). Though the latter studies, like others (1), reported solely on differential screening rates across social groups following program implementation (rather than both before and after), they are aligned with the present study's observation that social disparities in screening may persist despite the implementation of population-based screening programs.

The observed increase in the stool-based screening inequality between those with and without a physician in PEI's patient-reliant program setting (but not in the provinces with systematic programs) may be due to the features of the programs' designs. PEI's program relies on residents to access screening tests through, among other routes, their physicians. Residents without physicians (approximately 13% of Canadians in 2014) are therefore at a marked disadvantage in experiencing the full benefits of programs adopting this design. Not having a primary care physician is a prominent barrier to screening (12, 13, 16-18)—and one that may be exacerbated if program participation is predicated on physician access. Systematic screening programs may circumvent this problem by sending screening tests to all residents, regardless of physician access. Further, since PEI's patient-reliant program did not appear to influence screening among individuals without a physician, the observed overall program effect on recent screening (10-percentage point increase) is likely driven by the effect among the 90% of the population who have a physician (11-percentage-point increase). It is unclear whether patient-reliant programs in provinces with lower physician access would have similar overall effects. This potential source of effect modification may be important to consider for regions planning patient-reliant colorectal screening programs.

These findings are bound by certain limitations. First, the validity of this study's assertions of program effects rely on the satisfaction of the causal assumptions underpinning the DiD framework. (46) Though pre-intervention trends were parallel, and sensitivity analyses

suggest that changes in screening are not likely due to secular changes in health service utilization, some residual confounding is likely present, namely from unmeasured sources such as potential province-specific changes in cancer-related beliefs or behaviours. Second, since self-reported screening data tends to over-estimate recent screening (i.e. previous two-year FOBT sensitivity is 77.4% and specificity is 89.8%), (47) and studies at other cancer sites have observed differential self-reporting of screening according to racial and ethnic subpopulation, (47, 48) social or economic screening gaps may be underestimated when using self-reported data. However, given the restricted time frame of this study and the systematic nature of wording in the CCHS questionnaire, we believe any mis-classification of screening outcomes are likely consistent through time. Lastly, this does not represent an exhaustive evaluation of Canadian colorectal cancer programs. Excluded from this study were programs that had previously been evaluated, such as those in Manitoba and Ontario.

6.6 CONCLUSION

Both systematic and patient-reliant programs appear to improve screening participation overall. However, programs that rely on individuals to access the programs through pre-specified channels such as through primary care physicians, may increase screening disparities according to individuals' ease in accessing those channels Provinces with patient-reliant programs may need to consider whether and/or how the design of their program may exacerbate known barriers to screening. Future work may benefit from assessing the acceptability, feasibility, and effectiveness of complementary targeted interventions in settings where screening disparities persist.

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6.8 SUPPLEMENTARY MATERIAL

Figure captions

eFigure 1. Graphical explanation of Difference-in-Difference estimation

eFigure 2. Trends in lifetime stool-based screening, stool-based screening in the previous 1 year, and stool-based screening in the previous 2 years in Saskatchewan, Nova Scotia (Systematic Screening Programs) and New Brunswick and Newfoundland (comparison groups) before 2009 (the year of intervention).

eFigure 3. Trends in lifetime stool-based screening, stool-based screening in the previous 1 year, and stool-based screening in the previous 2 years in Prince Edward Island (Patient-reliant Screening Programs) and New Brunswick (comparison groups) before 2011 (program initiation).

Table captions

eTable 1. Eligible comparison provinces for the evaluation of systematic and patient-reliant organised screening programs, based on the start times for organised screening programs across Canadian provinces, as well as the CCHS cycles for which colorectal cancer screening data were collected in each of the provinces. Selected comparison groups are encircled.

eTable 2. Stool-based screening inequalities before and after implementation of systematic programs (in Saskatchewan and Nova Scotia) and comparison provinces (New Brunswick and Newfoundland): Proportion (%) of respondents who did not receive stool-based screening in the previous two years according to social indicators of education, income, rural residence, and access to a primary care physician.

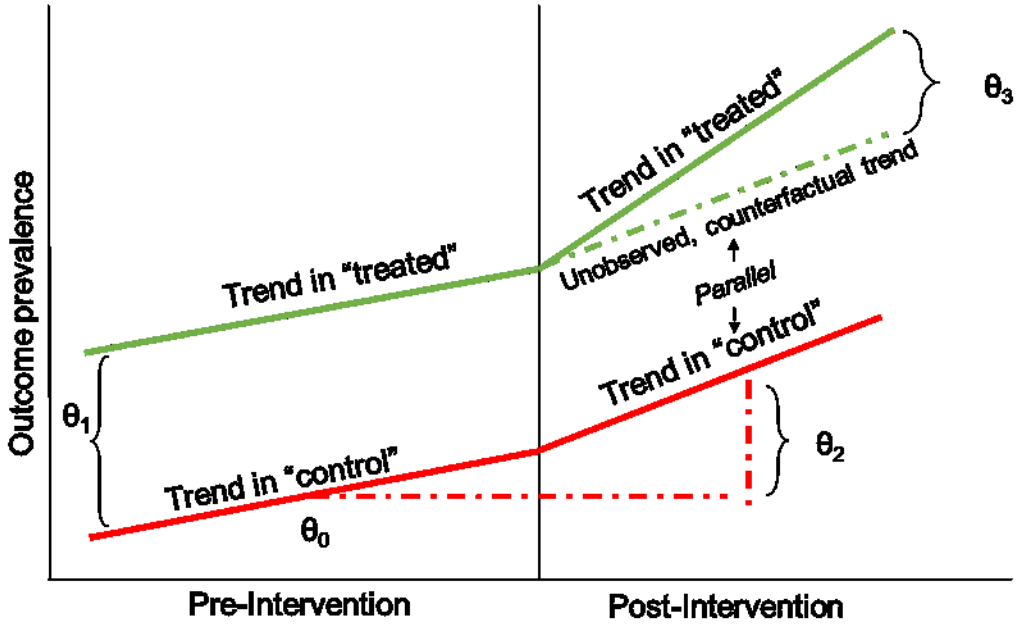
eTable 3. Stool-based screening inequalities before and after implementation of a patient-reliant program (in Prince Edward Island (PEI) versus comparison group in New Brunswick):

Proportion (%) of respondents who did not receive stool-based screening in the previous two years according to education, income, rural residence, and access to a primary care physician.

eTable 4. Results of covariate-adjusted difference-in-differences analyses examining the effects of Saskatchewan's (N=6,589) systematic screening programs (vs. New Brunswick & Newfoundland as comparison groups; N=9,580) on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

eTable 5. Results of covariate-adjusted difference-in-differences analyses examining the effects of Nova Scotia's (N=4,662) systematic screening programs (vs. New Brunswick & Newfoundland as comparison groups; N=9,580) on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

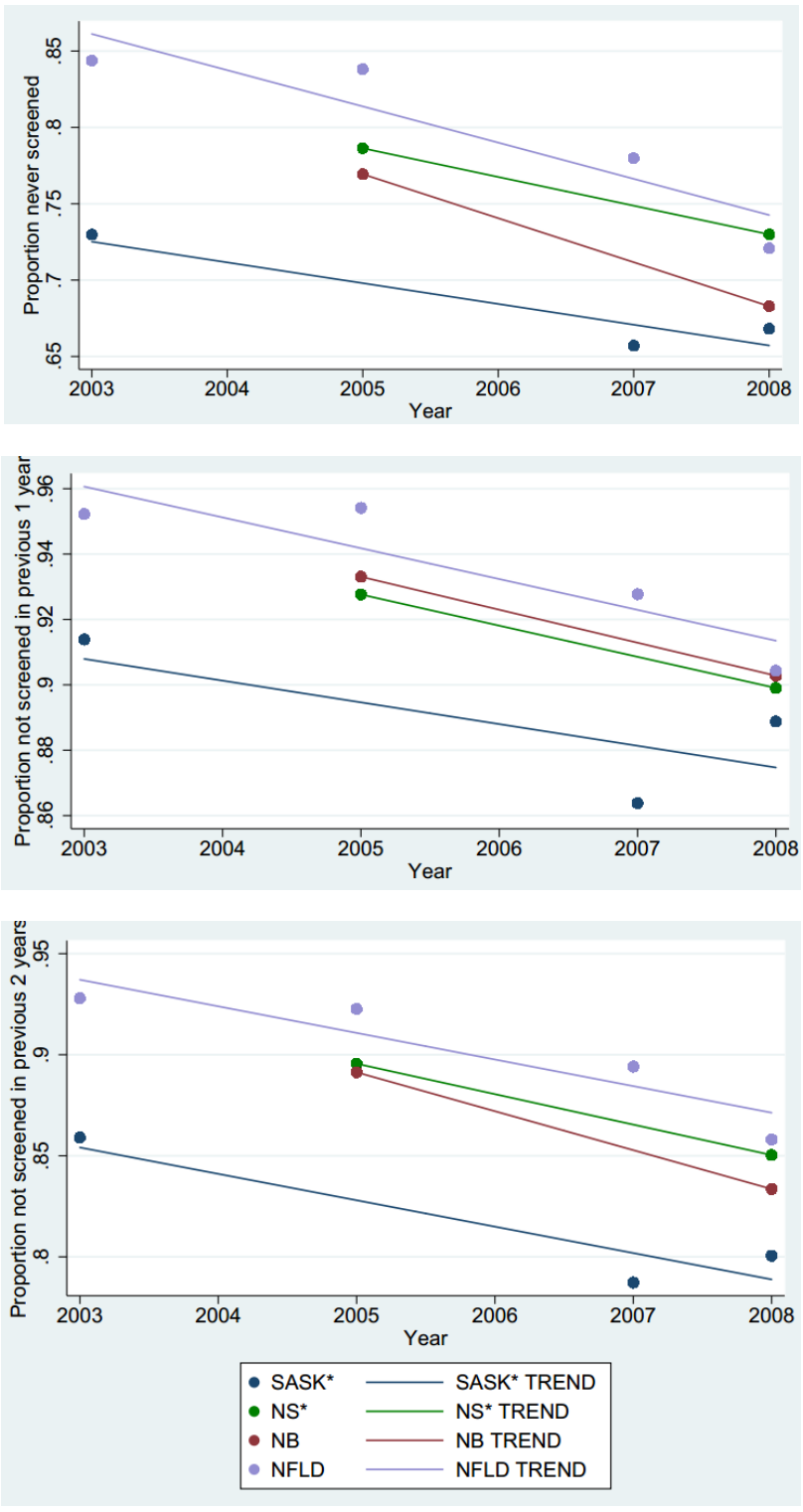
Supplemental Figures



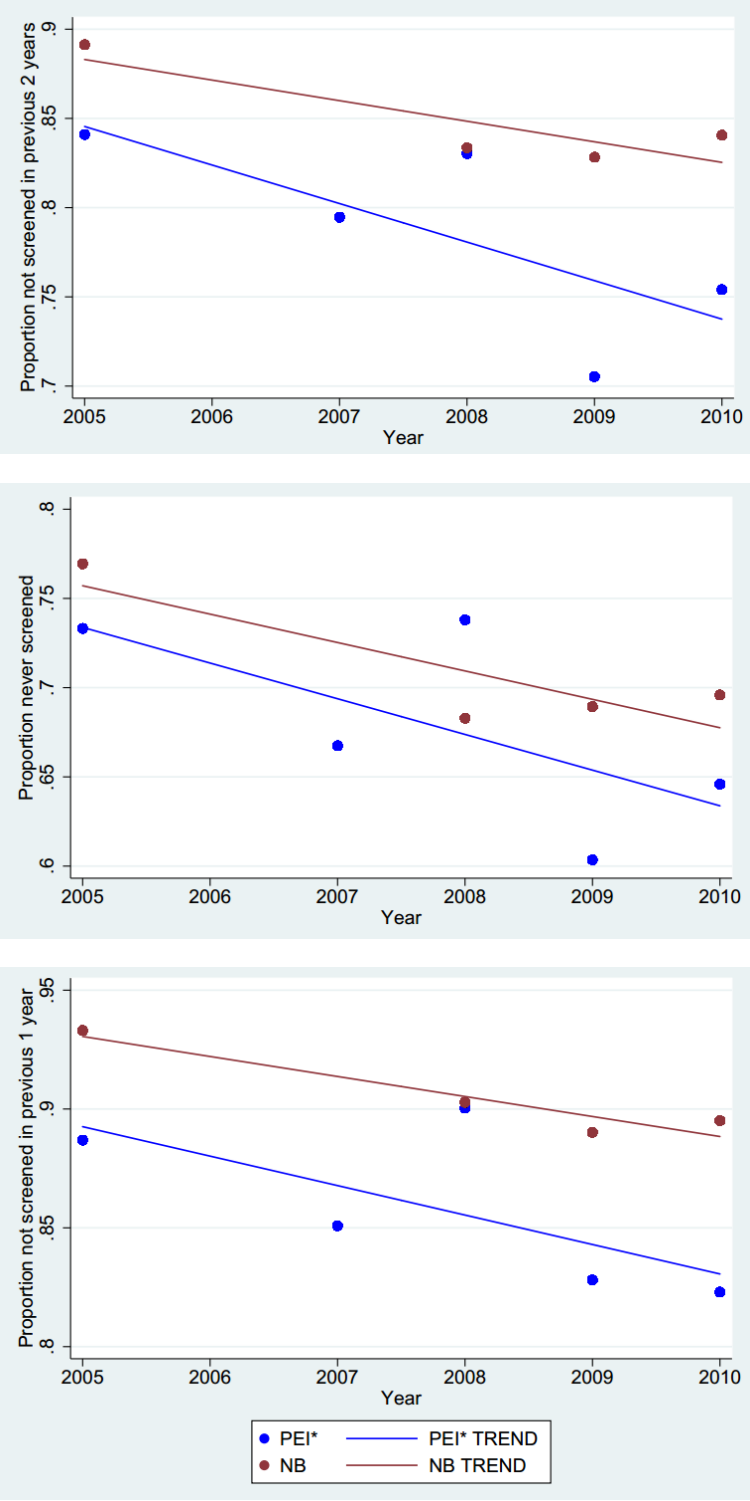
Model: log(E[Y] treated, post, covariates])= θ_0+ θ_1(treated) + θ_2(post) + θ_3(treated*post) + θ'(covariates)

Coefficient	Interpretation
θ_0	Baseline (pre-intervention) average in screening prevalence in the control group
θ_1	Difference between treated and control groups pre-intervention
θ_2	Difference in average screening pre- and post-intervention in the control group
θ_3	Change in screening in post-intervention period that is unique to the treated group (i.e. intervention effect); it represents the pre-post difference in screening among the treated minus the pre-post difference among the controls

eFigure 1. Graphical explanation of Difference-in-Difference estimation



eFigure 2. Trends in lifetime stool-based screening, stool-based screening in the previous 1 year, and stool-based screening in the previous 2 years in Saskatchewan, Nova Scotia (Systematic Screening Programs) and New Brunswick and Newfoundland (comparison groups) before 2009 (the year of intervention).



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Supplemental Tables

eTable 1. Eligible comparison provinces for the evaluation of systematic and patient-reliant organised screening programs, based on the start times for organised screening programs across Canadian provinces, as well as the CCHS cycles for which colorectal cancer screening data were collected in each of the provinces. Selected comparison groups are encircled.

Province	Program Start Year[a]	CCHS cycles with available screening data[b]	Eligible comparison[c] for Nova Scotia and Saskatchewan? ✓= Yes X = No			Eligible comparison[c] for Prince Edward Island? ✓= Yes X= No		
			Pre-2009	Post-2009	Pre-And Post	Pre-2011	Post-2011	Pre-And Post
Potential comparisons								
Alberta	2007	2008, 2011, 2012, 2013	X	X	X	X	X	X
British-Columbia	2013	2003, 2008, 2012	✓	X	X	✓	X	X
Manitoba	2007	2008, 2012, 2013	X	X	X	X	X	X
New Brunswick	2014	2005, 2008, 2009, 2012, 2013	✓	✓	✓	✓	✓	✓
Newfoundland and Labrador	2010	2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012, 2013	✓	✓	✓	✓	X	X
Ontario	2008	2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012	X	X	X	X	X	X
Quebec	NA	2008, 2012, 2013	X	✓	X	X	✓	X
Intervention								
Nova Scotia	2009	2005, 2008, 2009, 2010, 2012						
Prince Edward Island	2011	2005, 2007, 2008, 2009, 2010, 2011, 2012, 2013						
Saskatchewan	2009	2003, 2007, 2008, 2009, 2010, 2012						

[a] Provincial programs can include mail-outs, self-referral through pharmacies, self-pick up of screening tests, media campaigns, promotion through other cancer screening programs. In 2014, all provinces except Quebec had some sort of programming installed to promote colorectal cancer screening. [b] Within the range of years 2003-2014, covered by the Canadian Community Health Survey. [c] To be an eligible comparison group, provinces must have (1) available colorectal cancer screening outcome data for at least 2 cycles in the periods specified, and (2) must have not been exposed to an organised screening program themselves in the periods specified.

eTable 2. Stool-based screening inequalities before and after implementation of systematic programs (in Saskatchewan and Nova Scotia) and comparison provinces (New Brunswick and Newfoundland): Proportion (%) of respondents who did not receive stool-based screening in the previous two years according to social indicators of education, income, rural residence, and access to a primary care physician.

	Pre-intervention				Post-intervention			
Characteristics	**Intervention** Sask. & Nova Scotia (N=5,658) % (95% CI)	**Intervention** Saskatchewan (N=3,371) % (95% CI)	**Intervention** Nova Scotia (N=2,287) % (95% CI)	**Comparison** N.B. & NFLD. (N=5,818) % (95% CI)	**Intervention** Sask. & Nova Scotia (N=5,593) % (95% CI)	**Intervention** Saskatchewan (N=3,218) % (95% CI)	**Intervention** Nova Scotia (N=2,375) % (95% CI)	**Comparison** N.B. & NFLD. (N=3,762) % (95% CI)
Overall	85 (84, 86)	83 (81, 85)	88 (85, 90)	90 (88, 91)	76 (74, 84)	75 (72, 77)	76 (74, 79)	84 (83, 86)
Education								
≥High School	85 (84, 87)	85 (82, 86)	87 (84, 89)	90 (89, 91)	75 (73, 77)*	74 (71, 77)*	76 (73, 79)	85 (83, 87)
<High School	84 (82, 87)	82 (78, 85)	88 (83, 91)	89 (87, 90)	80 (77, 83)*	80 (75, 84)*	80 (76, 84)	82 (79, 85)
Income (CAD)[b]								
<30,000	87 (84, 89)	85 (91, 88)	90 (86, 92)	89 (87, 91)	80 (76, 84)*	81 (75, 86)*	79 (74, 84)	84 (81, 87)
≥30,000	85 (83, 86)	83 (80, 85)	87 (84, 89)	90 (88, 91)	75 (73, 77)*	74 (71, 77)*	77 (74, 79)	85 (83, 86)
Rural								
Yes	86 (84, 88)	83 (81, 86)	88 (85, 91)	87 (86, 89)*	77 (75, 80)	72 (67, 77)	80 (77, 83)*	83 (81, 85)
No	85 (83, 86)	83 (81, 86)	86 (83, 89)	91 (90, 93)*	75 (73, 78)	76 (73, 79)	75 (71, 78)*	85 (83, 88)
Physician access[b]								
Yes	84 (83, 86)*	82 (80, 84)*	87 (85, 89)*	90 (89, 90)	75 (73, 77)*	74 (71, 76)*	76 (74, 79)*	83 (82, 85)*
No	96 (93, 97)*	95 (92, 98)*	97 (91, 99)*	87 (81, 92)	88 (84, 91)*	87 (81, 91)*	91 (83, 95)*	92 (86, 95)*

NOTE: Sask.=Saskatchewan. N.B.=New Brunswick, NFLD.=Newfoundland. PEI=Prince Edward Island. CI=Confidence Interval.

***** Indicates a difference between covariate strata (chi-squared statistic, $p<0.05$).

[a] The pre-intervention period for Saskatchewan and Nova Scotia included all CCHS years before 2009; whereas the pre-intervention period of Prince Edward Island was 2011.

[b] "CAD" indicates Canadian dollars, "Physician access" indicates access to a primary care physician.

eTable 3. Stool-based screening inequalities before and after implementation of a patient-reliant program (in Prince Edward Island (PEI) versus comparison group in New Brunswick): Proportion (%) of respondents who did not receive stool-based screening in the previous two years according to education, income, rural residence, and access to a primary care physician.

Characteristics	Pre-Intervention (2011)		Post-Intervention (2011)	
	Intervention PEI (N=1,836) % (95% CI)	**Comparison** New Brunswick (N=3,871) % (95% CI)	**Intervention** PEI (N=1,280) % (95% CI)	**Comparison** New Brunswick (N=1,638) % (95% CI)
Overall	79 (77, 81)	87 (85, 88)	65 (61, 68)	82 (79, 84)
Education				
≥High School	81 (77, 85)	88 (86, 90)*	64 (59, 68)	82 (70, 85)
<High School	78 (75, 81)	83 (81, 86)*	68 (61, 74)	80 (73, 85)
Income (CAD)[b]				
<30,000	82 (77, 87)	86 (83, 88)	67 (60, 74)	81 (76, 85)
≥30,000	78 (76, 81)	87 (85, 89)	64 (60, 68)	82 (76, 85)
Rural				
Yes	80 (77, 83)	86 (83, 88)	65 (60, 70)	84 (80, 88)
No	78 (74, 82)	88 (86, 90)	64 (58, 70)	79 (75, 83)
Physician access[b]				
Yes	78 (76, 80)*	86 (85, 88)*	62 (58, 66)*	81 (78, 84)*
No	89 (82, 93)*	95 (91, 97)*	88 (77, 94)*	87 (76, 94)*

NOTE: Sask.=Saskatchewan. N.B.=New Brunswick, NFLD.=Newfoundland. PEI=Prince Edward Island. CI=Confidence Interval. * Indicates a difference between covariate strata (chi-squared statistics, $p<0.05$). [a] The pre-intervention period for Saskatchewan and Nova Scotia included all CCHS years before 2009; whereas the pre-intervention period of Prince Edward Island was 2011. [b] "CAD" indicates Canadian dollars, "Physician access" indicates access to a primary care physician.

eTable 4 Results of covariate-adjusted difference-in-differences analyses examining the effects of Saskatchewan's (N=6,589) systematic screening programs (vs. New Brunswick & Newfoundland as comparison groups; N=9,580) on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

	Saskatchewan				
	Overall	By Education	By Income	By Physician access	By Area (Rural/Urban)
Outcomes	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)
Stool test - Ever	3.8 (-0.5, 8.1)	-7.7 (-16.4, 1.0)	-2.6 (-11.9, 6.7)	14.4 (0.8, 28.1)[a]	3.9 (-4.9, 12.3)
Stool test ≤ 1y	2.6 (-0.3, 5.4)	-3.8 (-10.2, 2.5)	-0.6 (-7.3, 6.0)	6.8 (-0.5, 14.2)	2.2 (-3.6, 8.0)
Stool test ≤ 2y	3.5 (-0.3, 7.4)	-8.9 (-16.4, -1.4)[b]	4.6 (-12.4, 3.2)	9.5 (0.2, 18.7)c	5.6 (-2.1, 13.4)
Endoscopy - Ever	-0.4 (-3.3, 4.1)	-1.7 (-9.1, 5.7)	3.1 (-5.3, 11.5)	9.2 (1.3, 17.1)[d]	6.5 (-0.9, 13.9)
Endoscopy ≤ 5y	1.0 (-4.3, 2.3)	0.0 (-6.4, 6.6)	2.0 (-5.9, 10.0)	7.7 (1.6, 13.8)e	2.5 (-4.0, 9.1)
Flu vaccine ≤1y	-3.4 (-9.1, 2.3)	18.7 (6.2, 31.4)[f]	10.7 (-2.5, 24.0)	1.3 (-23.2, 26.0)	-6.2 (-18.2, 5.8)

[a] PD=14.4 captures the difference in program effect between those without a physician (PD=16.6%, 95% 3.7%, 30.1%) and those with a physician (PD=2.4% 95% CI -2.1%, 6.9%). [b] PD=-8.9 captures the difference in program effect in those without a high school diploma (5.3% 95% CI 1.0%, 9.6%) and those with a high school diploma (-3.6%, 95% CI -10.2%, 3.1%). [c] PD=9.5 captures the difference in program effect in those without a physician (PD=12.2%, 95% CI 3.8%, 20.6%) and those with a physician (PD=2.7% 95% CI -1.4%, 6.8%). [d] PD=9.2 captures the difference in program effect among those without a physician (8.9%, 95% CI 2.1%, 15.7%) and the program effect among those who had a physician (-0.3%, 95% CI-4.3%, 3.7%). [e] PD=7.7 captures the difference in program effect among those without a physician (6.1% 95% 1.1%, 11.2%) and the program effect among those who had a physician (-1.6% CI -5.2%, 2.0%). [f] PD=18.7 captures the difference in program effect in those without a high school diploma (10.6%, 95% CI 0.0%, 21.3%) and those with a diploma (-8.1% 95% CI -14.9%, -1.4%)

eTable 5 Results of covariate-adjusted difference-in-differences analyses examining the effects of Nova Scotia's (N=4,662) systematic screening programs (vs. New Brunswick & Newfoundland as comparison groups; N=9,580) on lifetime and recent (≤1, ≤2 years) stool-based screening, lifetime and recent (≤ 5 years) endoscopic screening, and past-year flu vaccination, expressed as prevalence differences (PD), overall and on screening inequalities according to education, income, access to a primary care physician, and area of residence.

	Nova Scotia				
	Overall	By Education	By Income	By Physician access	By Area (Rural/Urban)
Outcomes	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)	PD (%, 95% CI)
Stool test - Ever	2.2 (-2.4, 6.9)	6.5 (-2.7, 15.7)	-2.9 (-13.5, 7.7)	5.8 (-9.4, 21.0)	1.8 (-7.4, 11.2)
Stool test ≤ 1y	3.4 (0.0, 6.8)	-1.2 (-7.9, 5.6)	4.2 (-2.7, 11.1)	7.8 (-1.0, 16.6)	-2.8 (-9.1, 3.6)
Stool test ≤ 2y	5.4 (1.5, 9.2)	4.0 (-12.0, 4.0)	-0.6 (-8.7, 7.5)	6.4 (-3.9, 16.8)	1.3 (-8.9, 6.4)
Endoscopy - Ever	-2.0 (-5.9, 1.9)	2.8 (-4.5, 10.1)	2.8 (-4.5, 10.1)	-10.1 (-43.8, 23.6)	2.1 (-5.7, 9.8)
Endoscopy ≤ 5y	-2.3 (-5.6, 1.0)	3.5 (-3.2, 10.2)	3.5 (-3.2, 10.2)	6.8 (-8.1, 21.7)	-1.0 (-7.7, 5.6)
Flu vaccine ≤1y	-3.7 (-9.4, 2.0)	10.0 (-2.3, 22.4)	5.4 (-18.6, 7.8)	12.6 (4.9, 20.2)[a]	0.3 (-11.6, 12.2)

[a] PD=12.6 captures the difference in program effect among those without a physician (9.4% 95% 2.3%, 16.2%) and the program effect among those who had a physician (-3.1%, 95% CI -6.6%, 0.3%).

CHAPTER 7: DISCUSSION AND CONCLUSION

The overarching goals of this thesis were to contribute knowledge on the social determinants of colorectal cancer screening in Canada and to explore potential pathways of intervention—both by identifying mechanisms that explain existing social disparities and by evaluating how current population-level intervention strategies affect screening uptake overall and among vulnerable populations. In doing so, this thesis contributes to building the evidence needed to inform public health interventions to promote screening and reduce screening inequalities. In addition to a discussion of the thesis findings and contributions, this chapter presents overall limitations and strengths, potential implications for public health, as well as directions for future research.

7.1 Summary of main findings

In the first analysis presented in Manuscript 1 (Chapter 4), the association between local area-level income and lifetime and recent colorectal cancer screening was examined. Overall, a significant association was observed between local area-level income and lifetime screening, but not between local area-level income and having been screened recently. This finding highlights the potential influence of social and environmental contexts on colorectal cancer screening uptake above and beyond individual-level factors. The role of socioeconomic contexts on screening behaviour was identified as an important area of future research and surveillance.

The second manuscript (Chapter 5) aimed to push further our current understanding of social determinants of colorectal cancer screening by assessing potential mediating pathways of known social disparities in screening. In this study, regression- and inverse probability weighting-based methods of mediation analysis were used to assess whether access to primary care physicians mediates the observed screening inequality between individuals who recently immigrated to Canada and individuals born in the country. Specifically, we aimed to estimate the total effect of recent immigration on screening—regardless of physician access—as well as the controlled direct effect of recent immigration on screening (that is, the would-be association between recent immigration and screening if all had access to a primary care physician). Findings from these analyses suggest that if all had access to primary care physicians, overall screening participation would likely increase. However, large screening disparities would likely

remain, as gains in screening would be observed in Canadian-born individuals, but not among recent immigrants. Future studies of alternative modifiable pathways to reduce immigration-based screening disparities appear warranted.

Finally, the third manuscript (Chapter 6) aimed to strengthen current knowledge of potential intervention pathways to promote screening and reduce screening inequalities. Two types of organised screening programs were assessed: Saskatchewan and Nova Scotia's systematic screening programs, which send screening tests to all age-eligible adults; and Prince Edward Island's patient-reliant screening program, which requires patients to request screening tests via their physicians, a designated phone line, or website. Findings were that both systematic and patient-reliant increase overall stool-based screening (with overall small or null effects for endoscopic screening). However, neither type of program influenced screening disparities by income, education, rural residence, or access to a primary care physician. Instead, Prince Edward Island's patient-reliant program appeared to result in an increased gap in stool-based screening based on respondents' access to a primary care physician. These results suggest that provinces which rely on patients' initiative to access screening tests may need to consider additional interventions to target vulnerable populations.

7.2 Thesis contributions

In light of the findings summarised above, three themes emerge from this doctoral thesis: 1) the need to incorporate a socio-ecological perspective in the study and surveillance of colorectal cancer screening in Canada; 2) the benefits of social epidemiologic methods for the study of the social determinants of colorectal cancer screening—particularly of pathways to screening inequalities; and 3) the need to take social determinants and health equity into account in the planning of future interventions to promote colorectal cancer screening.

7.2.1 A socio-ecological understanding of colorectal cancer screening

This thesis is grounded in a conceptual framework (Figure 1, Chapter 2) that postulates that colorectal cancer screening is influenced, in part, by the conditions in which people live, and

the resources to which they have access.[83] This thesis' first study was predicated on the assumption that local-area level features may influence screening likelihood, above and beyond individual-level characteristics. Contextual environments are believed to shape outcomes such as screening participation by shaping individuals' access enabling resources such as health and transportation infrastructure, services, social capital, community support.[47,88]

With this thesis, knowledge has been gained on the association between local area-level income and screening in Canada. Area-level income was found to be associated with having never been screened—an observation that remained statistically significant after adjusting for individual-level covariates, including individual-level income. This finding suggests that local areas of residence may influence screening behaviour in the country. To date, socio-ecological considerations have largely been neglected in studies of colorectal cancer screening and screening disparities in Canada. As such, surveillance of area-level disparities in screening in Canada have been under-reported in both peer-reviewed and grey literature. This thesis emphasizes the importance of considering the influences of local area-level contexts in future surveillance efforts, interventions, and studies of colorectal cancer screening.

7.2.2 Assessing mediating pathways to screening

As a discipline, epidemiology has at times been criticized for conducting research according to a "black box" framework—one where associations between two factors are assessed, without consideration of the mechanisms that may be driving the causal relationship to arise.[193] These types of epidemiologic studies have been critiqued for their limited ability to identify potential areas for public health interventions. Previous research on the social determinants of colorectal cancer screening in Canada can largely be described as "black box" studies. Studies have largely overlooked the need to empirically assessed the modifiable mechanisms or mediating pathways of social disparities in screening. Pathways had been posited hypothetically but rarely been studied. The second manuscript of this aimed to fill this gap in Canadian literature by assessing a potential mediator of the association between recent immigration and screening: access to primary care physicians. This was done by applying three methods of mediation analysis across which to assess the consistency of study results.

Despite extant literature's twofold observations that not having a primary care physician is an important barrier to screening, and that recent immigrants are less likely than non-immigrants to have a primary care physician,[194] we did not find that access to a physician mediates the association between recent immigration and screening. Instead, this thesis observed that if all had access to a primary care physician, the immigration-based disparity in screening would not be significantly reduced, much less eliminated. This finding underscores the importance of testing plausible hypotheses pertaining to the mediating pathways of known associations. It also highlights the pressing need to identify, and test, alternative mediating pathways. As the burden of the colorectal cancer remains high in Canada, accompanied by persistent gaps in screening, research on modifiable pathways and potential areas of intervention are needed. As demonstrated in this thesis, the field of social epidemiology is well-positioned to offer the methods and theoretical frameworks necessary to pursue such analyses.

7.2.3 Planning future interventions

To date, colorectal cancer screening in Canada has either been pursued opportunistically, or through an organised program approach. As of 2007, all Canadian provinces except Quebec began establishing organised programs to promote stool-based screening uptake.[1] These interventions are defined by their universal, population-based approach, and their reliance on communication materials to promote screening. Most organised programs in Canada use mail-based screening invitation letters to inform residents of screening guidelines, with some provinces also sending screening tests directly to residents.

These communication strategies are assumed to tackle need-based determinants of screening described in Figure 1 (Chapter 2)—particularly perceived need—by impressing upon individuals' the relevance and benefits of screening. In doing so, they are also assumed to reduce reliance on the prescribing habits of physicians and on individuals' regular use of health services.[49] Indeed, the observed screening gains attributed to both systematic and patient-reliant programs (Manuscript 3) contribute evidence that support these assumptions.

However, in observing persistent social inequalities in screening, despite program implementation, this thesis also contributes evidence as to the limitations of universal, population-based interventions in promoting screening among vulnerable populations in Canada. As such, findings are aligned with the inverse equity hypothesis—wherein interventions tend to reach privileged or affluent populations first, with a lagged effect for the more marginalised.[99] Insofar as letter-based campaigns promote protective health behaviours (i.e. screening), they may only be reaching individuals who are already more susceptible to being screened. The thesis findings suggest that organised screening programs as they are presently designed in Canada may not be able to modify the social factors and conditions (i.e. systemic barriers) that prevent individuals from seeking screening. Future interventions may be needed to address modifiable systemic barriers to screening. Previous studies of organised screening for other cancer sites have suggested that culturally-sensitive in-person counselling or phone calls may be needed in combination with the primary invitation letter to reduce the psychosocial barriers to screening uptake.[58] Future studies should explore the acceptability, feasibility, and effectiveness of targeted interventions across Canadian provinces.

7.3 Limitations

7.3.1 Study sample and design

A first limitation of the studies in this thesis is the external validity, or generalizability, of study findings to the entire Canadian population. Each of the papers apply distinct inclusion criteria that affect the generalizability of the findings. For example, the first study restricts the sample to solely those living in urban areas. This suggests that the observed associations between local area-level income and lifetime screening participation may not be generalizable to residents living in rural areas. Further, in all three studies, the sample was restricted to those who reported no family or personal history or symptoms or colorectal cancer (i.e. those at "average risk" of developing the disease). Though this criterion was applied to ensure that the studies assessed preventive (rather than diagnostic) screening prevalence, its application suggests that results may not be generalizable to Canadian respondents who are at elevated risk of colorectal cancer.

Beyond these imposed inclusion criteria, the studies' generalizability is also affected by the sampling strategy of the CCHS. By design, the CCHS aims to be representative of the Canadian population. At every cycle, the survey targets approximately 98% of the Canadian population aged twelve years and above. [131] However, participation in the CCHS is voluntary, and over the course of the survey's existence, decreases in response rates have been observed. Response rates for the CCHS were 84.7% in 2001,[134] 80.7% in 2003,[135] 78.9% in 2005,[136] 78% in 2008,[137] 68.9% in 2012,[138] 66.8% in 2013 and 65.6% in 2014.[139] These decreases may indicate that the CCHS is capturing a more restricted population—one that may be more interested or able to participate in the survey due to its social, demographic, economic, and health make-up. For example, in our studies at most 20% of our sample of 50 to 75 years old had not obtained a high school diploma. In contrast, Government of Canada reports suggest that approximately up to 38% percent of Canadian seniors (aged 65 and above) do not have a high school diploma.[195] Selection bias in CCHS survey response may lead to overestimations of true screening prevalence if persons answering the CCHS questionnaire are healthier and more proactive in seeking screening. This possibility is minimized, however, when sampling weights are used (as was done for objectives 1 and 3 of this thesis). These weights are designed to help ensure that the CCHS sample is theoretically representative of at least 98% of the Canadian population.[131] The excluded 2% of the population include individuals who are institutionalised (e.g. in prisons, medical facilities and in-patient unites), are members of the Canadian Armed Forces, live on First Nation reserves, Crown lands, or in very remote regions.[131] Our findings are not generalizable to these populations. We expect that the screening prevalence estimates observed in the thesis studies represent an overestimation of the screening that would be observed among these excluded populations. Future studies of social inequalities in colorectal cancer in Canada may merit a closer look at these more marginalized populations.

The studies also face threats to internal validity. Namely, a limitation of the studies in the thesis, particularly those designed for Objective 2 and Objective 3, is their reliance on strong causal assumptions. Both rely, for example, on the assumption of no unmeasured confounding (or "conditional exchangeability"[120]). Sensitivity analyses were applied in both papers to assess the sensitivity of findings to unmeasured confounding.[126] In both studies, we concluded that the

potential of unmeasured confounding to severely bias findings is low. Nonetheless, in each of the studies we held the conservative position that residual confounding of the associations is likely.

Due to the cross-sectional nature of the CCHS, all three studies also rely on assumptions of the temporal ordering between exposures and screening outcomes. For Objective 1, we assumed for example, that exposure to local-area level income precedes screening behaviour in time. The cross-sectional CCHS data does not preclude the possibility that individuals who had less intention to pursue screening may have been more likely to move to, or stay, in areas where health-related resources, including screening, are not available. Additional sensitivity analyses were therefore performed to assess if associations between low income and lifetime screening were consistent across individual-level income and education groups. That findings were consistent across these groups, and with findings from a longitudinal study of area-level deprivation on screening behaviour in the United States,[93] offered some (albeit incomplete) evidence against a hypothesis of reverse-causation. Secondly, for Objective 2, the temporal ordering of associations between immigration, access to physicians, and screening was assumed in order to perform mediation analyses. We assumed it unlikely that having access to Canadian physicians would occur before immigration to Canada. However, the temporal ordering of physician access and screening experience may be more ambiguous. Further, certain other factors in the study, such as income, are likely time-dependent. If data on income through time (e.g. even before immigration) was available, these data could be incorporated as potential time-varying confounders[196] in the analyses. For example, though recent immigration is known to be associated with lower income, immigrant families' household income levels in the first 10 years since arrival is likely also associated with households' economic capital prior to arrival to Canada.[170] Given the cross-sectional nature of the data, household income reported in the CCHS was treated as a potential mediator in the association between recent immigration and screening. However, if additional data on income (or economic position) throughout the life course was available, these data could have been incorporated as potential time-varying confounders in the analyses. Thus, replication of this analysis using longitudinal data is warranted. Lastly, for Objective 3, we assumed the temporal ordering of associations between year of survey completion and province of residence (and thereby exposure or absence of exposure to an organised screening program), and screening behaviour. Though rather unlikely,

it is possible that certain individuals could have moved across provinces in response to planned or executed implementation of provincial organised screening programs (or, due to the quality or accessibility of provincial health services more generally)—thereby shifting population-level distributions of screening risk factors. Approximately 7% of Canadians aged 50 to 75 years are estimated to have migrated between provinces in 2016.[197] Unfortunately, the CCHS does not include data on respondents' provincial mobility, which limits the possibility of tracking potential bias due to interprovincial contamination.[128,189] By applying analyses with a comparison population, and adjusting analyses for several social, demographic, and economic covariates both before and after program implementation, we aimed to minimize this source of bias. Repeating program evaluation studies with longitudinal data, and longer follow-up periods, will be useful to validate findings.

7.3.2 Measurement

Many of the sociodemographic and health measures used in this thesis are based on self-reported data in the CCHS. Although these data are among the best sources of information available on population-wide social, demographic, economic, and screening characteristics in Canada, they are bound by certain limitations. A key limitation in each of the thesis studies is the potential misclassification of self-reported colorectal cancer screening. Studies have found that individuals self-reporting screening tend to over-estimate the recency of screening (this phenomenon is also called "telescoping bias").[198,199] The sensitivity of self-reported FOBT screening in the previous two years is 77.4%, and specificity is 89.8%.[199] Reported large numbers of screening false-positives in self-reported screening data suggest that using self-reported data from the CCHS may lead to over-estimation true screening participation. Further, evidence from extant literature suggest that the sensitivity and specificity of self-reported cancer screening can vary across population sub-groups.[199] However, studies have found that the observed consistency between self-reported screening and recorded screening is higher for colorectal cancer screening than it is for breast and cervical cancer screening—for which social disparities in screening after often underestimated.[199] Nonetheless, is it possible colorectal cancer screening inequalities measured in this thesis are also underestimated.

7.4 Strengths

The thesis has several strengths. First is its use of interdisciplinary social and public health theories to guide the studies' design and the interpretation of results. Drawing on socio-ecological theories of health,[200,201] the first study explores determinants of colorectal cancer screening that operate beyond the level individual-level. In doing so, it provides novel evidence that supports incorporating an understanding of context when studying the determinants of colorectal cancer and colorectal cancers screening in Canada. The second study incorporates social theories and conceptual frameworks pertaining to social marginalization. These include Intersectional Theory,[115,202] the Social Determinants of Health framework,[65] and the Core Domains of [Immigrant] Integration framework.[114] Drawing from these theories and frameworks, the second study presents a novel way to study immigration-based disparities in screening—namely, by exploring mediating pathways, and by stratifying analyses by respondents visible minority status. This design enabled an assessment of the mediating pathways of access to primary care physicians, while accounting for the potential intersection between recent immigration experience and the experience visibility minority status in Canada.[203] Lastly, the third manuscript drew from theories of population-level distributions of risk[34] and from knowledge of the Inverse Equity Hypothesis.[99] By analysing two types of programs, this study permitted more a detailed understanding of how types of organized screening programs influence population-wide and sub-population specific screening uptake. Grounded in interdisciplinary social and public health theories, each of the thesis studies provide relevant information for public health planning and colorectal cancer screening promotion in Canada, and for the optimization of health and health equity.[204]

Second, with regards to data and design, the studies' use of the CCHS' population-based sample allows for conclusions to be made about the social determinants of colorectal cancer screening across Canada. Drawing from CCHS data, all three studies took a large set of demographic and socioeconomic covariates into account, thereby enabling a discussion of the potential independent, predictive associations between each of the exposures and outcomes of interest.

Third, the distinct statistical methods pursued for each objective are innovative and constitute an important strength of the thesis. Each analysis was designed to address the complex research questions while accounting for CCHS data structure and availability. The first manuscript's application of GEE-based estimation enabled sampling and bootstrap weights to be used while also accounting for inter-dependence between observations at the dissemination area level. GEE estimation yielded population-averaged estimates (rather than area-specific estimates[159]) of the association between local area-level income and screening. These averaged estimates were especially relevant in providing a first-ever general summary of the relation between area-level income and screening in Canada. The second manuscripts' application of several mediation analyses enabled an assessment of the consistency of results across statistical approaches and lent greater credibility to the study's findings. Comparing results across methods of mediation analysis has rarely been done in social epidemiology literature and is especially relevant now, as a growing number of methods have been proposed but are rarely compared.[205] Lastly, using the quasi-experimental difference-in-differences (DD) framework for the third objective enabled an assessment of the effectiveness of organised screening programs while accounting for temporal trends in screening, and for differences in confounders in treated and comparison provinces.[39,98] The use of several sensitivity and falsification analyses in this third study, as in the previous two, also provide additional confidence in the studies' results.

Lastly, all three studies lay the groundwork for future analyses on the social determinants of colorectal cancer screening, and on surveillance effort of social inequalities in cancer screening in Canada. This thesis generated hypotheses based on available measures and cross-sectional data that can be tested in future, longitudinal analyses. Further, the use of directed acyclic graphs (DAGs) provides a graphical formulation of the assumed structure and direction of associations between factors.[206] These assumptions can continue to be tested (and DAGs modified accordingly) in future work.

7.5 Potential implications for public health and future research

Cancer control efforts in Canada are currently faced with the challenge of understanding how screening rates for colorectal cancer remain low, and what can be done to improve them. This thesis has five implications for public health and future epidemiologic research.

Foremost, low screening participation observed in all three of the thesis studies requires public health attention. The first study's observation that most people who have not been screened recently for colorectal cancer have in fact never been screened in their lifetime is a novel observation that is relevant for Canadian cancer prevention. It implies that public health interventions to promote colorectal cancer screening must consider the predisposing, enabling, and need-related characteristics of individuals who have never been screened. Future research on colorectal cancer screening in Canada will benefit from the inclusion of two outcome measures: lifetime screening and recent screening. Knowledge of the determinants of both screening initiation and continued screening follow-through will be essential for public health planning.

Second, this thesis helped elucidate the independent association between area-level income and screening. The observed association between area-level income and lifetime screening has implications for public health planning and surveillance—particularly in the context of provinces' implementation of organised screening programs. As of 2015, all Canadian provinces except Quebec had implemented a province-wide organized colorectal cancer screening program. These programs are thought to modify the pathways through which residents access screening services. Our finding of an area-level income-based gradient in lifetime screening implies that surveillance of the programs' impact on area-level screening disparities may be warranted. Future studies will be able to utilize mandatory long-form census data from the 2016 Canadian Census (soon to be released), and new CCHS cycles, to assess more recent trends in screening by area-level income (specifically, post-intervention trends). Findings from these future studies may help inform any future targeted interventions to improve screening equity across income groups.

Third, this thesis offers evidence that epidemiologic studies of the mediators of known screening disparities may be useful in determining future areas of research and intervention. The mediation analyses performed in this thesis suggest that increasing all individuals' access to

primary care physicians may not be sufficient to eliminate immigration-based disparities in screening. Other intermediary factors are likely to play a more important role in determining this screening disparity, and future studies of alternative modifiable pathways are recommended. Use of longitudinal data and quasi-experimental design to assess these pathways will likely prove useful, especially in ensuring appropriate temporal ordering between factors. Future studies may also benefit from a mixed-methods approaches[207] that combine both empirical assessments of potential modifiable mediators with qualitative assessments of individuals' reported barriers and facilitators to screening. Mixed method approaches could ensure triangulation of findings—to assess consistency of findings and aid in their interpretation.[207]

Fourth, this thesis offers valuable information on province-wide organized screening programs and their strengths and limitations in promoting screening overall and reducing screening disparities. Our findings suggest that though both patient-reliant and systematic organised screening programs can increase overall levels of screening, neither were associated with reductions in known screening disparities by income, education, rural residence, or access to primary care physicians. Understanding why these social disparities persist, and what can be done to modify or enhance existing programs represent important areas of future research. Future organised screening interventions will benefit from the consideration of the predisposing, enabling, and need-related factors that influence behaviour among vulnerable populations—targeting factors (or distributions of factors) that can be modified to promote screening equity.[69] As Michie et al. discuss in their Behaviour Change Wheel framework for the design of interventions to change individual behaviours, future organised screening interventions may benefit from considering potential modifications of the environments in which people live in order to enable screening behaviour, and from considering the role of emotional processing and social norms in motivating and facilitating screening uptake.[208] For example, integrating members of vulnerable communities in intervention design and tailoring messaging to specific communities have been reported as effective means to reach more marginalised population sub-groups.[209] Studies of interventions to promote screening for other cancer sites (such as breast, cervical, and prostate cancer) have also found that "peer-education" or "lay health worker" interventions—based in relevant community spaces in which vulnerable populations assemble and interact—may help reach more marginalised groups.[210,211] Research on peer-education

suggests that individuals tend to be more responsive when messaging is tailored to them, and when a sense of affinity is shared with the messenger.[212]

Above all, this thesis reaffirms that colorectal cancer screening is indeed influenced by social determinants. These social factors (or social conditions) are often more "distal" in their influence on health outcomes than individual-level factors such as beliefs or behaviours. Social conditions have been defined as factors that define a person's relationship to others and to the structures of their society.[213] They include factors such as socioeconomic status, race, ethnicity, or gender.[213] Many of these determinants have been described as "fundamental causes" of population health and health behaviour, both because they shape individuals' access to health promoting resources, and because of their consistent associations with a plethora of health outcomes.[213] The theory of "fundamental causes" of disease suggests that without tackling inequitable social conditions, associations between social factors and health outcomes will persist, and new associations will emerge through time.[213] Findings from this thesis highlight the importance of considering social determinants of colorectal cancer screening when considering potential interventions to promote screening uptake.[214]

7.6 Conclusion

Colorectal cancer remains the second most commonly diagnosed cancer in Canada, and the third most common cause of cancer death.[3] Although some gains in overall screening participation have been achieved in recent years, screening prevalence remains low, and social disparities in screening persist.[5,20-22] There continues to be an urgent need to identify pathways for intervention to promote screening and reduce screening disparities. The overarching goal of this thesis was to contribute knowledge on the social determinants of colorectal cancer screening in Canada, and to explore potential pathways of intervention—both by identifying mechanisms that explain existing social disparities and by evaluating how current population-level intervention strategies affect screening uptake overall and among vulnerable populations.

This thesis supports the notion that colorectal cancer screening is a socially patterned health behaviour, determined by social factors and conditions. This thesis demonstrates that

above and beyond individual-level characteristics, the places where people live, and the make-up of their communities affects individual screening behaviour. Individuals' access to health resources such as primary care physicians also determines screening behaviour. However, when studying social inequalities in screening—namely between recent immigrants to Canada and individuals who were born in the country—we found that though improving access to primary care physicians may increase screening overall, it would likely not be sufficient to reduce or eliminate the observed disparity. Immigration status and its related experiences influence screening above and beyond access to primary care physicians. This observation highlights the need for future health interventions and research that consider social conditions and markers of social status as fundamental determinants of screening. Moreover, findings that population-wide organised screening programs—be they systematic or patient-reliant in nature—increase overall screening participation, but do not appear to decrease screening disparities by income, education, access to physicians or rural residence, reinforce the notion that reductions of social inequalities in screening may require complementary, targeted interventions. Population-based screening promotion efforts that target social determinants of screening may be required to achieve significant decreases in screening inequalities.

7.7 Chapter references

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APPENDICES

Appendix I: Curriculum Vitae

ALEXANDRA BLAIR
alexandra.blair@umontreal.ca

EDUCATION

2014-2018 **PhD Public Health, Specialization in Epidemiology**. University of Montreal, CHUM Research, Montreal, Canada.
Topic: Multilevel determinants of colorectal cancer screening, pathways to cancer screening inequalities, and program evaluation
Supervisors: Geetanjali Datta and Lise Gauvin

2012-2014 **MSc Psychiatry**. McGill University, Douglas Mental Health University Institute Montreal, Canada.
Topic: Measuring Neighborhood Change and Psychological Distress using the National Population Health Survey of Canada.
Supervisor: Norbert Schmitz

2008-2012 **BA Environmental Studies (Ecological Determinants of Health) and Women's Studi**es. McGill University, Montreal, Canada.
Graduated with Distinction.

2006-2008 **DEC Liberal Arts.** Heritage College, Gatineau, Canada.
Valedictorian, Dean's Honor Roll.

EPIDEMIOLOGY AND PUBLIC HEALTH RESEARCH EXPERIENCE

2018-present **Researcher and Analyst.** Public Health Agency of Canada, Quebec Regional Office, Montreal, Canada.
Unit: Public health capacity and knowledge management unit
Areas of work: Surveillance, research, and knowledge mobilization for infectious disease prevention and health equity promotion, specifically on topics of antimicrobial resistance, zoonotic diseases and climate change, and sexually transmitted and blood-borne infections.

2014-2018 **Research Assistant and PhD Student.** CHUM Research Center, Montreal, Canada.
Supervisor: Dr. Geetanjali Datta.
Areas of work: Cancer Screening and Prevention, Social Epidemiology, Policy Evaluation, Health Equity

2017-2018 **Visiting Research Fellow.** Scottish Collaboration for Public Health Research and Policy, University of Edinburgh, Edinburgh, Scotland.
Supervisors: Dr. John Frank, Dr. Louise Marryat
Areas of work: Adverse Childhood Experiences, Poverty, Causal Inference, Knowledge Transfer, Policy Development

2014 **Research Associate.** Institute for Health and Social Policy, Montreal, Canada
Supervisor: Dr. Frank Elgar
Areas of work: Child Health, Mental Health, Social Determinants of Health and Youth Resilience

2012-2014 **Research Assistant.** Douglas Mental Health University Institute, Montreal, Canada.
Supervisor: Dr. Norbert Schmitz
Areas of work: Psychiatric Epidemiology, Diabetes, Adult Mental Health, Social Determinants, Neighborhood and Community Determinants of Health

OTHER TRAINING

2017 **Certificate: A Framework for Analyzing Public Policies.** National Collaborating Centre for Healthy Public Policy.
2014 **Advance use of SAS software.** Quebec Inter-university center for social statistics
2014 **Public health research ethics**. Fonds de la recherche en santé du Québec.

AFFILIATIONS

2014-present Member, Society for Epidemiologic Research
2013-present Member, Canadian Society for Epidemiology and Biostatistics.

AWARDS

2018 **Lieutenant Governor Youth Engagement Medal.** Lieutenant Governor of Quebec, the Honorable J. Michel Doyon.
2017 **Dean's Prize for Community Engagement.** University of Montreal School of Public Health ($1000).
2016 **Jury's Prize for Best Oral Presentation.** Colloque de l'Association des étudiants et étudiantes en santé publique de l'Université de Montréal ($250).
2014 **Roger Bland Award for Beast Presentation by a Trainee.** Canadian Academy of Psychiatric Epidemiology (CAPE) ($200).
2014 **Marion Birmingham-Trevor Dennis Award for Best Student Presentation.** Department of Psychiatry, McGill University ($100).
2014 **Winner—*3 Minute Thesis* Competition.** McGill University ($800).
2012 **Graduate Excellence Award in Psychiatry**. McGill University ($1500).

SCHOLARSHIPS

2015-2018	**Vanier Canada Graduate Doctoral Scholarship**. Canadian Institutes of Health Research (CIHR)	$150,000
2015-2018	**Doctoral Training Award.** Fonds de la recherche en santé du Québec (FRSQ) (Declined)	$60,000
2017-2018	**Michael Smith Foreign Study Supplement**. CIHR.	$6,000
2018	**Travel Award.** CIHR-Institute for Population and Public Health.	$500
2018	**Student Award.** Canada's Applied Research in Cancer Control Conference.	$150
2017	**Travel Award.** CIHR-Institute for Cancer Research	$1,000
2016	**Travel Award.** CIHR-Institute for Population and Public Health.	$2,300
2015	**Scientific Production Award.** Quebec Inter-University Center for Social Statistics (QICSS)	$600
2015	**Travel Scholarship.** Canadian Society for Epidemiology and Biostatistics.	$250
2013-2014	**Masters Training Award.** FRSQ.	$30,000
2014	**Social Statistics Research Entrance Scholarship.** QICSS	$2,000
2014	**Travel Award.** CIHR- Institute for Population and Public Health.	$1,500
2014	**Graduate Research Outcome Grant**, QICSS.	$1000
2013	**Graduate Research Excellence Award for Travel**. McGill University.	$900
2008-2012	**National Award.** Canadian Millennium Scholarship Foundation.	$32,000

KNOWLEDGE DISSEMINATION AND TRANSLATION

Peer-reviewed journal publications

2019 [Accepted] **A. Blair**, L. Gauvin, S. Ouedraogo, G. Datta. Area-level income disparities in colorectal cancer screening in Canada: Evidence to inform future surveillance. *Current Oncology.*

2019 [Accepted] **A. Blair**, L. Gauvin, M.E. Schnizter, G. Datta. The role of access to a regular primary care physician in mediating immigration-based disparities in colorectal cancer screening: Application of multiple mediation methods. *Cancer Epidemiology Biomarkers and Prevention.*

2018 **A. Blair,** A. Siddiqi. J. Frank. Canadian report card on health equity across the life-course: Analysis of time trends and cross-national comparisons with the United Kingdom. *Social Science and Medicine – Population health.*

2018 G. Datta, **A. Blair**, MH. Mayrand, MP. Sylvestre, L. Gauvin. Cervical cancer screening in Montreal: A cross-sectional study building evidence to support primary care and policy interventions. *Preventive Medicine.*

2015 Oskoui M., Messerlian C., **Blair, A.**, Gamache, P., Shevell, M. Variation in cerebral palsy profile by socio-economic status. *Developmental Medicine & Child Neurology.*

2015 **Blair, A.** G. Gariepy, N. Schmitz. The longitudinal effects of neighborhood social and material deprivation change on psychological distress in urban, community-dwelling Canadian adults. *Public Health.*

2014 Gariepy, G., Kaufman, J.S., **Blair, A.**, Kestens, Y., Schmitz, A. Place and health in diabetes: The neighborhood environment and risk of depression in adults with Type 2 diabetes. *Diabetic Medicine.*

2014 Gariepy, G., **A. Blair,** Y. Kestens, B. Thombs, J. S. Kaufman, N. Schmitz. Neighbourhood characteristics and 10-year risk of depression in Canadian adults with and without a chronic illness. *Health & Place*.

2014 **Blair, A.,** G. Gariepy, N. Ross, N. Schmitz. Why do neighborhoods affect depressive symptoms? A realist review of causal pathways. *Journal of Social Psychiatry and Psychiatric Epidemiology*.

Oral Presentations

2018 *Canadian Public Health Association Conference.* Can community resources mitigate the effects of household poverty on ACE (Adverse Childhood Experience) incidence? Montreal, Canada, May 2018.

2018 *Applied Research in Cancer Control Conference.* The role of access to a primary care physician in mediating immigration-based disparities in colorectal cancer screening: Applying multiple mediation analysis techniques. Montreal, Canada, May 2018.

2017 (Invited speaker) *Glasgow University Center for Adverse Childhood Experiences.* Community resources, household poverty, and ACE incidence: Preliminary results of a Scottish study. Glasgow, UK, November 2017.

2017 *Society for Longitudinal and Lifecourse Studies Conference.* The Prevalence of Adverse Childhood Experiences in the General Population of Scottish Children. Stirling, UK, October 2017.

2016 *Université de Montréal Ma thèse en 180 secondes.* La promotion du dépistage du cancer colorectal au Québec et au Canada: Enjeux et pistes d'action. March 2016.

2016 *Epidemiologic Congress of the Americas.* Disparity in colorectal cancer screening between recent and non-immigrants in Canada: Mediation by access to a regular medical doctor. Miami, USA, June 2016.

2015 *Canadian Society for Epidemiology and Biostatistics Conference.* Cervical cancer screening in First Nations, Métis, and Inuit women in Quebec. Toronto, June 2015.
2014 *Canadian Academy of Psychiatric Epidemiology Annual Meeting.* Neighborhood deprivation change, urban renewal, social mobility, and psychological distress in Canada. September 2014.
2014 *Three Minute Thesis Competition.* How do neighborhoods impact mental health? McGill University (Winner), and Dalhousie University. March-April 2014.

Poster Presentations

2018 *Society of Epidemiological Research.* Impact of organized colorectal cancer screening programs on socioeconomic and health-service related screening inequities: A study of three provincial programs in Canada. Baltimore, USA.
2017 *Society of Epidemiological Research.* Urban area-level income and likelihood of non-recent colorectal cancer screening in Canada. Seattle, USA
2016 *Epidemiologic Congress of the Americas.* Disparity in colorectal cancer screening between Aboriginal and non-Aboriginal adults in Canada: Magnitude and meditational role of socioeconomic, health care access. Miami, Florida, June 2016.
2014 *Society of Epidemiological Research.* The effects of neighborhood social and material deprivation change on psychological distress of Canadian adults living in urban areas. Seattle, USA. June 2014.
2013 *Canadian Academy of Psychiatric Epidemiology Conference*. A Systematic Review of Causal Pathways Linking Neighborhoods to Depression Outcomes. Ottawa, Canada. September 2013
2013 *International Federation of Psychiatric Epidemiology Conference*. How Do Neighborhoods Affect Depression Outcomes? Leipzig, Germany. June 2013

Newspaper articles and report writing

2017 *Magazine article.* Faut bouger ses fesses! Journal l'Actualité, June 2017.
2017 *Blog interview.* Ma thèse en 150 mots. May 2017.
2017 *Newspaper interview.* Le Québec tarde à dépister un cancer meurtrier. Le Forum de l'Université de Montréal. May 2017.
2015 *Newspaper interview.* Un colloque sur l'innovation en santé publique. Quartier Libre de l'Université de Montreal. February 2015.
2014 A. Blair**,** C. Allen, "From Evidence to Policy: Report on the McGill University Institute for Health and Social Policy and the Montreal Health Equity Research Consortium Annual Meeting", McGill University Institute for Health and Social Policy. August 2014.

COMPETENCIES

- Fluently bilingual (English, French)
- Extensive experience with Stata, R, SAS, SPSS, EndNote, Microsoft Office Suite.
- Strong written and oral communication skills
- Experience in coordination and working with stakeholders

Appendix II: Risk factors for colorectal cancer

This appendix summarizes the risk factors for colorectal cancer. Discussed below, risk factors for CRC include diseases of the digestive tract, family history and genetic factors, and

behavioural or dietary factors. Colorectal cancer is most likely to occur in adults aged 50 years and above.[215]

Diseases of the digestive tract

Diseases of the digestive tract associated with colorectal cancer incidence include the following: ulcerative colitis, an inflammatory bowel disease causing the presence of ulcers in the digestive tract; familial or multiple polyposis (including familial polyposis colonae, polyposis coli, familial intestinal polyposis, hereditary gastrointestinal polyposis, multiple familial polyposis, Gardner's syndrome, Peutz-Jaegher's syndrome, Canada-Cronkhite syndrome, and Turcot syndrome), symptoms of which are the presence of adenomatous (benign) polyps in the colon; and Crohn's Disease, which is a granulomatous inflammatory disease (i.e. granuloma inflammation caused by the accumulation of immune cells) of the colon.[215] These conditions are thought to be risk factors of colorectal cancer through the pathway of chronic inflammation.[216] Chronic inflammation is associated with oxidative stress—that is, inflammatory cells produce reactive oxygen and nitrogen—and these, in turn, can affect the expression of tumor suppressor genes such as p53. [216] The p53 gene prevents cell growth if cells are mutated or abnormal. Mutations in these genes disempower growth-inhibitory mechanisms normally working at the check-points of the cell-cycle. Tumor growth will no longer be suppressed, and thus any dysregulation of p53 can lead to tumour development, in this case in the forms of adenomatous polyps.[217]

Hereditary conditions

Patients with personal or family history of rectal or colonic polyps more likely to develop colorectal cancer.[215] It is proposed that inherited genetic factors contribute to approximately 15-25% of CRC incidence.[218] Many of the digestive tract diseases listed in the previous paragraph are associated with hereditary features. Additionally, approximately 5% of colorectal cancer cases are in fact Hereditary Non-polyposis Colorectal Cancer (HNPCC) cases. HNPCC (also known as Lynch syndrome) is an autosomal dominant condition, and is caused by inherited germ-line mutation in one or more mismatch DNA repair genes hMHL1, hMSH2, hMSH6, PMS2.[219] DNA repair genes ensure the reparation of abnormal or mutated genes. Mutations of DNA repair genes result in accumulation of oncogenes and mutated tumor-suppressor genes that

disrupt the normal cell cycle and lead to carcinogenesis.[217] The remaining 75% of cases are sporadic.[218]

Dietary risk factors

In sporadic colorectal cancer cases (75% of all cases) behavioural risk factors related to diet play an important role. Dietary risk factors of colorectal cancer include consuming a diet that is low in fiber, and high in red and processed meats,[215] and smoking.[220] Fiber allows for a smoother, faster passing of food through the digestive tract. The hypothesized causal mechanisms linking fiber intake to reduced colorectal cancer risk are the following: 1) cereal fiber might bind carcinogens present in the colon or rectum, 2) cereal fiber might modify the glycemic index and thus reduce the potential of tumour production by lowering levels of insulin, glucose, and triglycerides in the colon and rectum.[221] Red and processed meats are thought to increase the risk of colorectal cancer through the following pathways: 1) the heterocyclic amines contained in cooked meat have the potential to be mutagenic; 2) carcinogenic N-nitroso compounds can be formed in the gastrointestinal tract following the breakdown of *heme* or of nitrites or nitrates used as preservatives, found in high concentrations in red meat.[222] Lastly, as for the risk associated with smoking, tobacco smoke is known to contain several carcinogens that when passing through the circulatory or digestive systems may increase likelihood of polyp development in the colon or rectum.[220]

Behavioral factors

Lack of exercise and obesity are both associated with increased risk of colorectal cancer. Both factors are associated though the mechanism of energy balance. Regular physical activity is thought to be protective of CRC via lowered insulin levels, and lowered insulin levels are associated with lowered cancer risk.[223] Physical activity is also associated with weight control. Higher weight is associated with insulin resistance (described above) and chronic inflammation (i.e. a large production of storage lipids and high levels of circulating glucose create a proinflammation environment).[224] Inflammation can lead to DNA damage, as discussed above.

Sex and gender differences

The sex differences in colorectal cancer burden are hypothesized to be explained by differential exposure to lifestyle factors (e.g. diet, physical activity) and to protective estrogen.[219,225]

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Appendix III: Natural history of colorectal cancer

Colorectal cancer is cancer that affects the colon (large intestine) or the rectum. Since cancerous polyps tend to affect both areas, colon and rectal cancers are usually combined when discussed, and described as "colorectal" cancer.[215] The natural history of CRC spans between 10 and 15 years.[226] First, precursor lesions appear in the colon or rectum in the form of adenomatous (benign) polyps (Stage 0: carcinoma in situ), and these may progress to further cancerous stages (e.g. malignant adenocarcinoma).[14,227]

At stage 1, the cancer has formed and spread from the innermost layer of the colon (mucosa) to subsequent layers (submucosa), or to the muscles around the colon wall. This cancer is considered localized. At stage 2, the cancer has spread further through the layers of the colon wall, either through the muscle to the outermost layer (i.e. serosa – Stage 2A), through the outermost layer but not surrounding organs (Stage 2B), or through the outermost layer and to nearby organs (Stage 2C). This cancer is considered regionalized. At Stage 3, the cancer has spread to up to six lymph nodes or formed near the lymph nodes (Stage 3A), the cancer has spread to up to seven lymph nodes (Stage 3B), or cancer cells have formed in nearby organs (Stage 3C). At stage 4, the cancer has spread to an organ that is distant from the colon (i.e. liver, lung, ovary) (Stage 4A), or has spread into the lining of the abdominal wall (Stage 4B).[14] At stages 3 and 4, the cancer is considered metastasized. Treatment strategies for colorectal cancer will vary according to the cancer's stage and patient characteristics. They can include surgery (local excision or resection of the colon), radiofrequency ablation, and chemotherapy.[14]

Polyp types

There are several types of colonic polyps. The most common types are hyperplastic polyps, adenomatous polyps, and malignant polyps.[228] These can be further subdivided based on morphological appearance and molecular alterations.[229] Hyperplastic polyps are usually small, located in the rectum or sigmoid colon, and are usually asymptomatic.[230] Though the malignant potential for hyperplastic polyps is low,[229] carcinoma has been observed to develop within hyperplastic polyps in a minority of cases.[231] Adenomatous polyps form two thirds of all colonic polyps. [228] Most do not develop into cancer. They are categorized in relation to their size, appearance and features. Larger adenomas (>5 mm) are more likely to develop into cancer. [228]

Malignant polyps contain cancerous cells. At visual inspection it is impossible to differentiate between polyp types –a biopsy is necessary to assess, via microscope, the removed cells.[228]

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230. International Classification of Diseases for Oncology ICD-O-3 online: 8213/o Mixed Adenomatous and Hyperplastic Polyp. 2019; http://codes.iarc.fr/code/312. Accessed January 21, 2019.
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Appendix IV: Screening tests and performance metrics

To prevent invasive CRC, the Canadian Cancer Society recommends that average-risk adults aged 50-74 have a stool test (guaiac-based fecal occult blood test (FOBT or gFOBT) or fecal immunochemical test (FIT or iFOBT)) at least every 2 years. Positive stool test results should be followed-up with a colonoscopy or flexible sigmoidoscopy—the best practice of which is the colonoscopy procedure. [5]

Fecal occult blood test (FOBT) and Fecal immunochemical test (FIT)

FOBT can be self-administered, as it involves the collection of three separate, small samples of stool on three consecutive days. The procedure involves defecating on a floating, flushable pad—which is placed in the toilet bowl. Then, using a thin stick, a small sample of stool is removed and placed on the sampling kit envelope (test card) that is to be sent to the lab or to the doctor via mail.[13] Identification of blood in the stool is confirmed using guaiac paper.[215] Consumption of red meat, radishes, melons, potato, grapefruit, cauliflower, pumpkin, zucchini, cucumber, figs, broccoli, carrot, parsley, turnip, cabbage, vitamin C and iron supplements, as well as certain pain and blood-thinning medications are recommended to be avoided for three days previous to the test.[13] The reported sensitivity and specificity of gFOBT varies in the literature. The sensitivity of a single gFOBT to detect advanced adenomas was 14%, to detect cancer was 31%, and to detect advanced neoplasia was 17%. The specificity of detecting each of the latter outcomes is 92%, 92%, and 93%.[11] To increase sensitivity, it is recommended to increase the number of stool samples.

The FIT sample collection is identical to the FOBT process, however instead of using guaiac paper to detect blood in the stool FIT uses protein antibodies.[13] No dietary restrictions are required prior to FIT screening.[14] The sensitivity of a three-sample FIT to detect advanced adenomas was 34%, to detect cancer was 85%, and to detect advanced neoplasia was 44%. The specificity of detecting each of the latter outcomes is 91%, 90%, and 92%.[11] Due to these performance characteristics, qFIT has been judged as a stronger screening tool than FOBT. [11]

For both these stool tests, costs are low, sedation is not necessary, are there are no risks of harm to the lining of the colon.[14] Using one of these tests every 2 years has been shown to reduce colorectal cancer morbidity by 15 to 33% at a population level.[14]

Sigmoidoscopy

A sigmoidoscopy involves screening the rectum and sigmoid colon (not the ascending or transverse colons) using a sigmoidoscope.[14] This procedure also permits the biopsy of identified growths. The preparation for a sigmoidoscopy involves drinking only clear liquids for 24 hours before the exam, and consumption of prescribed laxatives the night before the exam, in order to empty the colon and rectum.[13] No sedation is necessary for a sigmoidoscopy. The process takes up to 20 minutes, and slight bleeding or cramping following the procedure is normal.[13] A disadvantage to sigmoidoscopy screening is the inability to detect polyps beyond the sigmoid colon. The sensitivity of flexible sigmoidoscopy to detect all sizes of polyps is 72%, but 67% for >5mm polyps, 68% for >9mm polyps, and 97% for advanced colonic neoplasia. The specificity for each of the latter outcomes was 71%, 99%, 100%, and 60%. The positive predictive values for each of the latter outcomes were 59%, 91%, 94%, 18%. Whereas the negative predictive values were 81%, 95%, 97%, and 97%.[12] Sigmoidoscopy use every five years after age 50 reduces colorectal cancer mortality by 60-70%.[14]

Colonoscopy

The colonoscopy procedure uses a colonoscope to observe the entire length of the rectum and colon and remove abnormal growths for testing. Preparation for a colonoscopy is quite intensive. It involves drinking only clear liquids for 24-48 hours before the test, consumption of prescribed laxatives the night before the exam, fasting the morning of the test, and at times receiving an enema the morning of the test, in order to empty the colon and rectum.[13] Sedation is performed for the test, and therefore a caregiver is usually required to ensure persons undergoing colonoscopy are returned home safely.[13] The test lasts approximately 30 minutes. For one to two days after the test some blood may be observed in the stool due to contact of the colonoscope with the colon wall.[13] Perforation of the colon wall is possible though occurs infrequently.[13]

Performance measures of the colonoscopy procedure vary from study to study. It is estimated that sensitivity of colonoscopy to identify all size of polyp is 97%, and it is 98% for identifying >5mm polyps, 100% for >9mm polyps, and 100% for identifying advanced colonic neoplasia.[12] Specificity for each of these outcomes is 60%, 96%, 99%, and 43%.[12] The positive predictive values for each of the latter outcomes is 59%, 80%, 86%, and 16%, while the negative predictive values are 98%, 100%, 100%, and 100%.[12] If colonoscopies are performed every 10 years in adults aged 50-74, mortality from colorectal cancer can be reduced by 60-70%.[14]

Population screening

Currently, initial screening using stool-based screening tests is recommended, despite its performance limitations, insofar is it a cost-effective CRC prevention approach.[232] Despite its strong performance metrics, colonoscopy-based screening has not been shown to be cost-effective in relation to amount of life saved (i.e. cost less than $30,000 per year of life saved), and is therefore not used as the primary mode of prevention.[232]

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Appendix V: Projected incidence and costs of colorectal cancer

Projected incidence

The projected number of new cases of CRC by 2030 in Canada is just over 35,000 cases if no organized screening is in place, compared to approximately 32,500 cases if 30% of age-eligible adults received regular stool-based testing (through FIT test) and just less than 30,000 new cases if 80% of age-eligible adults received regular stool-based testing (through FIT test).[1]

Costs

In 2008, approximately 557 million Canadian dollars were spent on treatment of CRC in 2008.[18] These costs are expected to grow along with an increasing burden of colorectal cancer among the aging Canadian population.[1] In economic terms, preventive screening is more cost-effective than a no-screening, purely treatment-based approach[19] Because screening detects cancers at earlier stages, screening extends quality adjusted life years (QALY) (i.e. for an average-risk 50 year-old, discounted QALYs ranged from 15.20 years for no screening, 15.26 for annual FOBT, 15.30 for annual FIT, 15.32 for a colonoscopy every 10 years); and both colonoscopy and FIT screening offer the best value for money compared to no-screening (according to the benchmark of willingness-to-pay of $50,000 per life-year gained).[19]

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Appendix VI: Publication trends

The literature on colorectal cancer screening is younger than that on colorectal cancer itself—but even less developed is the literature on colorectal cancer screening inequalities. The literature on colorectal cancer screening began to grow in the mid-1990s, and the majority of studies have been set in the United States.[63]

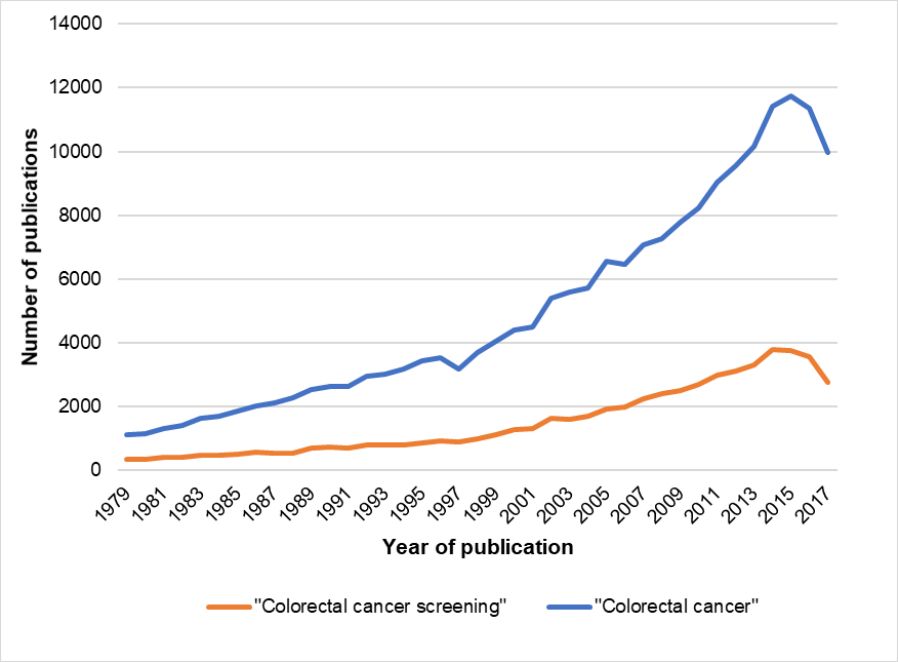

Figure 7: Number of publications on "colorectal cancer screening" and “colorectal cancer” published between 1946 and 2015 on the PubMed Database (graph created by A.Blair using PubMed publication counts), February 8, 2018.

Section reference

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Appendix VII: Colorectal cancer screening programs in Canada

Table 4.1: Description of provincial and territorial colorectal cancer screening programs in Canada

Province	Start	Program name and description	Screening approach for average risk adults (Age 50-74 years)	Screening for higher-risk adults	Method of distribution and pick-up of screening kit
British Columbia	2009	Colon Screening Program (Registration in BC Colon Screening Registry: Reminder Letters Program)	Fecal Immunochemical Test (FIT)	Colono-scopy	Lab pick-up and drop-off
Alberta	2007	Alberta Colorectal Cancer Screening Program	Fecal Immunochemical Test (FIT)	Colono-scopy	Lab pick-up and drop-off
Saskatchewan	2009	Screening program for colorectal cancer (Registration in SK Colon Screening Registry: Reminder Letters Program)	Fecal Immunochemical Test (FIT)	Colono-scopy	Mail pick-up and drop-off
Manitoba	2007	Coloncheck Manitoba (with Reminder Letters)	Guaiac fecal occult blood test (gFOBT)	Colono-scopy	Mail pick-up and drop-off
Ontario	2008	ColonCancerCheck Program (with Reminder Letters)	FOBT	Colono-scopy	Mail or pharmacy pick-up, mail drop-off
New Brunswick	2014	NB Colon Cancer Screening Program (Screening registry reminder letters)	Fecal Immunochemical Test (FIT)	Colono-scopy	Mail pick-up and drop-off
Nova Scotia	2009	Nova Scotia's Colon Cancer Prevention Program (Screening registry reminder letters)	Fecal Immunochemical Test (FIT)	Colono-scopy	Mail pick-up and drop-off
Prince Edward Island	2011	Colorectal Cancer Screening Program (Screening registry reminder letters)	Fecal Immunochemical Test (FIT)	Colono-scopy	Lab, health center or mail (after request) pick-up; Lab drop-off
Newfoundland and Labrador	2010	Province-wide: Newfoundland and Labrador Colon Cancer Screening Program (Screening registry reminder letters)	Fecal Immunochemical Test (FIT)	Colono-scopy	Mail pick up (after request); Mail drop-off
Quebec, Nunavut, Yukon, Northwest Territories	Not yet established	NA	NA	NA	

Source: Colorectal Cancer Screening in Canada: Environmental Scan. Toronto, Canada: CPAC, 2015.

Table 5.2: Description of provincial programs' methods of invitation, screening kit delivery and return

Province	Invitation letter sent?	Accessing kits			Returning kits		Reference
		Kit sent systematically via mail?	Kit sent via mail post-request?	Pick up kit in person	Return kit via-mail?	Drop-off kit in person	
NS	✓	✓			✓		link
SASK	✓	✓			✓		link
MAN	✓	✓			✓		link
ON	✓		✓		✓		link
NB	✓		✓		✓		link
PEI	✓		✓			✓	link
NFLD	X		✓		✓		link or link
BC	X			✓		✓	link
AB	X			✓		✓	link or link

Colour legend: "Systematic mail-based" | "Patient-reliant" | No invitation sent

Note: "NS" = Nova Scotia, "SASK" =Saskatchewan, "MAN" =Manitoba, "ON" = Ontario, "NB"=New Brunswick, "PEI" = Prince Edward Island, "NFLD"= Newfoundland., "BC" = British Columbia, "AB"= Alberta.

Appendix VIII: CCHS Questionnaire Items

Table 6: CCHS Questionnaire Items on Colorectal Cancer

Variable	Questionnaire Item	Possible Responses
FOBT screening	An FOBT is a test to check for blood in your stool, where you have a bowel movement and use a stick to smear a small sample on a special card.	
	Have you ever had this test?	Yes, No, Don't Know, Refuse to Answer
	[If yes] When was the last time?	Less than 1 year ago, 1 year to less than 2 years ago, 2 years to less than 3 years ago, 3 years to less than 5 years ago, 5 years to less than 10 years ago, 10 or more years ago, Don't Know, Refuse to Answer
Reason for FOBT screening	Why did you have it?	[Mark all that apply] (1) Family history of colorectal cancer (2) Part of regular check-up /routine screening (3) Age (4) Race (5) Follow-up of problem (6) Follow-up of colorectal cancer treatment (7) Other – Specify (8) Don't Know, (9) Refuse to Answer
Endoscopy	A colonoscopy or sigmoidoscopy is when a tube is inserted into the rectum to view the bowel for early signs of cancer and other health problems.	
	Have you ever had either of these exams?	Yes, No, Don't Know, Refuse to Answer
	[If yes] When was the last time?	Less than 1 year ago, 1 year to less than 2 years ago, 2 years to less than 3 years ago, 3 years to less than 5 years ago, 5 years to less than 10 years ago, 10 or more years ago, Don't Know, Refuse to Answer
Reason for colonoscopy	Why did you have it?	[Mark all that apply] (1) Family history of colorectal cancer (2) Part of regular check-up /routine screening (3) Age

	(4) Race (5) Follow-up of problem (6) Follow-up of colorectal cancer treatment (7) Other – Specify (8) Don't Know, (9) Refuse to Answer

Questionnaire items are described on-line here:
http://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=assembleInstr&a=1&&lang=en&Item_Id=238890#qb244936
or https://tinyurl.com/ya5u24wx

Source: Statistics Canada, 2013.

Other relevant self-reported questionnaire items

Additionally, participants are asked "Do you have a regular medical doctor?" (yes/no). The reliability of self-reported access to a regular medical doctor has not been thoroughly studied in the literature. One study compared the proportion of Ontario residents without a regular medical doctor using two surveys: the CCHS 2007-2008 and the Primary Care Access Survey (PCAS) administered in 2006-2007. The former reported that 9% did not have a family doctor, while the latter reported 7%[233]—in absolute terms, these proportion are similar.

Section reference

233. Hay C, Pacey M, Bains N, Ardal S. Understanding the Unattached Population in Ontario: Evidence from the Primary Care Access Survey (PCAS). *Healthcare Policy.* 2010;6(2):33-47.

Appendix IX: Power considerations

IX.I Objective 1

For the first thesis objective, generalized estimating equation (GEE) models were specified, with an assumed exchangeable covariance structure. To estimate how large a sample would have to be to identify various effect sizes, we apply a formula proposed by Liu and Liang (1997). This formula was developed in the context of GEE modeling via logistic regression. We apply it here, even if we in fact applied a GEE model using a Poisson log-link; we assume that the output given a logit-link would offer approximations of a relative effect measure. Using a logistic model, the null hypothesis is that probability of screening is equivalent for those exposed and those unexposed (i.e., *p0= p1*) or that the regression coefficient is equivalent to 0 (i.e., OR =1).

If we let:

- $\pi 1$ be the proportion of individuals exposed (approximately 25% in each area-level income quartile);
- $\pi 0$ be the proportion of individuals unexposed (approximately 75%);
- n be the number of individuals per Dissemination Area (approximately 6);
- $z_{1-\frac{a}{2}}$ be the z score associated with an alpha value of 0.05 (value of 1.96);
- z_{1-B} be the z score associated with power (*B)* at 80% (value of 0.84);
- $p0$ be assigned the reference OR (value of 1);

and let the following parameters vary:

- ρ is the intra-class correlation of screening outcomes for respondents within the same Dissemination Area
- $p1$ is assigned an effect size OR value

Then, according to Liu and Liang (1997), the sample size needed (m) for GEE estimation is equivalent to:

$$m = \frac{\left(z_{1-\frac{a}{2}} + z_{1-B}\right)^2 (\pi 1 p0(1-p0) + \pi 0 p1(1-p1))(1+(n-1)\rho)}{n\pi 0 \pi 1 (p1-p0)^2}$$

We apply the latter formula varying values of $p1$ and ρ in the table below:

Table 7: Sample sizes needed to detect various associations sizes between area-level income and colorectal cancer screening using a GEE modeling approach (Objective 1)

	Alpha= 0.05, Power=0.80, N per dissemination area = 6		
Effect size (OR) (*p1*)	Intraclass correlation (ρ)	Number of clusters needed (*m*)	Total sample size needed
1.01	0.50	59,148	354,891
	0.30	42,249	253,493
	0.20	33,799	202,795
	0.15	29,574	177,445
	0.10	25,349	152,096
	0.05	21,124	126,747
1.05	0.50	2,073	12,439
	0.30	1,481	8,885
	0.20	1,185	7,108
	0.15	1,037	6,220
	0.10	889	5,331
	0.05	740	4,443
1.1	0.50	427	2,561
	0.30	305	1,829
	0.20	244	1,463
	0.15	213	1,281
	0.10	183	1,098
	0.05	152	915
1.15	0.50	149	894
	0.30	106	639
	0.20	85	511
	0.15	75	447
	0.10	64	383
	0.05	53	319
1.20	0.50	61	366
	0.30	44	261
	0.20	35	209
	0.15	30	183

*Blue highlight indicates detectable RR with approximately *m=7,200* Dissemination Areas available, alpha=0.05 and power= 80.

IX.II Objective 2

For the second thesis objective, several mediation methods were applied. Though few if any sample size and power estimation tools have been developed for inverse probability weighting-based analyses, a limited number of tools do indeed exist for regression-based methods. Below, some of these methods are applied to estimate how large a sample would have to be to identify various sizes of total and controlled direct effects estimated using a generalized product method approach.

Total effects

To estimate what level of power would be achieved given sample parameters and various sample sizes, the powerMedation package in R was used, which applies a formula proposed by Hsieh et al. (1998). This formula was developed in the context of logistic regression modeling. We apply it here, even if we in fact specified Poisson models for total and controlled direct estimation; we assume that the output given a logit-link would offer approximations of a relative effect measure (i.e. prevalence ratio). Letting:

n	be the total number of sample size (size to vary)
$p1$	be the event rate among the unexposed (size to vary)
$p2$	be the event rate among the exposed (0.716 or 71.6%)
B	be the proportion of the sample that is unexposed (value of 0.0061 or 0.61% for visible minority recent immigrants, 0.38 or 38% for white recent immigrants)
α	be the Type 1 error rate (value of 0.05)
$z_{1-\frac{\alpha}{2}}$	be the z score associated with an alpha value of 0.05 (value of 1.96);
z_{power}	be the z score associated with power (B) at 80% (value of 0.84);

The sample size formula derived by Hsieh et al. (1998) is:

$$n = \left(\frac{\left[z_{1-\alpha/2} \sqrt{\mathrm{p(1-p)/B}} + Zpower \sqrt{\mathrm{[p1(1-p1)+p2(1-p2)(1-B)/B]}} \right]^2}{\mathrm{[(p1-p2)\text{^}2\ (1-B)]}} \right)$$

Plugging in various values of n in the formula above, the PowerMed package solves the equation for Z_{power}. Assuming the parameter levels stated above, Figure 8 below describes the sample sizes needed to achieve various minimal total effect sizes at 80% power, comparing visible minority recent immigrants to white, Canadian-born (blue line) and white recent immigrants to the same reference group (orange line).

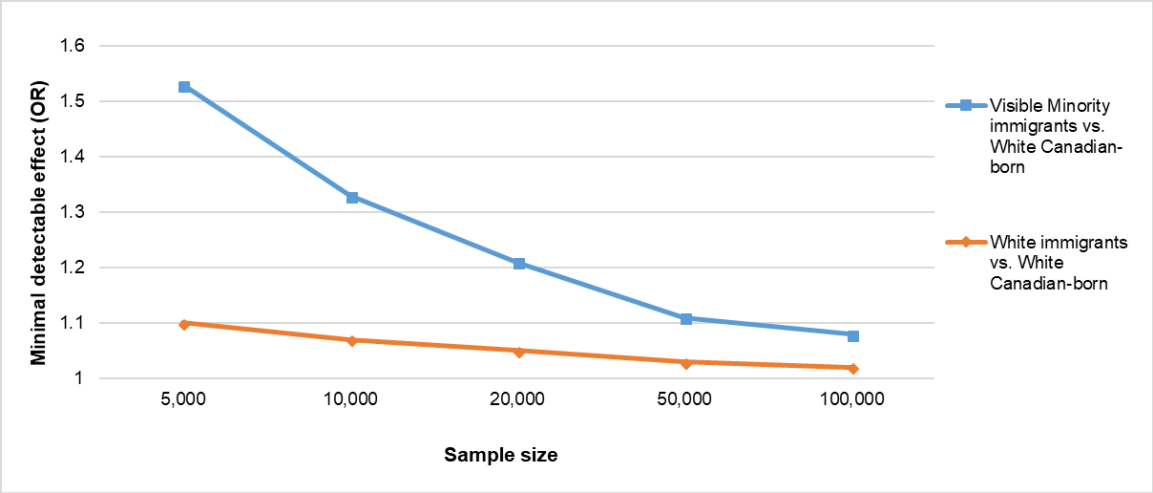

Figure 8: Sample sizes needed to achieve various levels of statistical power in estimating the total association between recent immigration (among visible minority recent immigrants, and among white recent immigrants) and lifetime screening, given sample characteristics (graph created by A. Blair to depict output of sample size calculations using the PowerMediation package in R).

Given the available sample sizes in the CCHS (n=659 visible minority recent immigrants, n=408 white recent immigrants, and n=102,366 white Canadian-born respondents) and the sample characteristics, we estimate that our analyses are sufficiently powered (80% or above) to detect a minimal PR of 1.08 between visible minority recent immigrants and white Canadian-born respondents (true PR>1.50); and a PR of 1.02 between white recent immigrants and white Canadian-born respondents (true PR>1.20).

Controlled direct effects

Unlike the total effects model, which is estimated by fitting an outcome model (for Y=1, never have been screened) without the mediator, the control direct effect (CDE) model includes

the mediator, and a product-term between the exposure (a) and mediator (m_1) (i.e. the am_1 indicator variable):

$$\log(E[Y|a, m_1,m',c']) = \beta_0 + \beta_1 a + \beta_2 m_1 + \beta_3 am_1 + \beta' m + \beta' c)$$

Since the CDE is estimated by taking the sum of coefficients β_1 and β_3, here is it relevant to consider how large a sample would have to be to identify various effect sizes for these two coefficients. Most importantly, however, is the ability to detect the principal coefficient of β_1, insofar as the product term am_1 is recommended to be included in the analyses, regardless of whether a statistically significant exposure-mediator interaction is present.[120]

To assess how large the sample size would have to be to identify various total effect sizes of β_1, a formula derived by Vittinghoff et al. (2009)[185] for mediation analyses using a logistic outcome models an be applied (here, again, estimates from this formula are taken as approximations of a relative effect measure that would be obtained via Poisson regression in our analyses):

$$n = \frac{\left(z_{1-\frac{a}{2}} + z_{1-B}\right)^2}{(\beta_1\sigma_2)^2(1-\rho^2)p(1-p)}$$

Where

- n is the sample size needed;
- p is the marginal prevalence of the outcome (value of 0.47);
- $z_{1-\frac{a}{2}}$ is the z score associated with an alpha value of 0.05 (value of 1.96);
- z_{1-B} is the z score associated with power (B) at 80% (value of 0.84);
- ρ is the correlation between the exposure and mediator (value of 0.01 for visible minority recent immigrants and White, Canadian-born, 0.03 for White recent immigrants and White, Canadian-born);
- β_1 is the log(OR) associated with recent immigration (value of 3.05 for visible minority recent immigrants, 1.47 for white recent immigrants);

σ_1 is the standard deviation of the exposure (recent immigration) (value of 0.08 for visible minority recent immigrants and White, Canadian-born, 0.06 for White recent immigrants and White, Canadian-born);

Applying this formula in the PowerMediation package in R (version 3.4.1),[181] using the values specified above, we find that the CCHS sample is likely sufficiently powered (80% or above) to detect significant regression coefficients for exposure to recent immigration in a controlled direct effects regression model (Figure 9). A sample of N=100,000 respondents could detect at minimum a main effects coefficient of OR=1.25 for visible minority recent immigrants (true OR≈3.05), and an OR=1.35 for white recent immigrants (true OR≈1.47), at 80% power.

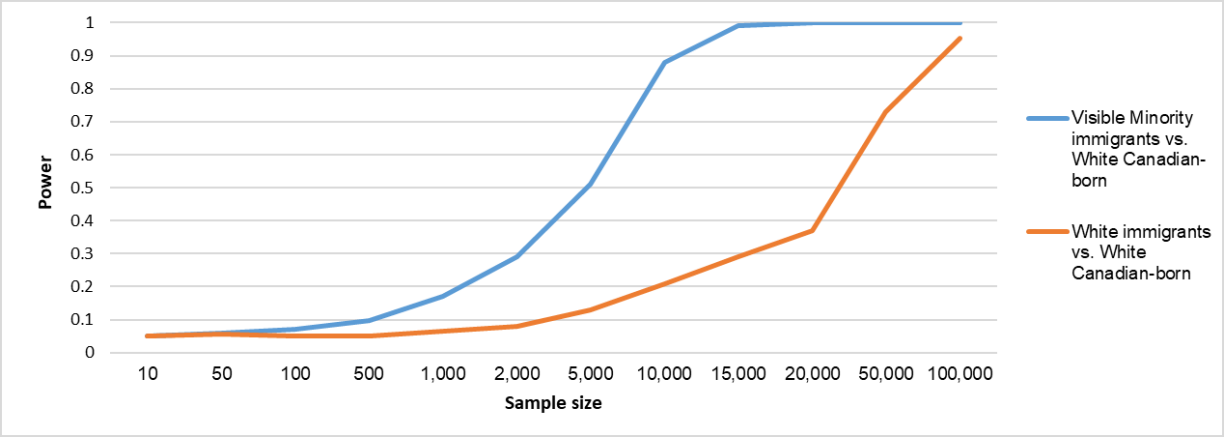

Figure 9: Sample sizes needed to achieve various levels of statistical power in estimating controlled direct effect coefficient (OR=3.05 visible minority recent immigrants; OR = 1.47 for visible minority recent immigrants) in a regression model that contained both the exposure and mediator, given sample characteristics (graph created by A. Blair to depict output of sample size calculations using the PowerMediation package).

IX.III Objective 3

For the third thesis objective, a regression-based Difference-in-Differences design framework was applied. In this framework, specified regression-models include indicator variables for time (pre- or post-intervention), treatment group (treated province or comparison province) and the joint exposure of time and treatment group (product term):

$$\log(E[Y|\ treated,\ post,\ covariates]) = \theta_0 + \theta_1(treated) + \theta_2(post) + \theta_3(treated*post) + \theta'(covariates)$$

As the parameter of interest in this regression model is θ_3, we can consider the following question: given the Difference-in-Differences study design and the available sample size, what is the smallest intervention effect that can be detected (i.e. the "minimum detectable impact"[191])? Assuming that the coefficient θ_3 represents an average treatment effect (ATE) of the program, and assuming a normal distribution of screening prevalence, we can perform a crude analysis of the minimum detectable effect (MDE) for the average treatment effect (ATE). Letting:

n	be the total number of sample size (size to vary)
p	be fraction of respondents exposed to a provincial screening program (approximately 50%)
$\text{Var(Y)}_{\text{hat}}$	be the estimated variance of the outcome (value of 0.60)
α	be the Type 1 error rate (value of 0.05)
$q_{1-\frac{\alpha}{2}}$	be the quantile of the standard normal distribution pertaining to the alpha value of 0.05 (value of 1.96);
q_{λ}	be the quantile of the standard normal distribution associated with power (*B)* at 80% (value of 0.84);

The minimum detectable effect (MDE) for the average treatment effect (ATE)—as discussed in Bloom (2006) and elsewhere is:

$$MDE = \sqrt{\frac{\widehat{Var\ (Y)}}{n}} \sqrt{\frac{1}{p(1-p)}} \left(q_{1-\alpha/2} + q_{\lambda}\right)$$

If the observed treatment effect is smaller than MDE, we would have to conclude that our study may be underpowered.[192] As we see in Figure 10 below, the minimum detectable effect size decreases as the sample size increases. Insofar as the available sample population is of

approximately 20,000 respondents, a crude expectation is that we could detect a minimal prevalence difference (PD) of approximately 3%. This is possibly an over-estimate insofar as the number and distribution of covariates were not taken into account in the above analyses.

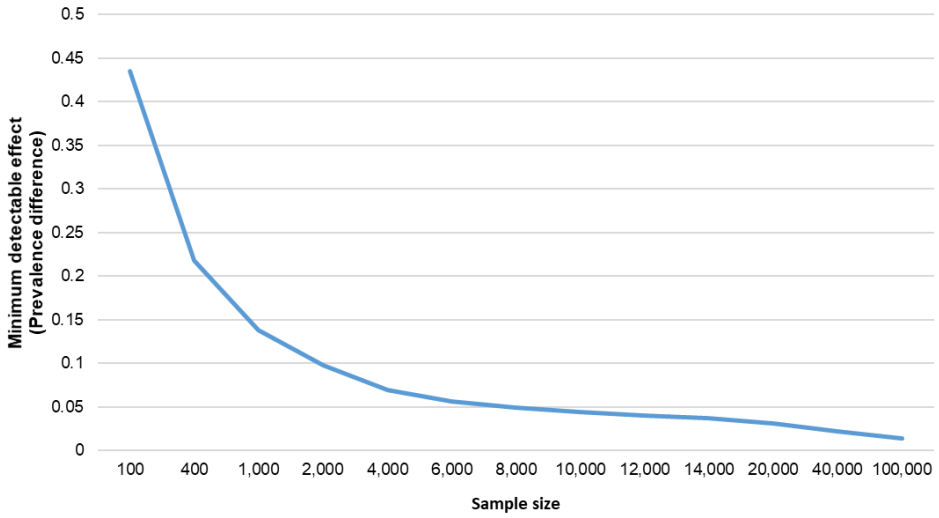

Figure 10 Minimal detectable average treatment effect (ATE) effect sizes (expressed as prevalence differences) according to sample size, given sample characteristics (i.e., 1:1 ratio of treated and comparison assignment, mean screening variance of 0.60 variance, alpha=0.05, power=80%) (graph created by A. Blair to depict output of sample size calculations).

An alternative sample size and power estimation tool that can be used in the context of regression-based analyses with interaction terms is a set of formulas derived by Vanderweele (2012).[234] If we recall that the coefficient θ_3 in the Difference-in-Differences regression model above represents an interaction term between the measures of province of residence (*treated)* and time (*post)* (i.e., *treated*post*), we can consider a log-linear model in which θ_3 is the prevalence difference in screening between treated and untreated populations across time. Here we let

$z_{1-\frac{a}{2}}$ be the z score associated with an alpha value of 0.05 (value of 1.96);

z_{power} be the z score associated with power (*B)* at 80% (value of 0.84);

θ_3 be the value of the prevalence difference for joint exposure;

V be the variance of θ_3*;* obtained by applying formulas described in detail in VanderWeele (2012, p.161-162), using the prevalence differences for each strata of exposure (i.e., $\theta_0, \theta_1, \theta_2, \theta_3$*)* and proportions of respondents in each stratum (here, value 0.71)

The sample size needed to detect various prevalence differences (θ_3) can be estimated according to the formula:

$$n = \frac{\left(z_{1-\frac{a}{2}} + z_{power}\right)^2 * V}{\theta_3^2}$$

As we see in Figure 11 below, the minimum detectable prevalence difference (θ_3) decreases as the sample size increases. Application of this formula indicates that with a sample population of approximately 20,000 respondents, a crude expectation is that we could detect a minimal prevalence difference (PD) of approximately 2% (with alpha set at 0.05, and 80% power). This is possibly an over-estimate insofar as the number and distribution of covariates were not considered in the above analyses.

These sample size estimates are quadrupled[235] to obtain a conservative estimate of the sample size needed to test a three-way interaction (which are used in the Difference-in-Differences-in-Differences analyses of social inequalities in screening):

$$\begin{aligned}\log(E[Y|\,Xi]) = \; & \beta_0 + \beta_1(\textit{treated}) + \beta_2(\textit{post}) + \beta_3(\textit{treated*post}) \\ & + \beta_4(\textit{inequality}) + \beta_5(\textit{inequality*treated}) \\ & + \beta_6(\textit{inequality*post}) + \boldsymbol{\beta_7(\textit{inequality*treated*post})} + \beta'(\textit{covariates})\end{aligned}$$

As we see in Figure 11 below, the minimum detectable prevalence difference (β_7) also decreases as the sample size increases. With a sample of approximately 20,000 respondents, a crude expectation is that we could detect a minimal prevalence difference (PD) in inequalities of approximately 4% (with alpha set at 0.05, and 80% power). This too is possibly an over-estimate insofar as the number and distribution of covariates were not considered in the above analyses.

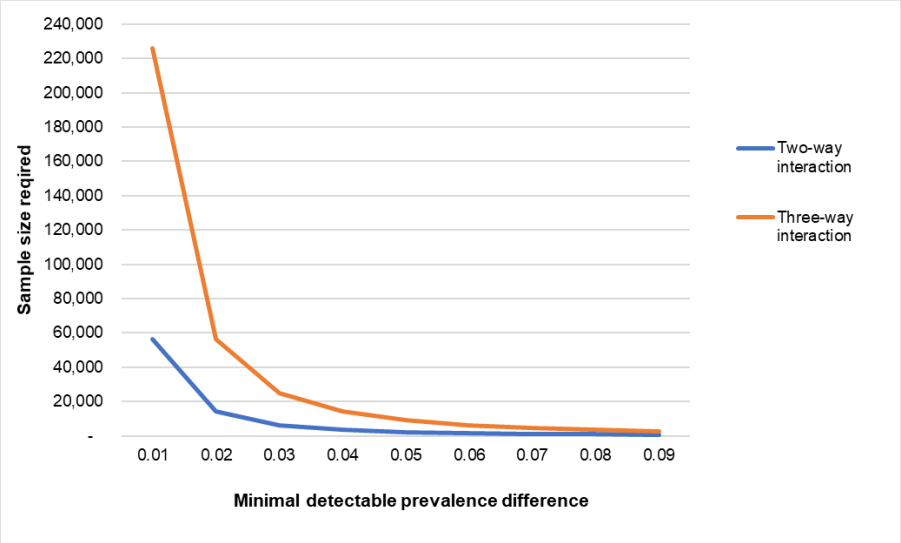

Figure 11: Minimal detectable two-way and three-way interaction in Difference-in-Difference models, according to sample size, and given sample characteristics (i.e., outcome variance of 0.71, alpha=0.05, power=80%) (graph created by A. Blair to depict output of minimal detectable effects given available sample sizes).

Appendix X: Eligible comparison provinces (Objective 3)

To be an eligible comparison, provinces must have (1) available colorectal cancer screening outcome data for at least 2 cycles in the periods specified, and (2) must have not been exposed to an organised screening program themselves in the periods specified. Below are the years of initial implementation of organised screening programs across Canadian provinces, as well as the CCHS cycles for which colorectal cancer screening data were collected in each of the provinces.

Table 8: Eligible comparison provinces for the evaluation of systematic and patient-reliant organised screening programs (selected controls are encircled)

Province	**Program Start Year**[a]	**CCHS cycles (between 2003-2014) with available screening data**[b]	**Eligible comparison for Nova Scotia and Saskatchewan?** ✓= Yes X = No			**Eligible comparison for Prince Edward Island?** ✓= Yes X= No		
			Pre-2009	Post-2009	Pre-And Post	Pre-2011	Post-2011	Pre-And Post
Potential controls								
Alberta	2007	2008, 2011, 2012, 2013	X	X	X	X	X	X
British-Columbia	2009	2003, 2008, 2012	✓	X	X	✓	X	X
Manitoba	2007	2008, 2012, 2013	X	X	X	X	X	X
New Brunswick	2014	2005, 2008, 2009, 2012, 2013	✓	✓	✓	✓	✓	✓
Newfoundland and Labrador	2010	2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012, 2013	✓	✓	✓	✓	X	X
Ontario	2008	2003, 2005, 2007, 2008, 2009, 2010, 2011, 2012	X	X	X	X	X	X
Quebec	NA	2008, 2012, 2013	X	✓	X	X	✓	X
Treated								
Nova Scotia	2009	2005, 2008, 2009, 2010, 2012						
Prince Edward Island	2011	2005, 2007, 2008, 2009, 2010, 2011, 2012, 2013						
Saskatchewan	2009	2003, 2007, 2008, 2009, 2010, 2012						

[a] Provincial program can include mail-outs, self-referral through pharmacies, self-pick up of screening tests, media campaigns, promotion through other cancer screening programs. In 2014, all provinces except Quebec had some sort of programming installed to promote colorectal cancer screening. [b]

Section references

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235. Heo M, Xue X, Kim MY. Sample size requirements to detect a two- or three-way interaction in longitudinal cluster randomized clinical trials with second-level randomization. *Clinical Trials.* August 1, 2014 2014;11(4):503-507.

Appendix XI: Ethics approval and project approval

Ethical approval from the CRCHUM Ethical Review Committee

CHUM

Comité d'éthique de la recherche du CHUM
Pavillon R, 900 rue St-Denis, 3e étage
Montréal (Québec) H2X 0A9

Le 20 mai 2016

Madame Geetanjali Datta
Chercheuse, CRCHUM
Professeure agrégée
Département de médecine socile et préventive, Université de Montréal
Axe de recherche : risques à la santé

a/s : Mme Alexandra Blair
courriel : alexandra.blair@umontreal.ca

Objet :	**16.063 – Approbation initiale et FINALE CÉR restreint**
	Combler les lacunes dans le dépistage du cancer colorectal au Canada: Déterminants multiniveaux de dépistage, inégalités de dépistage, et évaluation de programmes de dépistage

Madame,

Nous accusons réception, en date du 20 mai 2016, des documents soumis en vue de l'approbation du projet mentionné en rubrique. Votre projet a été évalué en comité restreint compte tenu qu'il s'agit d'un projet considéré à risque minimal pour les participants. Nous avons examiné les documents suivants :

- Formulaire de demande d'évaluation éthique d'un projet (formulaire 11)
- Protocole de recherche, version 3 datée du 20 mai 2016
- Document attestant que le projet de recherche porte sur une utilisation secondaires de données issues de Staistiques Canada et qu'il n'y aura aucun recrutement ou communication avec des participants, daté du 25 janvier 2016
- Lettre d'offre de bourse (Bourse Vanier), IRSC, datée du 31 mars 2015
- Lettre d'octroi de bourse, CIQSS, datée du 27 octobre 2015
- Microdata Research Contract, Statistiques Canada, document signé en mars 2015
- Contrat de recherche pour l'utilisation de microdonnées - modifications, Statistiques Canada, document signé en octobre et novembre 2015
- Microdata Research Contract - amendment, Scotts Medical Database, document signé en février 2016

Le tout étant jugé satisfaisant, il nous fait plaisir de vous informer que la présente constitue l'approbation finale de votre projet de recherche, **valide pour un an à compter du 20 mai 2016**.

Vous devrez compléter le formulaire de renouvellement que nous vous ferons parvenir annuellement. De même, vous devrez soumettre pour approbation préalable, toute demande de modification ou document de suivi requis par le comité d'éthique conformément à ses Statuts et Règlements et ce via Nagano.

Lorsque cela s'applique à votre situation, veuillez noter que le projet ne peut débuter tant que le contrat n'est pas finalisé et dûment signé.

Le comité suit les règles de constitution et de fonctionnement de l'Énoncé de Politique des trois Conseils (ÉPTC 2) et des Bonnes pratiques cliniques de la CIH.

Pour toute question relative à cette correspondance, veuillez communiquer avec le secrétariat du comité par téléphone ou courriel: **ethique.recherche.chum@ssss.gouv.qc.ca – 514 890-8000, poste 14485.**

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, nous vous prions d'accepter, Madame, nos salutations distinguées.

Camille Assemat
Vice-présidente
Comité d'éthique de la recherche du CHUM

Project approval by the Canadian Research Data Center Network (Statistics Canada):

RECEIVED MAR 2 3 2015

Contract number : 15-SSH-MTL-3768-S001

MICRODATA RESEARCH CONTRACT

(Hereinafter referred to as the "Contract")

BETWEEN:

HER MAJESTY THE QUEEN IN RIGHT OF CANADA, as represented by the Minister responsible for Statistics Canada,

(Hereinafter referred to as "Statistics Canada"),

AND:

√Alexandra Blair ; Université de Montréal

√ Geetanjali Datta ; Université de Montréal

(Hereinafter referred to as Researcher(s))

Each a "Party" and collectively referred to as "Parties".

Recitals

1. Statistics Canada requires the services of the Researcher(s) to perform Special Services of statistical research and analysis, as described herein, pursuant to the *Statistics Act* R.S.C. 1985 chapter S-19;

2. The performance of these Special Services requires that the Researcher(s) has/have access to the Information in Appendix D;

3. Subsection 5(3) of the *Statistics Act* provides that any persons retained under contract to perform Special Services for the Minister pursuant to the *Statistics Act*, and the employees and agents of those persons shall, for the purposes of the *Statistics Act*, be deemed to be employed under the *Statistics Act* while performing those services;

4. Subsection 6(1) of the *Statistics Act* provides that any person deemed to be employed pursuant to the *Statistics Act* shall, before entering on his/her duties, take and subscribe the oath or solemn affirmation contained in that subsection;

5. To perform these services and to have access to confidential information, the Researcher(s) must become Deemed Employee(s) of Statistics Canada, and is/are required to take the Oath of Secrecy and must adhere to Statistics Canada's security and confidentiality requirements;

6. The Proposed Output and all materials (excluding Other Source Data) brought into Statistics Canada premises (which includes Research Data Centres) by Researcher(s) pursuant to the execution of the Special Services will be subject to the *Access to Information Act*, R.S.C., 1985, c. A-1 and the *Privacy Act*, R.S.C., 1985, c. P-21;

7. Other Source Data brought into Statistics Canada premises by Researcher(s) pursuant to the execution of the Special Services will be subject to the confidentiality provisions of the *Statistics Act*.

8. Statistics Canada wishes to establish the terms and conditions under which the Researcher(s) is/are retained to perform Special Services for the Minister pursuant to the *Statistics Act*, notably to ensure the appropriate use and the protection of the confidentiality of the Information to which the Researcher(s) may have access during the performance of these Special Services;

NOW THEREFORE the Parties agree as follows:

1. DEFINITIONS AND INTERPRETATIONS

1.1 Definitions

In this Contract, a capitalized term has the meaning given to it in this section, unless the context indicates otherwise:

"Deemed Employee"
Deemed Employee means any person, not currently an employee of Statistics Canada, retained to perform Special Services for Statistics Canada pursuant to the *Statistics Act*, for which access to Information protected by the *Statistics Act* is required in order to perform the Special Services.

"Information"
Information means the confidential identifiable microdata provided to Researcher(s) by Statistics Canada and listed in Appendix D, pursuant to this Contract, and statistical aggregates thereof that could directly or indirectly identify a Person.

"Other Source Data"
Other Source Data means data brought into Statistics Canada premises by Researcher(s) for use in the performance of Special Services and listed in Appendix C.

"Person"
Person means an individual, a corporation incorporated under any Act of Canada or a province or territory, a partnership, an association or an unincorporated business.

"Proposed Output"
Proposed Output means output/work created by Deemed Employee(s) as a result of providing Special Services outlined in Appendix C.

"Special Services"
Refers to statement of work described in Appendix C.

1.2 Interpretation of Appendices

This Contract contains the following Appendices, which form an integral part of this contract:

(a) Appendix A - Security Requirements
(b) Appendix B - Operational Requirements
(c) Appendix C - Description of Special Services to be provided to Statistics Canada by Researcher(s)
(d) Appendix D - Information and related documentation provided to

4.4.5 Having declared in Appendix C:

4.4.5.1 That the sole purpose of the research project is statistical research,

4.4.5.2 The sources of monetary or in kind support they are receiving to carry out the Research Project;

4.4.6 The Researcher(s) understand the potential penalties should they contravene the terms and conditions of access to the Information and the penalties should the Researcher(s) contravene the *Statistics Act* and any applicable related Acts, including the *Income Tax Act* or the *Excise Tax Act*.

5. LIMITATIONS ON USE OF INFORMATION

5.1 The Researcher(s), in the course of carrying out this Contract, may not use any of the information gained by accessing the Information for any other purpose except that which was agreed upon in this Contract.

5.2 Access to the Information is being provided for the statistical and research purpose outlined in the Statement of Work in Appendix C.

5.3 The Researcher(s) shall not disclose any of the Information to anyone other than current Statistics Canada employees involved in the review or evaluation of any aspect of the research project.

5.4 The Researcher(s) shall ensure that no attempts are made to link the Information supplied herein to any other files in order to relate the particulars to any identifiable Person.

6. PENALTIES

As Deemed Employees of Statistics Canada, and having taken the oath/solemn affirmation of secrecy set out in section 6 of the *Statistics Act*, Researcher(s):

6.1 Remains/Remain subject to the oath/solemn affirmation of secrecy even after the term of the Contract has ended.

6.2 Is/are subject to all the applicable penalties provided for in the *Statistics Act* for contravention of any of the confidentiality provisions and are liable on summary conviction to any of the applicable fines or imprisonment terms.

6.3 Is/are prohibited from disclosing information related to any Person (subsection 17(1) of the *Statistics Act*) obtained under the *Statistics Act*. Researcher(s) contravening subsection 17(1) of the *Statistics Act* is/are guilty of an offence and liable on summary conviction to a fine not exceeding one thousand dollars or to imprisonment for a term not exceeding six months or to both (paragraph 30(c) of the *Statistics Act*).

6.4 Is/are prohibited from disclosing confidential information obtained through the course of their employment that might exert an influence on or affect the market value of any stocks, bonds or other security or any product or article, or using the same information to speculate in any stocks, bonds or other security or any product or article (section 34 of the *Statistics* Act). Researcher(s) contravening section 34 of the *Statistics Act* is/are guilty of an offence and liable on summary conviction to a fine not exceeding five thousand dollars or to

imprisonment for a term not exceeding five years or to both.

6.5 Is/are reminded that if they are accessing data from sources other than Statistics Canada, in accordance to this Contract, then they are subject to all the applicable penalties provided for in related and applicable laws for contravention of any of the confidentiality provisions and are liable on summary conviction to any of the applicable fines or imprisonment terms.

7. OWNERSHIP AND COPYRIGHT OF INFORMATION

7.1 Statistics Canada is the owner and/or steward of the Information and related documentation listed in Appendix D and Parties agree that this Contract pertains to the use of the Information and related documentation to produce the Proposed Output for Statistics Canada. Nothing contained herein shall be deemed to convey any title or ownership interest in the Information or the related documentation to the Researcher(s).

7.2 Copyright in the Proposed Output shall vest in Her Majesty the Queen in Right of Canada. The Researcher(s) may be required to provide to Statistics Canada, at the completion of the Contract, or at such other time as Statistics Canada may require; a written permanent waiver of Moral rights from every author who contributed to the Proposed Output.

7.3 Copyright in any subsequent work created by the Researcher(s) using the Proposed Output shall vest in the Researcher(s).

8. USE OF AND PUBLISHING OF PROPOSED OUTPUT

8.1 Release of the Proposed Output by Statistics Canada may be considered by Statistics Canada in consultation with the Principal Researcher.

8.2 Statistics Canada reserves the right:

8.2.1 To publish in whole or in part or an amended/derived version of the Proposed Output; or

8.2.2 Not publish at all, any part of the Proposed Output

8.3 Use of the Proposed Output by Researcher(s) will be governed by the Statistics Canada Open License Agreement which can be found at the link below. This license agreement allows Researcher(s) to use Statistics Canada information without restrictions on sharing and redistribution, for commercial and non-commercial purposes.

http://www.statcan.gc.ca/eng/reference/licence-eng

9. CONFLICT OF INTEREST

9.1 Researcher(s) engaged as Deemed Employee(s) in the course of carrying out this Contract shall conduct themselves in accordance with the principles and spirit of the *Values and Ethics Code for the Public Sector*, Code of Conduct at Statistics Canada and the Policy on Conflict of Interest and Post-Employment found in Appendix E.

9.2 Researcher(s) must complete the Conflict of Interest Declaration Form found in Appendix F.

9.3 If Researcher has a conflict, the Researcher must fill out a Confidential Report to be provided by the Statistics Canada representative. This Report must be approved by the Director General, Human Resources Branch, Statistics Canada, who may require corrective action prior to providing the approval.

10. DESIGNATED REPRESENTATIVES

10.1 Any notice to be given to Statistics Canada pursuant to this Contract will be addressed to:

Director
Microdata Access Division
Statistics Canada
9A, R.H. Coats Building
Ottawa, ON K1A 0T6

10.2 And any notice to be given to the Researcher(s) will be addressed to:

Alexandra Blair
[redacted]

11. PAYMENT

Funding arrangements and payment modalities for purposes of this Contract are outlined in a separate Letter of Agreement between Statistics Canada and the Researcher(s).

12. TERM

This Contract comes into force when signed by all Parties, beginning on the date of the later signature, and shall continue until 2019-09-30 unless terminated earlier in accordance with section 13.

13. TERMINATION

13.1 This Contract may be terminated for any reason by either Party upon thirty (30) day
Notice of termination having been made in writing to the other Party, or at a time otherwise agreed upon by the Parties. Such termination will take effect on the expiry of the notice period.

13.2 Statistics Canada will terminate this contract immediately upon giving written notice to the Researcher(s) where the Researcher(s) commits or permits a breach of any of the terms and conditions contained in this Contract.

14. NOTICE OF CHANGE

Researcher(s) shall inform Statistics Canada, in writing, within thirty (30) days of any changes in their programs and policies, as well as of any legislation or regulation that may affect this contract.

15. AMENDMENT

No amendment to this Contract will be effective unless it is made in writing and signed

signed by the persons occupying the positions of the signatories of this Contract.

16. GENERAL

16.1 No Assignment
The Researcher(s) acknowledges that this Contract will not be assigned in whole or in part without the prior written consent of Statistics Canada, and any assignment made without such consent will be void and of no effect.

16.2 Notices
Unless otherwise specified in the Contract, where in this Contract any notice or other communication is required to be given or made by either Party, it will be in writing and be effective if sent by registered mail, e-mail, facsimile, postage prepayment or delivered in person, addressed to the respective Party at the contact information outlined under Section 10 of this Contract. Any notice or other communication will be deemed to have been given: if by registered mail when the postal receipt is acknowledged by the other Party; if by e-mail or facsimile on the day after the e-mail or facsimile was sent; if by mail on the eighth (8th) calendar day following the day of mailing.

16.3 Survival
The sections of this Contract regarding restrictions on use, confidentiality, conflict of interest, offenses and punishment, disclaimer of warranty, termination and general, and any other provisions which by their nature survive the termination or expiry of this Contract, will survive any termination or expiration of this Contract.

16.4 Law
This Contract shall be governed by and construed in accordance with the laws of the Province of Ontario and all applicable laws of Canada.

16.5 Entire Agreement
The Contract constitutes the entire agreement between Parties with respect to the subject matter described herein and supersedes all previous negotiations, communications and other agreements on the same topic, unless specifically incorporated by reference in this Contract.

16.6 Waiver
Any tolerance or indulgence demonstrated by one Party to the other, or any partial or limited exercise of rights conferred on a Party, shall not constitute a waiver of rights, unless expressly waived in writing by that Party.

16.7 Severance
If any provision of this Contract, whether in whole or in part, is held by a court of competent jurisdiction to be void or unenforceable, such provision or portion thereof declared invalid or unenforceable shall be deemed to be severable and shall be deleted from this Agreement and all remaining terms and conditions of this Contract will continue to be valid and enforceable.

Contract number : 15-SSH-MTL-3768-S001

IN WITNESS WHEREOF, this Contract has been executed on behalf of:

FOR STATISTICS CANADA:

[redacted]

Dir[redacted]sion — David Price
Print Name

Wit[redacted] — Sun Te
Print Name

DATED at Ottawa, Province of Ontario, this 26 day of Mar (month) 2015 (year).

FOR THE PRINCIPAL RESEARCHER AND CO-RESEARCHER(S):

[redacted]

Pri[redacted]e) — Geetanjali Datta
Print Name

Wit[redacted] — Catherine Blanchard Gagnon
Print Name

DATED at Montreal, QC, this 11 day of March (month) 2015 (year).

[redacted]

Co-[redacted] — ALEXANDRA BLAIR
Print Name

Wit[redacted] — Catherine Blanchard Gagnon
Print Name

DATED at Montreal, QC, this 11 day of March (month) 2015 (year).

(Complete for all deemed employees signing contract)

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