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Durée de l'exposition avec symptômes, séquelles et coûts de l'asthme professionnel en relation avec le statut psychologique et socioéconomique

par

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Résumé

Le facteur le plus important de pronostic de l'asthme professionnel (AP) est la durée des symptômes avant le retrait de l'exposition à l'agent causant l'AP. La qualité de vie réduite, la détresse psychologique et les maladies psychiatriques sont des conditions souvent associées à l'AP.

Notre objectif était d'identifier les facteurs, incluant le statut socioéconomique, qui ont une influence sur l'intervalle de temps nécessaire pour présenter une requête à une agence médicolégale à la suite de l'apparition de symptômes d'asthme et de confirmer qu'un tel délai est associé à un moins bon pronostic respiratoire et à des coûts directs plus élevés. En outre, nous avons examiné la relation entre les variables cliniques et socio-économiques d'une part et leur influence sur les facteurs psychologiques et économiques d'autre part chez des travailleurs atteints d'AP. Ensuite, nous avons voulu évaluer si les individus souffrant de détresse psychologique (DP) et de morbidité psychiatrique pourraient être identifiés en utilisant un instrument mesurant la qualité de vie (QV).

L'étude a été effectuée auprès d'individus ayant déposé des demandes d'indemnisation pour'AP auprès du Commission de la sécurité et de la santé du travail du Québec (CSST). Les données ont été recueillies au moment de la réévaluation, soit environ deux ans et demi après le diagnostic. Outre la collecte des marqueurs cliniques de l'asthme, les individus ont été soumis à une évaluation générale de leur histoire sociodémographique et

médicale, à une brève entrevue psychiatrique (évaluation des soins primaires des troubles mentaux, PRIME-MD) et à un ensemble de questionnaires, incluant le Questionnaire sur la qualité de vie - AQLQ(S), le Questionnaire respiratoire de St. George (SGRQ) et le Psychiatric Symptom Index (PSI).

Soixante personnes ont été incluses dans l'étude. Etre plus âgé, avoir un revenu supérieur à 30 000$ CA etêtre atteint d'AP dû à un allergène de haut poids moléculaire ont une association positive avec le nombre d'années d'exposition avec symptômes avant le retrait. Au cours de la période de suivi, le nombre d'années d'exposition avec symptômes était plus grand chez les individus ayant une hyperréactivité bronchique persistante. Par ailleurs, la présence de symptômes au poste de travail pendant moins d'un an est associée à une réduction des coûts directs. Les paramètres de QV et de DP avaient des corrélations modérées avec les marqueurs cliniques de l'AP. Les plus fortes associations avec ces variables ont pu être observées dans les cas de la sévérité de l'asthme, des statuts d'emploi et matrimonial, du revenu et de la durée de la période de travail avec l'employeur. Un seuil de 5,1 au niveau de la sous-échelle de la fonction émotionnelle de l'AQLQ(S) s'est avéré avoir la meilleure valeur discriminante pour distinguer les individus avec ou sans détresse psychiatrique cliniquement significative selon le PSI.

Nous avons été en mesure d'identifier les variables socio-économiques associées à un intervalle plus long d'exposition professionnelle en présence de symptômes d'asthme. De même, une plus longue période d'exposition a été associée à un moins bon pronostic de la maladie et à des coûts de

compensation plus élevés. Ces résultats s'avèrent utiles pour la surveillance de l'AP qui pourrait cibler ces sous-groupes d'individus. La QV et la PS sont fréquemment réduites chez les individus atteints d'AP qui perçoivent une compensation. Elles sont associées à des marqueurs cliniques de l'asthme et à des facteurs socio-économiques. En outre, nos résultats suggèrent que le questionnaire de l'AQLQ(S) peut être utilisé pour identifier les individus avec un niveau de détresse psychologique potentiellement significatif.

Mots-clés : Analyse des coûts, délai de diagnostic, économie, asthme professionnel, troubles psychiatriques, détresse psychologique, qualité de vie, Québec, dépistage, facteurs socioéconomiques.

Abstract

The most important factor in the prognosis of occupational asthma (OA) is the length of exposure with symptoms prior to removal from exposure. Impaired quality of life, psychological distress and psychiatric disease are conditions frequently associated with OA.

Our goal was to identify factors, including socio-economic status, that can influence the delay in submitting a claim to a medicolegal agency after the onset of asthmatic symptoms, and to confirm that such a delay is associated with a worse respiratory prognosis and higher direct costs. Further, we examined the association between clinical and socio-economic variables and their influence on psychological and cost outcomes in individuals with OA. Next, we wanted to evaluate whether individuals with clinically significant psychological distress (PD) and psychiatric morbidity could be identified by using a quality of life (QOL) measurement instrument.

This is a study of individuals who filed claims for compensation for occupational asthma from the Workers' Compensation Board of Quebec (the CSST). Data were collected at re-evaluation, approximately two and a half years after diagnosis. Besides collecting clinical markers of asthma, individuals underwent a general socio-demographic and medical history evaluation, a brief psychiatric interview (Primary Care Evaluation of Mental Disorders, PRIME-MD) and completed a battery of questionnaires, including the Asthma Quality of Life Questionnaire - AQLQ(S), the St. George's

Respiratory Questionnaire (SGRQ), and the Psychiatric Symptoms Index (PSI).

Sixty individuals were included in the study. Being older, having a revenue of >$30,000 Can. (CAD$) and having OA due to high- molecular-weight agents were all positively associated with the number of years of exposure with symptoms before removal from exposure. Individuals with persistent airway hyperresponsiveness at follow-up had a higher number of years with symptoms. Experiencing symptoms in the workplace for less than one year generated lower direct costs. QOL and PD parameters had moderate correlations with clinical markers of OA. Asthma severity, employment and marital status, income and length of employment with the employer showed the strongest associations with QOL and PD. More impaired QOL was associated with higher direct costs for compensation. A cut-off of 5.1 on the AQLQ(S) emotional function subscale had the best discriminative value to distinguish individuals with or without clinically significant psychological distress according to the PSI.

We were able to identify socio-economic variables that were associated with a longer interval during which individuals remained symptomatic in the workplace before being removed from exposure. This longer exposure time was associated with worse disease outcomes and higher compensation costs. These findings could prove to be useful in surveillance programs that could be preferentially targeted for these subgroups of individuals. Impaired QOL and PD are frequent among individuals with OA receiving compensation

and are associated with clinical markers of OA and socio-economic factors. Further, our findings suggest that the AQLQ(S) questionnaire could be used to identify individuals with potentially clinically significant levels of psychological distress.

Keywords: Costs and Cost Analysis, Diagnosis Delay, Economics, Occupational Asthma, Psychiatric disorder, Psychological Distress, Quality of Life, Quebec, Screening, Socioeconomic Factors

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Abbreviations

ACCP	American College of Chest Physicians
AHR	Airway Hyperresponsiveness
AIRA	Allergic Rhinitis and its Impact on Asthma
AMA	American Medical Association
AQLQ(S)	Standardized Form of the Asthma Quality of Life Questionnaire by Juniper
BPTs	Bronchial Provocation Tests
CAD$	Canadian dollars
CAW	Center for Asthma in the Workplace (Montreal, Canada)
COPD	Chronic Obstructive Pulmonary Disease
CSST	Commission de la Santé et de la Sécurité du Travail du Québec
DALYs	Disability-Adjusted Life Years
DAP	Permanent Disability Indemnity
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAACI	European Academy of Allergy and Clinical Immunology
ENO	Exhaled Nitric Oxide
ECRHS	European Community Respiratory Health Survey
FEV1	Forced Expiratory Flow in One Second
FVC	Forced Vital Capacity

GINA	Global Initiative for Asthma
HADS	Hospital Anxiety and Depression Scale Questionnaire
HMW	High Molecular Weight
IgE	Immunoglobulin E
IRR	Income Replacement Indemnity and Rehabilitation
LMW	Low Molecular Weight
LWAQ	Living with Asthma Questionnaire
MCMI-III	Millon Clinical Multiaxial Inventory I-III
OA	Occupational Asthma
PC20	Concentration of methacholine causing a fall in forced expiratory volume in one second greater than or equal to 20%
PEF	Peak Expiratory Flow
PRIME-MD	Primary Care Evaluation of Mental Disorders Questionnaire
PSI	Psychiatric Symptom Index
RADS	Reactive Airways Dysfunction Syndrome
RAST	Radioallergosorbent Test
ROC	Receiver Operator Characteristic Curve
SIC	Specific Inhalation Challenge
SGRQ	St. George's Respiratory Questionnaire
SPT	Skin Prick Test
WEA	Work-Exacerbated Asthma

WHO	World Health Organization
WRA	Work-Related Asthma
TMA	Trimellitic Anhydride
YWS	Years of Exposure with Symptoms before Removal from Exposure
YI	Youden Index

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1. Introduction

In this chapter, I will first briefly discuss the definition and specific features of asthma that is caused by the workplace. I will discuss which tests can be used to diagnose and treat occupational asthma (OA), and report on the expected natural course in individuals who remain exposed to the causal agent in the workplace and how the outcome differs in those individuals who are able to decrease or stop their exposure. I will then highlight the strong and important association of socio-economic and psychological factors with health in general before summarizing findings of past studies on the association of OA with various socio-economic and psychological factors. I will also briefly explain how a claim made to the compensation agency in Quebec/Canada is handled and what compensation is offered to individuals whose claim is accepted.

1.1. Asthma in the workplace

1.1.1. Definition of asthma

The Global Initiative for Asthma (GINA), launched in 1993, brings together committees made up of leading asthma experts from around the world to develop guidelines for asthma care. According to GINA, "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment" (www.ginasthma.org). Asthma has been classified by Rackeman into two different types based on causative factors: extrinsic asthma is often due to an allergy to antigens and frequently occurs before the age of 30, while intrinsic asthma usually occurs later in life, secondary to chronic or recurrent infections of the bronchi, sinuses, or tonsils and adenoids (1).

To avoid exacerbation of asthmatic attacks and further progression of the disease, triggering situations or substances should be avoided whenever possible. The treatment of asthma involves treating the underlying

inflammation and bronchospasm. It has been estimated that about 300 million people worldwide are affected by asthma. The global prevalence of asthma ranges from 1% to 18% of the population in different countries, and the number of disability-adjusted life years (DALYs) lost due to asthma is similar to years lost for diabetes, cirrhosis of the liver or schizophrenia (2).

Work-related Asthma

Several terms are used to describe asthma in relation to the workplace, as summarized in the American College of Chest Physicians' (ACCP) statement on work-related asthma (3) (Figure 1):

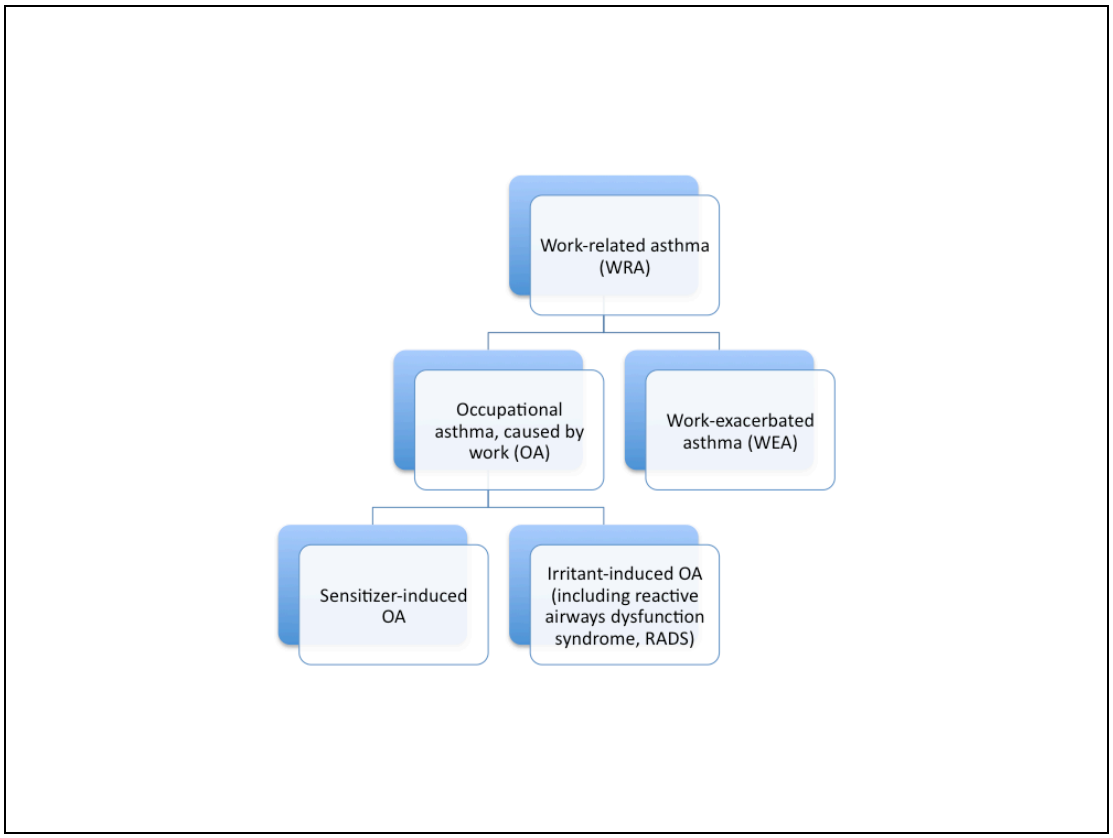

Figure 1: Different subtypes of work-related asthma

Work-related asthma (WRA) is the term used to define asthma that is induced or exacerbated at the workplace. In population studies, a diagnosis of WRA is assigned to respondents with self-reported physician-diagnosed asthma who report that their work environment is causing asthma symptoms (4). Self-reporting of work-related symptoms and exposure to airway irritants can, however, be prone to recall bias in individuals with lung disease. Evidence for this comes from studies investigating the association of occupational exposure to airway irritants with chronic obstructive lung disease. In an American study, the association between self-reported

exposure and chronic obstructive lung disease was much stronger than a more objective measure of exposure by a job-exposure matrix (5).

Work-exacerbated Asthma

Work-exacerbated asthma (WEA) is the term used in the case of workers with pre-existing or concurrent asthma (asthma that occurs at the same time but is not caused by workplace exposures) that is worsened by work-related factors like airway allergens, irritants and exercise (3). Subjects may notice an increased frequency or severity of asthma symptoms and/or may need to increase their medication in order to control symptoms during or after their work days. In rare cases WEA and OA may coexist in workers: Subjects who work at different workplaces may become sensitized to an allergen causing OA. Their asthma may be exacerbated by other irritating factors encountered during work; for example, when performing a job task without exposure to the allergen or at a different workplace.

Occupational Asthma

Occupational asthma (OA) is the term used for asthma that starts when the subject is exposed to a substance present in the workplace. Rarely, it may occur in subjects with a history of childhood asthma that became quiescent during adolescence before resurfacing as a consequence of occupational exposure through a sensitizing or irritating mechanism (3). OA can be divided into two categories:

Immunological OA appears after sensitization to a substance that is specific to the workplace. Symptoms appear after a latency period that seems to vary according to the nature of the agent (6). For some allergens, an allergic immunoglobulin E (IgE)-mediated mechanism has been demonstrated, whereas for others the mechanisms of sensitization are presently unclear. Another approach often used is to distinguish allergens according to their molecular weight: high-molecular-weight (HMW) allergens are often proteins with a mass >10 kd, while low-molecular-weight (LMW) allergens are those such as chemicals, like diisocyanates.

Non-immunological OA may occur after a single or multiple high-concentration exposures to an inhaled non-specific irritant in the workplace. Subjects complain of symptoms within the first 24-48 hours of exposure and

demonstrate non-specific AHR. Brooks defined this condition in 1985 as asthma occurring after a single exposure to high levels of an irritating vapour, fume or smoke, and suggested the term reactive airways dysfunction syndrome (RADS) (7).

1.1.1.4. Etiologies of OA

Substances that are known to cause immunological OA encompass a broad spectrum of natural and synthetic chemicals found in a diverse range of materials and industrial processes. These agents can be divided into two broad categories by their mechanism of action: immunological is the sensitizer-induced form of OA and non-immunological is the irritant-induced form of OA (8). In immunological OA, asthma is induced through an IgE-dependent mechanism, whereas in some patients specific IgEs are apparently not involved despite a clear asthmatic reaction in specific inhalation challenges (8). Etiologic agents can be classified according to their propensity for IgE-dependent or non-dependent action (9), as shown in Table 1.

HMW Agents	Selected Examples	LMW Agents	Selected Examples
Plant antigens	Cereals, flour; green coffee beans; tobacco; gums	Isocyanates	Polyurethane foam production and end-user applications (auto-spray painters)
Animal antigens	Rodents; cats and dogs; farm animals; mites	Wood dusts	Western red cedar (carpenters and sawmill workers)
Bioaerosols	Moulds and bacteria	Highly reactive compounds	Anhydrides, amines and acrylates
Enzymes	Detergent enzymes, amylase in baking	Aldehydes	Glutaraldehyde and formaldehyde
Latex	Gloves (health-care workers and others)	Colophony	Solder fluxes
Seafood	Crabs, prawns and fish	Dyes	Reactive dyes (textile workers)
Drugs	Antibiotics; psyllium laxatives	Persulfate	Hairdressers
		Metals	Metal plating (chrome, nickel and cobalt), platinum (catalysts)

Table 1: Illustrative examples of specific agents (and workers) associated with sensitizer-induced OA

OA induced by these two groups of allergens differs in clinical presentation, the type of reaction produced during inhalation tests and the characteristics of the population at risk, as shown in Table 2 (3).

Characteristic	Sensitizer-induced OA		Irritant-induced OA
	IgE-dependent	IgE-independent	
Clinical			
Interval between onset of exposure and symptoms	Longer	Shorter	Within hours
Pattern of asthmatic reaction on specific inhalation testing	Immediate, dual	Late, atypical	Testing not done
Epidemiologic			
Prevalence in exposed population	<5%	>5%	?
Host predisposition	Atopy, probably smoking	?	?

Table 2: Types of OA according to Chan-Yeung and Malo

The most common agents for asthma without latency or irritant-induced asthma are chlorine and ammonia (9).

1.1.1.5. Epidemiology of Work-related Asthma

There is much debate in the medical community about how to define asthma and about the “gold standard” for the diagnosis of asthma (10). One way of defining asthma in studies is by asking study participants if they have ever been diagnosed by a physician as having asthma. Respiratory symptoms can be misinterpreted by a physician as being caused by asthma, especially if no objective investigation with lung function and bronchial challenge testing is performed. Diseases such as chronic bronchitis, chronic

obstructive pulmonary disease (COPD), vocal cord dysfunction or upper airway cough syndrome are known to present with symptoms similar to asthma. In a recent study, Aaron and co-workers objectively assessed subjects with self-reported physician-diagnosed asthma and found that one-third of patients did not have asthma on the basis of bronchial provocation test (BPT) results and problem-free withdrawal of medication (11).

Toelle and co-workers have suggested that in epidemiologic studies, asthma should be defined as having airway hyperresponsiveness (AHR) plus recent wheezing in the 12 months prior to study (12). However, it is well known that not all patients with asthma do have AHR or complain of wheezing (13).

Not surprisingly, different definitions of OA exist. By consensus, a widely used definition of OA has been formulated: “Occupational asthma is a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.” (14)

Depending on the population studied and the objective of the epidemiologic studies, the definition of OA can vary. When using a broader definition of WRA, this includes WEA and the two forms of OA: non-immunological OA and immunological OA. This precludes the general comparability of prevalence and incidence determined in different

epidemiologic investigations. Furthermore, different methods can be used to determine the frequency (incidence and prevalence) of OA (Table 3).

	Advantages	**Disadvantages**
Epidemiological studies -In the general population	Global coverage	Large sample size due to low prevalence in the study population and therefore high costs, participation rate variable.
-In the population at risk (apprentices, workers)	Smaller sample size and more extensive evaluation possible	Target population needs to be identified, selection bias (healthy worker effect)
-In outpatients consulting for asthma	Minimal costs	Selection bias, only subjects investigated for asthma included.
Database/register (e.g. Scandinavian countries)	Almost all of the population included	Only basic information available.
Medico-legal statistics	All subjects compensated for OA, information about diagnosis often available	Subjects with OA who are not insured or do not claim compensation are not registered, so information about diagnosis may be lacking.
Sentinel System	Minimal costs	Different diagnostic studies done, interest in reporting OA cases may decline over time.

Table 3: Methods for the determining the frequency of OA

OA is one of the most prevalent occupational respiratory diseases in the industrialized world. It has been estimated in systematic reviews and

meta-analysis that between 9% and 15% of diagnosed cases do have a professional origin (15). However, later studies have estimated a higher population-attributable risk of occupational exposure for adult-onset asthma in the United States (37%) (4) and Finland (29% for males and 17% for females) (16). In the European Community Respiratory Health Survey (ECRHS), the population-attributable risk for adult asthma due to occupational exposure ranged from 10% to 25%, equivalent to an incidence of new-onset OA of 250-300 cases per million people per year (17).

1.1.1.6. Risk factors for OA

1.1.1.6.1 Level of exposure

Studies have provided strong evidence supporting a dose-response relationship between the level of exposure to occupational agents and the development of IgE-mediated sensitization and work-related respiratory symptoms (18). For isocyanates - considered LMW agents - an exposure-response gradient has been documented for respiratory symptoms, sensitization (reflected by specific IgE and IgG) and the development of OA (19, 20). For acid anhydrides such as trimellitic anhydride (TMA), a dose-response relationship has been shown for respiratory symptoms and

sensitization (21). However, there are studies of bakers and laboratory animal workers showing that high-level exposures to flour or laboratory animal allergens may have a protective effect on the development of sensitization and respiratory symptoms (22-24).

1.1.1.6.2. Mode of exposure

In animal models, skin exposure has been shown to initiate IgE-mediated sensitization, eosinophilic airway inflammation and bronchial hyperresponsiveness (18). In humans, airway and skin exposure to offending allergens often occur simultaneously; however, there is evidence that OA to isocyanates consistently occurs in work settings with low diisocyanate exposure, due either to intermittent peak exposures or to skin exposure (25, 26).

1.1.1.6.3. Co-exposure to pollutants

Co-exposure in the workplace to environmental pollutants such as ozone, nitrogen dioxide, diesel exhaust particles and endotoxin can act as an adjuvant in allergic responses to inhalant allergens (18). Individual smoking

has been identified as a risk factor for work-related sensitization in laboratory animal workers (27). However, this finding was not present in larger and better controlled studies, and could not be shown in workers exposed to LMW agents (28). Smoking has also been identified as a risk factor for persistent respiratory symptoms after acute irritant inhalation exposure leading to irritant-induced OA (29).

1.1.1.6.4. Atopy

Atopy is defined as either a positive skin prick test (SPT) response or specific IgE response against a series of common aero-allergens (28). Atopy has been shown to be a risk factor for the development of sensitization and OA to HMW agents and to some LMW agents (18). In a follow-up study of laboratory animal workers in the Netherlands, a combination of atopy and elevated IgE (>100 IU/mL) when starting work with animals was associated with subsequent sensitization over the following two years (30). Other studies have shown that atopy is a stronger risk factor for sensitization in those with low levels of exposure compared with those having medium- to high-level exposure (24, 28, 31).

1.1.1.6.5. Genetic factors

Several genes have been shown to be associated with OA to LMW and HMW occupational allergens. While some of these loci seem to have protective properties, others confer a higher risk for OA (18). Identified genes are involved in protection against antioxidant stress, α-1-antitrypsin production and regulation of native immune pathways (18, 32). However, most of the data available are derived from cross-sectional studies and show only weak associations; some of the associations could not be confirmed in studies carried out in other samples (18).

1.1.1.6.6. Bronchial hyperresponsiveness

Increased non-specific bronchial hyperresponsiveness has also been considered a risk factor for subsequent development of OA: Gautrin and co-workers investigated apprentices in animal health technology and found that increased baseline immediate skin reactivity to pets (cats and dogs) and higher degrees of non-specific AHR were risk factors for the development of probable OA at follow-up after 3.5 and 8 years (33, 34).

1.1.1.6.7. Rhinitis

In the ECRHS, rhinitis was associated with asthma in cross-sectional analysis and shown to be a risk factor for the subsequent development of asthma at follow-up (35, 36). In individuals evaluated for WRA, Castano and co-workers showed that occupational rhinitis (OR) frequently coexists with OA (37). Symptoms of work-related rhinoconjunctivitis are risk factors for the later development of asthma in the workplace in apprentices and workers handling laboratory animals (38, 39), as shown in a study of patients in the Finnish Register of Occupational Diseases (40). The acknowledgement of OR as a risk factor for the development of OA has led the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Occupational Rhinitis to state in its position paper that the prevention of work-related rhinitis may also provide an excellent opportunity to prevent OA (41).

1.1.1.6.8. Sex

Most occupational health and exposure assessment studies have been carried out in male populations, so the findings cannot easily be extrapolated to estimate the risk for female workers. In workers processing snow crab, it has been shown that female workers were more likely to have OA and allergy

to snow crab than their male co-workers (42). Atopy is a risk factor for the development of OA to HMW allergens such as snow crab, and the risk for atopy is greater for females than for males of working age (43). There is accumulating evidence of a sex difference in susceptibility to exposure to tobacco smoke, irritants and allergens that needs to be taken into account when interpreting studies reporting a difference in respiratory disease rates according to sex (44). Furthermore, there is evidence that immune response in women differs from that in men, and that women are at much higher risk of developing autoimmune diseases than men (45).

While “sex” is the term usually used to refer to biological differences between men and women, “gender” most often refers to what is socially recognized as feminine and masculine (46). Further analysis in workers processing snow crab indicates that female workers more often perform work where higher exposure to snow crab allergen is present than their male co-workers (47). Eng et al. conducted a broad-based telephone survey of male and female workers in New Zealand that showed major differences in occupational exposure patterns between female and male workers, indicating that these exposure differences were present between and within occupations (48). Both studies highlight the fact that for OA, not only sex but also gender differences must be taken into account when interpreting results of research studies investigating risk factors.

1.1.2. Diagnosis of work-related asthma in Quebec

WRA is a major health challenge. Acute WRA can render suffering subjects unable to work, often for a prolonged period of time. OA can cause acute as well as long-term disability, which adversely affects quality of life and socio-economic factors.

To diagnose WRA, subjects undergo a comprehensive medical history in order to identify the presumed causal agent, followed by objective tests at the physician's office or at the workplace. When the offending allergen is in doubt, it may be necessary for industrial hygienists to inspect the workplace in order to identify irritating or sensitizing substances. Subjects who were exposed to high levels of irritants within a short time normally develop respiratory symptoms within the next 24 hours and often require emergency treatment. Whenever possible, WRA should be investigated with objective testing before the patient is advised to change profession or workplace.

1.1.2.1. Occupational history

In all working subjects with new-onset, worsening or difficult to treat asthma, WRA needs to be considered, and a detailed history of temporal relationships between asthma symptoms and work should be established.

Information about subjects' profession, work status and exposure characteristics must be obtained. Specific work environments have been shown to be associated with an increased risk of more severe asthma, especially in adult-onset asthma (49).

In real life, clinicians often neglect the importance of taking such a detailed occupational history. Shofer and co-workers conducted a structured retrospective comparison of occupational respiratory health history documented by clinicians in an academic medical centre, with data documented by patients on a structured questionnaire. While a job title was documented in 75% of patient medical records, additional occupational history data such as duties, exposures at work and use of protective equipment were charted much less frequently (50).

Dyspnoea, wheezing, chest tightness and cough are the cardinal symptoms of asthma as well as WRA. However, there are specific questions a physician who suspects that the patient's asthma is related to the workplace should ask (see Table 4) (3).

- Were there changes in work processes in the period preceding the onset of symptoms?
- Was there an unusual work exposure within 24 hours before the onset of initial asthma symptoms?
- Do asthma symptoms differ during times away from work such as weekends or holidays or other extended times away from work?
- Are there symptoms of allergic rhinitis and/or conjunctivitis symptoms that are worse with work?

Table 4: Key questions suggested in the American College of Chest Physicians' Consensus Statement on Diagnosis and Management of WRA

When work processes are changed, subjects may be exposed to new agents causing sensitization or increased exposure to previously occurring agents. Sometimes the work process of co-workers is changed, or the subject's workplace is moved to another place where he or she starts to be exposed to a sensitizing agent. Work conditions may have changed, such as new ventilation and exposure to cold air, exhaust gases or second-hand smoke. Sometimes, as in WEA, the underlying asthma worsens when subjects decrease their medication use, or during the spring/summer when the allergen concentration (e.g. pollen) rises.

After chemical spills or other high-level exposures to airway irritants, subjects may develop respiratory symptoms within short periods of time that result in them seeking emergency care. This form of WRA is called non-immunological OA. One form of non-immunological OA is RADS, initially described by Brooks and co-workers in 10 individuals who developed a persistent asthma-like illness after a single exposure to high levels of an irritating vapour, fume or smoke. In all subjects, the symptoms developed within a few hours and often minutes after exposure. All had bronchial hyperreactivity on methacholine testing (7). However, some subjects do not meet the criteria for RADS and develop symptoms after days and for a shorter period of time. Many of these subjects are exposed to lower concentrations of irritants over some days or weeks (51).

Often, a temporary pattern of symptoms related to exposure at the workplace can be established. When workers return to their workplace, they may notice an increase in symptoms the first day or at the end of the workday or realize that their symptoms slowly increase during the working week. On weekends the symptoms may disappear, but in subjects with long-standing illness this improvement may be insignificant. This correlation between symptoms and workplace exposure is present in about 88% of subjects with immunological OA; however, 76% of subjects without proven OA do also see improvement of symptoms when they are away from work (52). Chan-Yeung et al. reported that, even after a change of workplace, symptoms and non-specific AHR can persist in workers with asthma caused by Western red cedar: roughly 60% of workers still had asthma exacerbations after a mean follow-up period of four years (53).

All subjects with asthma should be questioned about upper respiratory and eye symptoms. This is especially true for subjects evaluated for OA. Rhinoconjunctivitis symptoms often precede or occur simultaneously with lower airway symptoms. Rhinitis may either be caused or exacerbated by exposures at the workplace. Occupational rhinitis is an inflammatory disease of the nose characterized by intermittent or persistent symptoms (i.e. nasal congestion, sneezing, rhinorrhea, and itching), variable nasal airflow limitation, and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace. The main concept of this broad definition is the causal relationship

between exposures at the workplace and the development of the disease (54).

Immunological occupational rhinitis is characterized by the acquisition of sensitization. This category includes occupational rhinitis caused by high and low molecular weight agents (55). Irritant-induced occupational rhinitis includes cases of occupational rhinitis caused by low molecular weight agents. This involves non-allergic, less well-known pathogenic mechanisms and is further sub-classified into acute irritant, chronic irritant, and corrosive rhinitis (55). Subjects with work-aggravated rhinitis have pre-existing rhinitis, the symptoms of which are triggered by exposure to irritants at the workplace (fumes, vapours, and dust) (55).

As mentioned earlier, work-related rhinitis symptoms are common in workers exposed to laboratory animals (42%) or who work in swine confinement units (62%). Vandenplas and co-workers have identified a positive relationship between symptoms such as nasal or ocular itching and the diagnosis of OA confirmed by specific inhalation challenge (SIC) (56). In the same study, work-related loss of voice was negatively associated with the diagnosis (56). Allergic rhinitis may precede asthma (57), and it has been shown that effective treatment of rhinitis can decrease the risk for emergency room visits or hospitalization for asthma (58). Contact urticaria has been described in snow-crab processing workers (59) and in health-care workers exposed to natural rubber latex (60).

1.1.2.2. Immunologic assessment

Atopy has been shown to be a risk factor for immunological OA in health-care personnel exposed to HMW allergens such as natural rubber latex (61) and in laboratory-animal handlers (62), but not in workers exposed to diisocyanates (63).

In immunological OA due to HMW allergens, specific IgE titers are elevated. Two methods are used to show sensitization: performing SPT or measuring specific IgE antibody assays (radioallergosorbent test (RAST)).

SPT is usually performed on the medial aspect of the forearm. Small drops of standardized allergen, histamine and isotonic saline solutions are applied on the untreated skin and inoculated with a prick needle (Figure 2).

Figure 2: Performing SPT on the forearm

The patient is told not to rub or scratch the skin until the test is read after 15 minutes. The diameter of the induration is noted and recorded. An induration of up to 3mm in diameter is considered negative. This test detects tissue-bound IgE (64). False positive results can occur in subjects with dermographism, whereas false negative results can occur if patients are on treatment with antihistamines or suffer from immunodeficiency syndromes that affect type I allergic reactions. Sensitivity is decreased if subjects are tested after not being exposed to the allergen for a prolonged time (65). Another limitation is that commercially available allergen solutions are often not standardized, in particular in the case of occupational agents.

SPTs have been shown to have high sensitivity for OA to HMW allergens with only moderate specificity. Vandenplas et al. investigated a sample of 45 workers evaluated for OA to natural rubber latex. In their sample sensitivity of the SPT for OA was 100%, specificity was 21%, positive predictive value 75% and negative predictive value 50%. The negative predictive value of SPTs for OA rose when the clinical history was incorporated into logistic regression analysis (64).

The RAST was developed in the late 1960s and marketed in 1974 by Pharmacia Diagnostics AB in Sweden. In brief, the patient's serum is incubated with the test kit containing specific allergens bound to a solid-phase support. The patient's specific IgE binds to the allergens of the test kit. Excess serum and unbound IgE are removed. Radio-labelled antihuman IgE antibody is added to the test kit, binding to the tail of the patient's specific IgE and building a sandwich complex. Unbound radio-labelled antihuman IgE is then removed and the sample is measured with a radioactivity counter. The radioactivity measured is proportional to the proportion of radio-labelled antihuman IgE, which is proportional to the amount of patient-specific IgE (66). This method has been further elaborated by using enzyme-based immunoassay systems with higher precision (67). In vitro, specific IgE measurements have been shown to be less sensitive to detecting specific IgE antibodies to HMW-allergens; in workers at enzyme manufacturing plants, SPTs with enzyme solutions had 100% sensitivity compared to 62% sensitivity for specific IgE antibody assays (68). The value of immunologic

assessment is lower in the case of LMW allergens. Extracts of these allergens often cause unspecific irritative cutaneous reactions. Specific IgEs have been described for a minority of LMW allergens: trimellitic anhydride (TMA) in plastic industry workers (69) and platinum salts in workers at a platinum refinery (70).

1.1.2.3. Non-invasive measures of airway inflammation

Sputum cell counts and measurement of exhaled nitric oxide (ENO) are measurements that assess airway inflammation in asthmatic subjects. Because they are easy to perform, their use has been evaluated in patients with OA.

For induced sputum cell counts, sputum is induced by using inhalations of increasing concentrations (3%, 4% and 5%) of hypertonic saline after inhalation of a short-acting bronchodilator (71). As hypertonic saline can cause bronchoconstriction, spirometry is performed to monitor lung function. Immediately afterwards, patients are asked to rinse their mouth, take a sip of water and blow their nose in order to minimize oral contamination of the sputum sample. They are then asked to try to bring up sputum into a container. The sputum is then processed and analyzed according to standardized procedures (72). An increase in sputum eosinophilia can be

observed after exposure to HMW allergens such as oilseed rape flour in farmers (73) and to different types of flours after SIC in a laboratory (74), as well as after exposure to LMW allergens such as cyanoacrylates (75), red cedar wood dust (76) and diisocyanates (77). However, sometimes diisocyanates (78) as well as metal working fluids (79) and grain dust (80) can induce sputum neutrophilia, though it is likely that this finding reflects different phenotypes of asthma (81). Lemiere and co-workers investigated 10 subjects with OA and observed a significant increase in sputum eosinophilia at work, which was not observed among controls (82). Girard and co-workers demonstrated that the addition of sputum cell count analysis to peak expiratory flow measurement (PEF) monitoring performed during work and during a period off work improved the specificity of diagnosis for immunological OA confirmed by SIC: a >2% increase in sputum eosinophils improved specificity by 26% (83).

Not all subjects with asthma are able to produce sputum for analysis. Matsuoka and co-workers estimated that only 73% of the asthmatics they investigated who were scheduled to undergo sputum cell count analysis produced sputum, and patients with long-standing disease and non-smokers were less likely to produce induced sputum successfully (84). Analysis of induced sputum cell counts is not available everywhere, as special equipment and expertise are needed to achieve reliable and reproducible results.

Measurement of ENO is a new non-invasive measurement of airway inflammation in asthma. NO is an endogenous messenger with a diverse

range of effects, including non-adrenergic, non-cholinergic neurotransmission as well as vascular and non-vascular smooth muscle relaxation (85, 86). Many questions remain to be answered about the role of NO in lung disease. NO has been described as a pro-inflammatory mediator with immunomodulatory effects that has been thought to predispose to the development of AHR (85). However, under physiological conditions NO is a weak mediator that causes smooth muscle to relax and provides protection against AHR (87). Epithelial inducible nitric oxide synthase activity is the major determinant of NO concentration in exhaled breath (88).

ENO is elevated in asthmatic subjects who are not currently on steroid treatment compared with non-asthmatic subjects (89). Atopy is a significant factor associated with elevated ENO in asthmatic and non-asthmatic subjects (90). ENO levels are elevated in subjects with non-specific AHR: 83% of asthma patients with AHR to mannitol and 88% of asthma patients with AHR to methacholine do have ENO levels >20 ppb (91). ENO levels have been shown to reflect sputum eosinophilia (92); Smith and co-workers have validated a treatment algorithm based on ENO measurements that makes it possible to reduce inhaled corticosteroids without compromising asthma control (93).

ENO levels may rise in asthmatic and non-asthmatic subjects after gassing incidents with exposure to ozone in bleachery workers (94) or toluene, xylene and methylethyl ketone solvents used by leather workers (95). It has been shown that ENO levels rise with respiratory symptom severity in

workers with laboratory animal allergy (96). Health-care workers had a significant increase in ENO levels one hour after a latex challenge but after 22 hours, levels remained significantly increased only in latex-sensitized subjects, this being related to AHR (97). However, there were no significant differences in ENO levels in latex-sensitized health-care workers when a comparison was made between the beginning and the end of a work week (98). After SIC with different agents, Piipari and co-workers demonstrated that ENO levels significantly increased mainly in subjects with pre-SIC ENO levels of <14.5ppb and a late asthmatic reaction, while subjects with pre-SIC ENO levels of >14.5 ppb and significant bronchoconstriction saw no significant increase in ENO (99). A rise in ENO occurred in two-thirds of subjects with a positive SIC test with diisocyanates, but also in half of subjects with a negative test (100).

Although ENO measurement is a promising new tool in non-invasive evaluation of airway inflammation, it has several limitations. Smoking can decrease ENO levels (101); however, smokers who are asthmatic still have elevated levels (102) and ENO levels tend to rise in smokers who stop smoking (103). Respiratory manoeuvres are known to transiently reduce ENO (104), and infection (105) and nitrate-rich meal intake (106) can transiently raise ENO levels.

Newer methods such as analysis of breath volatile organic compounds have been shown to help in discriminating healthy controls from patients with asthma, and also in identifying clinically important disease phenotypes related

to sputum inflammation and a measure of asthma control (107). However, to date this method has not been specifically applied in the investigation of individuals with OA.

1.1.2.4. Lung function tests

Lung function tests make it possible to measure the severity of airflow limitation, its reversibility and its variability. Two different methods have been proven to reliably assess these parameters: spirometry and peak expiratory flow measurement. Two-thirds of human beings have a diurnal rhythm of airway calibre, but asthmatic subjects have an exaggeration of this rhythm, especially if their asthma is not well controlled (108).

The volumetric spirometer measures lung volumes with a water bell or a bellows wedge, whereas the flow-measuring spirometer measures flow with a pneumotachograph, turbines or ultrasound and determines the volumes by extrapolation from measured flow values. Data are expressed in figures such as forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and PEF, or graphically as volume-time curve or flow-volume loop. With these values, we can calculate the Tiffenau Index by dividing the FEV1 value by the FVC value. Values below 0.70 are considered abnormal. It is then possible to perform a bronchodilator test (Figure 3). The subject inhales

two puffs of a short-acting bronchodilator. After 15 minutes spirometry is repeated and FEV1 and FVC values are compared with previously obtained values. Increases in the FEV1 value of ≥12% and ≥200ml are seen as diagnostic of asthma (109).

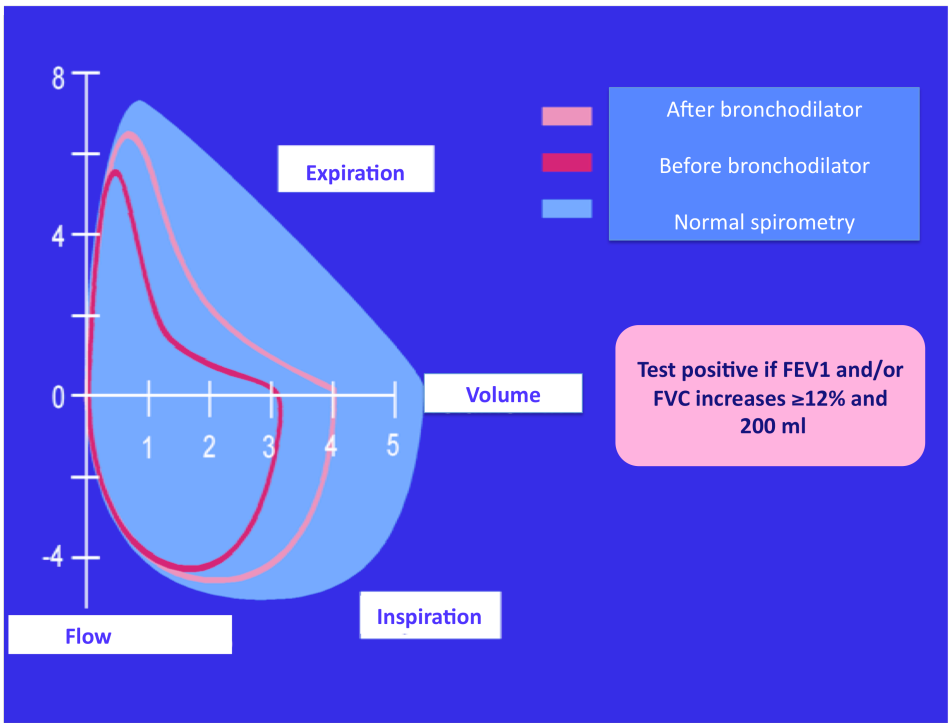

Figure 3: Flow volume curves during bronchodilator test

Population studies have obtained reference values for FVC, FEV1 and PEF based on age, sex and height (110). To be reproducible and comparable, measurements need to be performed according to published guidelines (111).

Lung function can be measured before and after the working shift, and the difference between these parameters is recorded as “cross-shift” changes. However, the value of determining cross-shift changes is limited, as subjects can have late asthmatic responses that occur after the work shift ends. It is also difficult to standardize the measurement as indirect work exposure when changing work clothes or leaving the workplace through an area of exposure. As workers may work on different shifts, the influence of spontaneous circadian variation adds further confusion to the interpretation of results (112, 113).

Patients can take their own peak flow measurements with compact and inexpensive devices. Patients are instructed to measure PEF on work days as well as days off and record the values in a diary. A minimum of four measurements is recommended; more frequent measurements do not seem to increase sensitivity and specificity (114). Ideally, the measurement period includes a time where the worker is on holiday for at least two weeks. According to the GINA guidelines, a diurnal variation in PEF of more than 20% suggests a diagnosis of asthma (115). Figure 4 shows an example of a PEF graph with a classic pattern of OA (116).

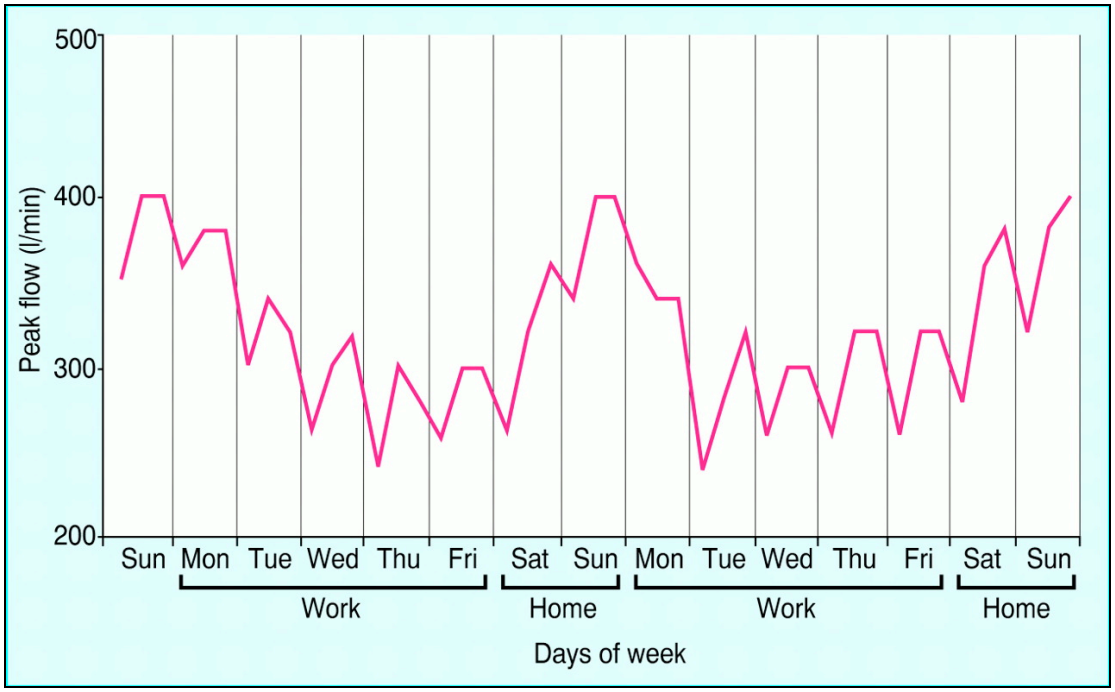

Figure 4: Self-recorded peak flow measurement showing classic pattern of OA

When analyzing PEF recordings of subjects with OA, three different reaction patterns may be noted: immediate reaction, late reaction and flat reaction.

Immediate reactions are indicated by a drop in lung function in the first hour after the worker is exposed to the allergen. Lung function values may improve shortly after leaving the workplace; for example, during lunch break or in the evening after leaving work.

Late reactions normally start several hours after the start of exposure at work and progress even once the worker has left the workplace. Workers frequently complain of symptoms in the evening after work or during the following night.

Flat reactions are demonstrated in subjects with chronic exposure and fixed airway obstruction. The diurnal variability of PEF recordings is blunted.

Reading peak flow recordings requires experience and even in experts, the results can vary, as demonstrated by Baldwin and co-workers (117). This favours a standardized approach using computer programs like OASYS-2 (OASYS Research Group, Midland Thoracic Society; Birmingham, UK) that were developed to analyze and simplify the reading of PEF recordings (118).

Although PEF variability is higher in workers with OA compared to workers with WEA, the method is too insensitive to reliably distinguish between the subjects (119). PEF recordings depend on the effort of the patients. PEF manoeuvres have been shown to be less reproducible if performed by the patient alone compared to performance under the supervision of a technician (120). Malo and co-workers asked patients evaluated for OA to perform PEF with a data-logging PEF device and write down the values in a diary. Only 52% of the recorded values and 71% of the indicated timing of the measurements in the diary corresponded with the stored values in the data-logging device (121).

The Agency for Healthcare Research and Quality reviewed studies evaluating PEF in OA confirmed by specific inhalation challenge. The pooled estimate of sensitivity was 63.6 %(95% CI: 43.4 to 79.9%); for specificity , it was 77.2 %(95% CI: 66.5 to 85.2%) (122).

1.1.2.5. Non-specific bronchial provocation tests

AHR is a hallmark of asthma that can be assessed by performing bronchial provocation tests (BPTs) using direct (methacholine, histamine) or indirect stimuli (exercise, hypertonic saline, adenosine-monophosphate and mannitol) (123). One of the advantages of using indirect stimuli to assess non-specific AHR is that all the common stimuli that provoke an asthma attack in daily life, such as allergens, cold air, exercise, sulphur dioxide and fog, act indirectly to cause airways to narrow (124).

In asthmatics, responsiveness to indirect BPT is a better reflection of indices of airway inflammation, such as sputum eosinophils or ENO, than that to direct BPT with methacholine (125). In a study of active firefighters, a BPT using mannitol had higher efficiency and Youden index than a BPT using methacholine (126). Indirect BPTs are more specific for diagnosis of asthma (127-129), although they are less sensitive for identifying AHR in a laboratory study population (130). Using a direct BPT for a young, healthy population often produces false-positive responses in subjects without asthma symptoms (131-134). Exercise-induced bronchoconstriction can be missed in direct BPTs, such as with a histamine or methacholine challenge (135, 136)but it may be better diagnosed using indirect BPTs (137-139).

A BPT using mannitol has been shown to be well correlated with other indirect BPTs; for elite athletes, a PD10 to mannitol had a sensitivity of 96%

to diagnose a 10% decline in FEV1 during eucapnic voluntary hyperpnea (140). The protocol for performing a BPT using mannitol has been standardized and validated, allowing easy comparisons. For most subjects, the duration of the test is <20 min. Compared to current wet aerosol tests, such as those using methacholine, the equipment used for this test is simple to use, inexpensive, and does not require any maintenance and cleaning (141). As with all BPTs, only an office spirometer is required.

For current, widely-used direct tests with methacholine and histamine, solutions of appropriate concentrations need to be prepared by hospital pharmacies according to the particular protocol. These solutions need to be transported to the location where the test is to be performed, and the cold chain needs to be maintained; otherwise, the vials cannot be used. In comparison, mannitol test kits come ready to use and can be stored at room temperature for longer time than methacholine solutions, allowing testing at the subjects' workplace (142).

For patients with OA who were investigated to assess their impairment/disability approximately 2 years after their initial diagnosis, we found that this test is a better marker of disease activity and can differentiate subjects based on disease severity. Further, concomitant assessment of airway responsiveness and collecting sputum can be performed at the same time (143).

However, the current standard in the evaluation of OA is to perform an indirect test with methacholine or histamine (3). Methacholine chloride, a

parasympathomimetic synthetic analog of acetylcholine, stimulates muscarinic, postganglionic parasympathetic receptors that cause the bronchial smooth muscle cells to contract (144). During the test, doubling concentrations of methacholine chloride in isotonic saline are nebulized and inhaled by the patient. After each dose step, spirometry is performed. There are different protocols for the administration of methacholine which have been published as internationally accepted guidelines (138, 145). The test is continued until the maximum concentration has been inhaled or a drop in the FEV1 of more than 20% from baseline occurs that allows intrapolation of the theoretical concentration leading to a fall of 20%, called PC20. Subjects with a PC20 of 8 mg/ml or less are considered to have bronchial hyperresponsiveness. The results of a PC20 between 8 and 16 mg/ml are considered indeterminate, and values greater than or equal to 16 mg/ml are considered normal (146).

It should be mentioned that non-specific BPTs are not 100% sensitive for the diagnosis of OA. As with SPT, non-specific BPTs may be negative when subjects have not been exposed for a prolonged period to a sensitizer that causes their asthma (147), even in subjects with a positive reaction to a specific inhalation challenge (148). Baur and co-workers demonstrated that non-specific BPTs cannot reliably differentiate asthma patients from occupationally exposed non-asthmatic subjects, or distinguish between OA and non-OA (149). Nevertheless, performing a non-specific BPT can help to determine the work-relatedness of asthma. It has been shown that a 3.2-fold

increase in non-specific AHR has a sensitivity of 48% and a specificity of 64% in OA confirmed by SIC (150). Non-specific BPTs may become negative some weeks after a patient is no longer exposed to an occupational allergen, as shown by Cartier et al. (151), whereas other workers still have non-specific AHR years after stopping exposure, as demonstrated in snow-crab workers (152) and workers exposed to red cedar wood dust (153). It has been shown that maximum improvement in non-specific AHR occurs in the first two years after stopping exposure and at a slower rate thereafter (154).

1.1.2.6. Specific inhalation challenge

This method has been called the reference standard test for the diagnosis of asthma and OA (122). This test is performed on workers who have a high probability of immunological OA. There are two methods of laboratory SIC: the realistic method and the method that is carried out with dust-generating machines. If specific agents cannot be identified or the SIC test is inconclusive, patients may undergo workplace challenge testing (155).

In the “realistic method,” workers perform their duties in the lung function laboratory, usually in small ventilated cubicles under regular monitoring with spirometry. The work process is simulated as close as possible, e.g. a baker with probable OA to wheat flour stirs or mixes flour,

while a painter uses the presumed product by painting a piece of wood. It is possible to monitor the concentration of isocyanides with an MDI monitor to avoid irritant or toxic exposure in the chamber.

To further standardize the exposure procedure, closed-circuit dust generators have been developed (156) that produce dust, aerosols and vapours; the concentration of these products in the inhaled air is then monitored precisely.

SIC can help to identify the specific agent by sequentially testing a worker who may be exposed to several potential asthma-causing substances (157).

1.1.2.7. Workplace challenge testing

Sometimes, however, when a specific agent cannot be identified, workplace exposures are too complex to simulate, or SICs are not available, testing needs to be performed at the workplace. On a control day, spirometry is performed while the subject is performing a task that does not causes symptoms or away from the workplace. On the day of exposure, the subject performs the tasks incriminated as causing asthma (3, 155).

Although the SIC test is seen as a reference standard, it has several limitations. SIC tests are not available in all regions of the world. SIC testing

requires specialized facilities and expertise that are expensive and time-consuming (3, 158).

SIC can yield false positive as well as false negative results. False positive results may occur in patients with unstable asthma or patients who are exposed to irritating levels of a provocation agent (3). False negative results may occur if the wrong agent has been tested or if the work environment created in the laboratory does not present the same triggers as those encountered in the workplace. If patients are on anti-asthmatic medications to control their asthma, the medication may influence the test results. As with SPT and non-specific AHR, SICs can become negative after a certain time away from exposure to the causing agent, although this occurrence is low (158, 159).

Despite its high cost and complexity, SIC should be performed when it is available. An accurate diagnosis of immunological OA is crucial: further exposure to the causing agent needs to be avoided, with the consequence that the worker needs to change his or her profession or workplace to avoid further deterioration in the disease and long-term functional impairment (160, 161). Compensation for OA by workers' compensation boards for loss of income and compensation for functional impairment averages about $50,000 CAD$ in Québec, and workers with OA generally present at a relatively young age, which makes rehabilitation possible and most often fruitful for the worker (162).

1.1.3. Management of patients with occupational asthma

The management of WRA is the same as for subjects with non-WRA. Asthma control is the goal of medical treatment and may require a “step up” in asthma treatment that has already been started (www.ginasthma.org). For individuals with immunological OA, full cessation of exposure to the causing allergen should be achieved. Harm reduction would mean that the worker remains exposed to the causing agent, but at a reduced level of exposure. This can be achieved, for example, by reducing the time the worker is exposed to the agent, by using personal protective devices such as a face mask, or by replacing powdered latex gloves with non-powdered gloves. A recent systematic review and meta-analysis, however, indicated, that reduction of exposure cannot be routinely recommended as an alternative to cessation of exposure: continued reduced exposure was associated with a lower likelihood of improvement or recovery and a higher risk of worsening of asthma symptoms and non-specific AHR compared with complete cessation of exposure (163). Complete cessation could be achieved by relocation within the same workplace so that there is no longer exposure to the agent, a change in work processes (e.g. replacing the causing agent with a new agent), or a change of profession.

Individuals with non-immunological OA or WEA may continue to work at their workplace. But control of work processes and monitoring of exposure levels are needed to ensure that the subject is not exposed to high concentrations of airway irritants. In those with WEA, the goal must be to achieve asthma control by decreasing asthma triggers in the workplace whenever possible and by adding or increasing the dose of anti-inflammatory treatment such as inhaled steroids or leukotriene antagonists or by considering anti-IgE treatment with omalizumab (www.ginasthma.org). Individuals with OA and WEA have been shown to have similar impairment in quality of life when evaluated in tertiary-care centres, and to have similar socio-economic outcomes when unemployment rates are compared with patients with OA (164-166).

Given the high prevalence of psychological distress and psychiatric disorders in the population of individuals with WRA, patients need to be evaluated for these conditions by specialists. Treatment options such as psychotherapy or medication should be considered, although so far there are no data available about the effects of such a treatment on OA-specific outcomes (167).

1.1.3.1. Natural history of OA

Figure 5 shows the natural course of OA based on a review article by Malo and Chan-Yeung (168). The steps in disease progression are shown in boxes, while the modulating factors are listed below the time axis.

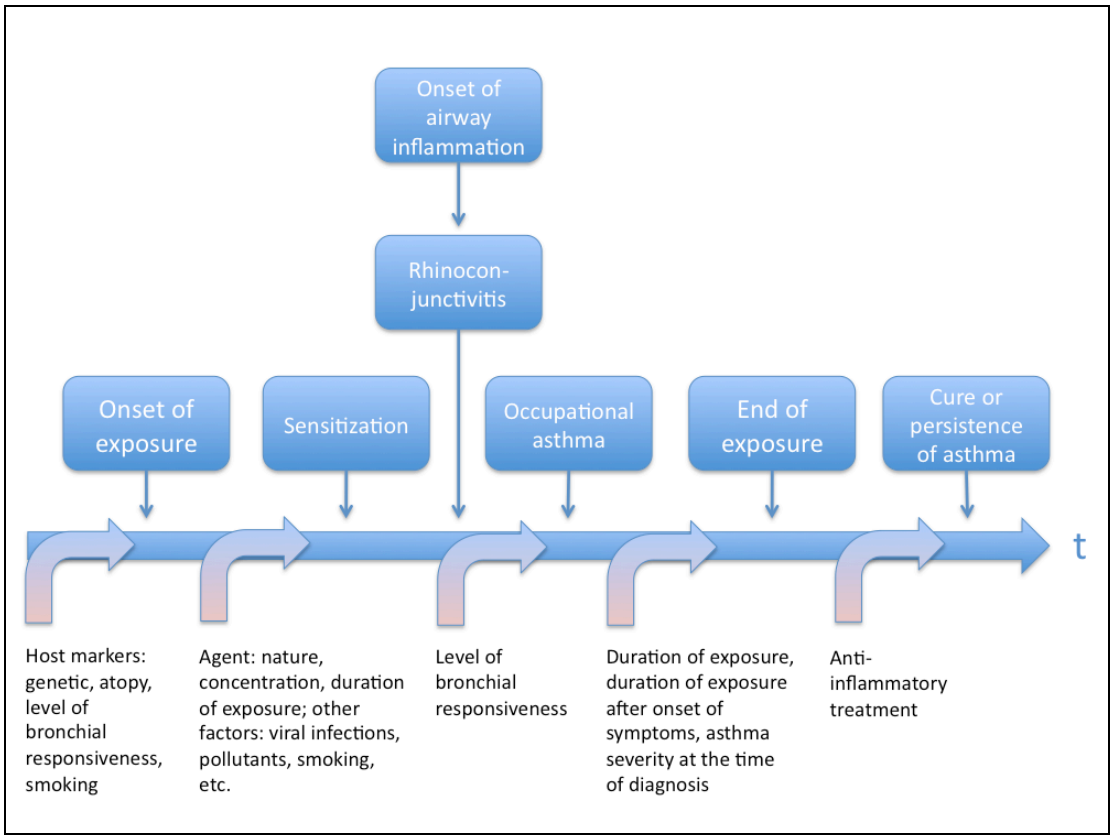

Figure 5: Natural history of immunological OA

The interval between onset of exposure and events such as allergic sensitization and the development of upper or lower respiratory symptoms is called the latency period. In workers exposed to laboratory animals, maximum

sensitization occurs in the first two years after the start of exposure to the animals (39, 169). The interval is sometimes shorter for OA to LMW agents (6). In general, upper respiratory symptoms and conjunctivitis precede lower respiratory symptoms in workers exposed to HMW allergens, while this is not always the case in workers exposed to LMW allergens (39, 170). However, about 10% of workers exposed to HMW or LMW agents may develop respiratory symptoms after more than 10 years of exposure to the allergens (171).

1.1.3.2. Prognostic factors for OA

Complete avoidance of exposure is considered the best standard of care for individuals with OA (3, 163, 172). Even when this can be achieved, many will continue to have respiratory symptoms and lung function impairment. A shorter duration of symptoms and a preserved FEV1 prior to cessation of symptoms seems to be a predictor of favourable subsequent outcome of OA in workers exposed to red cedar wood dust (53). In a systematic review investigating predictors for symptomatic recovery and persistent non-specific AHR, Rachiotis et al. reported that despite complete avoidance of exposure, about 32% (95% CI 26-38%) have persistent symptoms and 73% (95% CI 66-79%) have persistent bronchial

hyperresponsiveness (173). In this analysis, higher age was associated with a higher risk for persisting respiratory symptoms. There was a trend to a higher risk for persisting respiratory symptoms in individuals who had a longer duration of symptomatic exposure in their workplace and in those who were diagnosed during a study in the workplace ($p=0.120$ and $p=0.052$ respectively). The time interval since the end of exposure, duration of employment and classification of the causing allergen as LMW or HMW were not associated with symptomatic recovery. In persistent non-specific AHR, OA to LMW agents was identified as a significant predictor (173). Descatha investigated 229 individuals with immunological OA recruited by occupational health departments in France. In multivariate analysis, a longer duration of symptoms before diagnosis of OA was positively associated with moderate to severe OA when adjusting for several important co-factors (OR = 1.12, 95% CI 1.05–1.18, $P < 0.001$)) (174).

Those individuals who become symptom-free and lose their bronchial hyperresponsiveness to unspecific stimuli due to complete avoidance of exposure and medical treatment should not be re-exposed again, since this can still cause asthmatic reactions, as shown by Lemière and co-workers in an experimental setting (159, 175).

1.1.3.3. Asthma severity and Asthma control

In the past, overall asthma severity has been defined by incorporating different features such as respiratory symptoms, medication requirements, and physiologic abnormalities such as lung function, AHR and morbidity (e.g. number of asthma exacerbations) (176). GINA (www.ginasthma.org) subdivides asthma into four categories by severity, based on the level of symptoms, airflow limitation and lung function variability (Table 5). The worst feature of these parameters determines the severity classification.

Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month - FEV1 or PEF ≥ 80% predicted - PEF or FEV1 variability <20%
Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month - FEV1 or PEF ≥ 80 % predicted - PEF or FEV1 variability < 20-30 %
Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting B2-agonist - FEV1 or PEF 60-80 % predicted - PEF or FEV1 variability > 30%
Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities - FEV1 or PEF ≤ 60% predicted - PEF or FEV1 variability > 30%

Table 5: Classification of asthma severity by clinical features before treatment (from the Global Strategy for Asthma Management and Prevention, 2008. Copyright Global Initiative for Asthma (GINA), www.ginasthma.org.)

It is important to remember that the classification needs to be carried out before starting treatment. Asthma severity involves both the severity of the underlying disease and its responsiveness to treatment (www.ginasthma.org). For example, a subject may be classified as having severe persistent disease at initial presentation. After some weeks of successful treatment with anti-inflammatory medication, the subject may be classified as having mild persistent disease and, after a period of non-

adherence to therapy or the occurrence of new asthma-exacerbating factors, may be reclassified as having moderate persistent disease.

Nowadays, this classification is mainly used for the initial classification of asthma patients prior to the start of treatment or inclusion in an asthma study, but it is a poor predictor of what medications are needed to achieve asthma control. The latest edition of the GINA guidelines (www.ginasthma.org) suggests that asthmatics need to be assessed on a regular basis to determine the level of control of their asthma (Table 6).

Characteristic	Controlled	Partly controlled	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1)	Normal	<80% predicted or personal best	
Exacerbations	None	One or more/year	One in any week

Table 6: Levels of asthma control

(from the Global Strategy for Asthma Management and Prevention, 2010. Copyright Global Initiative for Asthma (GINA), www.ginasthma.org.)

1.1.3.4. Harm reduction or complete avoidance of exposure

It is recognized that avoidance of asthma triggers (e.g. smoking cessation, reducing exposure to second-hand smoke and occupational agents or medications known to cause symptoms) needs to be achieved to improve asthma control and reduce the need for medication (www.ginasthma.org). Removal from exposure to the sensitizing agent is therefore usually recommended as the most effective therapeutic approach in current guidelines (3, 172). However, this goal can be difficult to achieve, since subjects may be unwilling to change their profession if symptoms are mild at the beginning, the therapy seems to be effective and they fear losing their job, with the consequent loss of income. It has been estimated in several European countries and in British Columbia/Canada that about one-third of workers remain exposed at the workplace after a diagnosis of OA (177). Beach et al. conclude in their systematic review of studies on the management of workers with OA that subjects with continued exposure had worse outcomes, such as increased respiratory symptoms, airway obstruction and non-specific AHR, compared to workers who left exposed workplaces (122). Workers who continue to work in their environment without any change in exposure seem to have an increase in the severity of their asthma (178), an increased FEV1 decline (179) and higher medication use and expenses (178, 180). Unfortunately, there is not much evidence to show that asthma

anti-inflammatory medication can alter the long-term deterioration of asthma if exposure remains unchanged (179, 181).

Since workers with OA are sometimes unwilling to avoid complete exposure in order to keep their jobs, studies have investigated the outcome of OA with continued but reduced exposure. Reduced exposure can be achieved by changing work processes or substances at the workplace, relocating the workplace to a less exposed area or using respiratory protective equipment.

However, respiratory protective equipment should not be regarded as the single therapeutic option, especially in patients with severe disease. To date, there is no convincing evidence to support the widespread use of respiratory protective equipment in workers with OA, as only short-term effects have been documented and respiratory protective equipment, which can be impractical to use, may therefore not be able to provide complete protection (182).

For health-care workers, harm reduction can be achieved by personal avoidance of natural rubber latex-containing protection devices such as gloves and masks and distribution of non-powdered low-protein latex gloves to co-workers. This strategy has been associated with improvements in asthma severity, quality of life scores and bronchial hyperreactivity (183). Workers with OA due to platinum salts that have been transferred to other workplaces within the production building or outside the building but inside the plant saw a similar improvement in their respiratory symptoms and

sensitization measured by IgE compared to workers who left the plant (184). Recent systematic reviews and a meta-analysis have confirmed the finding that reduced exposure can lead to an improvement or even resolution of symptoms and non-specific AHR compared to workers with continued exposure. However, data also show that continued reduced exposure is associated with a lower likelihood of improvement and recovery from OA symptoms and a higher risk of worsening symptoms and increasing non-specific AHR (163, 173, 182).

Only limited information is available about the effects of harm reduction on employment status and income. Burge investigated electronics workers with OA to colophony in the UK over a follow-up period of one to four years, and reported that only about 35% of those who had left the electronics factory were employed at follow-up (185). Adverse socio-economic findings were confirmed in health-care workers in Belgium by Vandenplas and co-workers, who found the proportion of individuals with a major loss of income to be higher among those who ceased exposure to natural rubber latex gloves compared to those who markedly reduced exposure to airborne latex at follow-up (183).

The limited evidence and often adverse socio-economic impact on individuals with OA who have left their workplace point to the fact that current guidelines consider harm reduction to be a reasonable and pragmatic approach in those individuals where a complete avoidance of exposure is not achievable (3, 172).

1.1.3.5. Medical treatment of work-related asthma

The treatment of different forms of WRA is the same as for non-WRA and is based on a stepwise approach, with the goal of achieving total asthma control according to the GINA guidelines (www.ginasthma.org, Figure 6). For the management of upper airway symptoms, evidence-based guidelines for management have been developed by the Allergic Rhinitis and its Impact on Asthma (ARIA) working group (186).

The mainstay in asthma treatment is to treat inflammation with steroids if short-acting bronchodilators are not sufficient. Inhaled steroids have been shown to improve asthma specific quality of life, PEF variability and non-specific AHR in subjects with immunological OA who have left their workplace (187), but there is limited evidence for the use of other anti-asthmatic drugs (3).

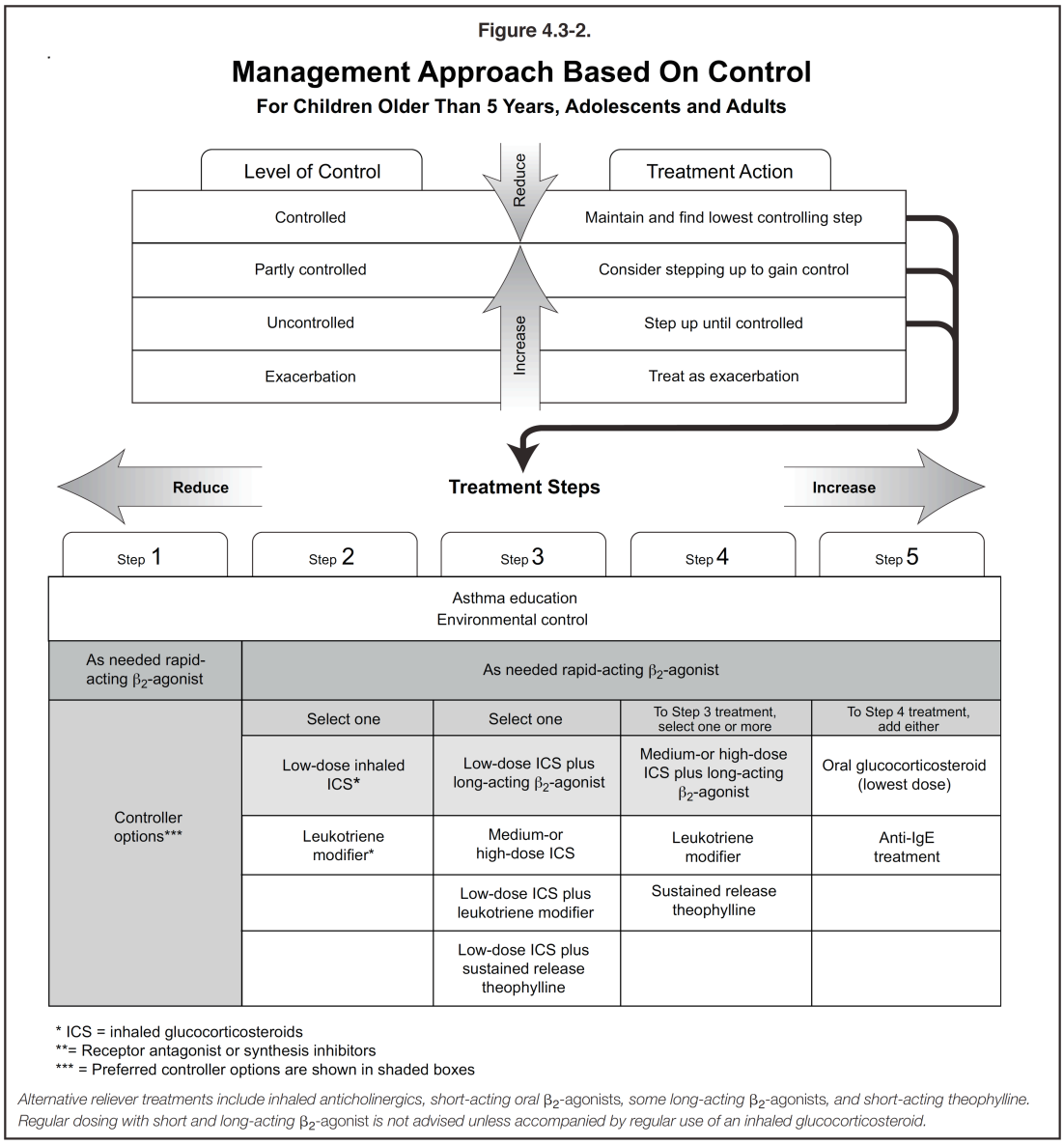

Figure 6: Management approach based on control of asthma symptoms

(from the Global Strategy for Asthma Management and Prevention, 2010. Copyright Global Initiative for Asthma (GINA), www.ginasthma.org.)

1.1.3.6. Immunotherapy

This method involves administering increasing amounts of offending allergens to patients with type I allergic disease. The active mechanism is through modulation of T-cells and response of B-cells accompanied by significant decreases of specific IgE and increases of specific IgG antibodies (188). Immunotherapy has been shown to reduce respiratory symptoms, SPT reactivity and medication use in health-care workers with OA to natural rubber latex (189). Bakers treated with immunotherapy have been shown to have fewer respiratory symptoms, decreased sensitization (measured as SPT reactivity and specific IgE levels) and less non-specific AHR than subjects who received placebo injections (190, 191). The ACCP consensus statement on Diagnosis and Management of Work-Related Asthma notes that "…in the absence of good control with pharmacotherapy and inability to completely avoid the allergen, and where validated extracts are available, immunotherapy for occupational allergens could be an effective treatment of allergy to and asthma from HMW antigens in work environments." (3)

1.1.3.7. Prevention of occupational asthma

Prevention can be classified into three categories: primary, secondary and tertiary prevention.

Primary prevention aims to protect against the development of disease and disability by:

- identifying workers susceptible to sensitization and avoiding their exposure to known sensitizers;
- limiting exposure to known respiratory tract irritants in general, and especially in subjects with already established asthma to prevent the development of WEA;
- eliminating known respiratory tract irritants or sensitizers from work processes if possible or making an effort to contain these work processes as far as possible;
- limiting the number of workers exposed to known respiratory tract irritants or sensitizers or the duration of exposure of each individual to these substances;
- providing protective equipment for workers exposed to known respiratory tract irritants or sensitizers.

Secondary prevention aims to diagnose the disease in its earliest stages, before symptoms develop. At this stage the disease can be treated successfully, its progression slowed or complications limited. In a project

recently carried out in Quebec, Labrecque and co-workers evaluated a medical surveillance program that targeted more than 2,000 workers from the motor vehicle body manufacturing industry who were exposed to diisocyanates. Subjects in the screening group were informed about OA at a session and asked to answer a self-descriptive screening questionnaire related to symptoms of asthma (Figure 7) and its work-relatedness. The questionnaire contained 5 validated questions from the ECRHS questionnaire (192) and an additional question (numbers 6) on how respiratory symptoms were related to the workplace. If three or more questions were answered positively, workers were urged to contact their occupational-health centre for further assessment. Compared to controls who were suffering from OA and had been referred to the Workers' Compensation Board in the usual fashion, i.e. without screening questionnaire, by referral from their own physician, workers in the screened group had less non-specific AHR at diagnosis of OA (193), less impairment as confirmed two years after the diagnosis, and lower costs to the CSST (Quebec Workers' Compensation Board, CSST) for functional impairment.

SCREENING QUESTIONNAIRE

To answer the questions please choose the appropriate box, if you are unsure of the answer please choose "NO"

1. Have you had wheezing or whistling in your chest at any time in the last 12 months?
   NO ☒ YES ☒

   If "NO" go to question 2, if "YES" :

   1.1 Have you been at all breathless when the wheezing noise was present?
   NO ☒ YES ☒

   1.2 Have you had this wheezing or whistling when you did not have a cold?
   NO ☒ YES ☒

2. Have you woken up with a feeling of tightness in your chest or been woken by an attack of shortness of breath at any time in the last 12 months?
   NO ☒ YES ☒

3. Have you been woken by an attack of coughing at any time in the last 12 months?
   NO ☒ YES ☒

4. Have you had an attack of asthma in the last 12 months?
   NO ☒ YES ☒

5. Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?
   NO ☒ YES ☒

AT WORK

6. When you are at work, do you ever

   6.1 start to feel short of breath or get chest tightness? NO ☒ YES ☒

   6.2 start to cough? NO ☒ YES ☒

   6.3 start to wheeze? NO ☒ YES ☒

   6.4 If "YES" to one of these statements, do these problems related to your work lessen or disappear during the weekend or during holidays? NO ☒ YES ☒

IF YOU ANSWERED « YES » AT THREE QUESTIONS OR MORE; YOU COULD HAVE ASTHMA; TAKE MORE INFORMATION

Figure 7: Questionnaire used by Labrecque and co-workers to screen for OA in diisocyanate-exposed workers

Tertiary prevention is aimed at limiting medical impairment in subjects with established disease by decreasing complications and disability, the progression of the disease and by providing help with rehabilitation.

Liss and Tarlo (194) summarized methods for prevention of OA, as shown in Table 7.

	Target	Intervention	Example of industry
Primary prevention			
At the source			
Elimination	Natural rubber latex (NRL)	Change to non-NRL gloves	Health care
Substitution	NRL	Change to low-protein, non-powdered NRL gloves	Health care
Enclosure	Detergent enzymes	Encapsulation	Detergent enzyme industry
	Diisocyanates	Robots in enclosed areas	Foam-making plants
For the worker			
Personal protective equipment	Farm allergens	Air supply respirator use	Dairy farmers
	Diisocyanates	Air supply respirator use	Spray painters
Secondary prevention			
Medical surveillance	Complex platinum salts	Skin prick tests, questionnaire, spirometry	Platinum workers
	Diisocyanates	Questionnaire, spirometry	Foam-making and other diisocyanate workers
	Enzymes	Skin prick tests, questionnaire, spirometry	Detergent enzyme industry
Tertiary prevention			
Removal from further exposure	All with sensitizer-OA	Work in a separate building from where the sensitizer is used	Any occupation using the specific agent
Marked reduction in exposure	NRL	Avoid personal contact, and co-workers use low-protein low-powder NRL gloves	Health-care workers
	Farm allergens	Air supply respiratory use	Dairy farmers, laboratory animal workers
Medical monitoring	All with sensitizer-OA and possible re-exposure	Symptoms, medication needs, peak flows, spirometry and airway responsiveness	Any occupation using the specific agent
Asthma management	All OA patients	Environmental control, pharmacologic management	
Immunotherapy	NRL-OA	Specific immunotherapy	Latex-sensitized workers

Table 7: Different methods of prevention for OA

1.2. Social determinants of health

Social factors are strongly associated with health status and mortality. For example, people living in the most disadvantaged parts of Glasgow, Scotland, were shown to have a 12-year-shorter life expectancy than people living in more affluent parts of town (195). The same findings hold true, but on a much larger scale, when comparing life expectancy between different countries. In 2005, the World Health Organization (WHO) estimated life expectancy for both sexes in the Russian Federation to be 64 years, compared to 81 years in Sweden or Switzerland (196). Responding to increasing concerns about persisting and widening inequities, the WHO set up the Commission on Social Determinants of Health in 2005 to provide advice on how to narrow the gaps (www.who.int./social_determinants/en). In this chapter, I will discuss how various social and economic factors can have an impact on health, life expectancy and mortality.

1.2.1. Sex and gender

Life expectancy does differ in favour of women in various regions of the world, with a mean difference of about 4 years. In the WHO health report, the life expectancy of women in Canada is estimated at 82 , compared with 78 for

men (196). Two factors may account for this finding. There are theories about differences in body functions and physiology that differ between women and men, and there are social and behavioural factors that can account for this gap (46).

Women are known to respond to infection, vaccination and trauma with increased antibody production and a different pattern of immune response than men, and most autoimmune diseases are more prevalent in females than in males (45). The incidence of vascular disease is higher in men than in women. It has been hypothesized that ovarian sex steroid hormones are responsible for the cardiovascular benefits in women, acting on the endothelial function of the blood vessels (197). It has been shown that endothelial dysfunction – an early event in atherosclerosis – starts about 10 years earlier in men than in women (198). Coronary heart disease is less common in premenopausal women, but that difference seems to disappear after menopause; this is most likely related to reduced levels of female sex hormones and an increased level of plasma androgens (199).

Adolescent and adult females have been shown to suffer more often from respiratory allergies, asthma, food allergies and anaphylaxis than males (200). The lifetime likelihood of developing asthma is greater in women than in men (201). While the prevalence in prepubertal boys is higher than in girls, asthma is becoming more prevalent after the age of 20 in the United States, and continues to widen until the age at which women enter menopause (201). This is paralleled by the finding that patients hospitalized for asthma who are

more than 15 years old are more likely to be female, while those who are less than 15 years old are more likely to be male (201).

Females with asthma have been shown to report more respiratory symptoms and more impaired quality of life than males, even when the analysis is controlled for lung function (202-204). Some of these differences may be explained by the fact that females may have a higher prevalence of anxiety symptoms, which can further decrease quality of life (203, 205). Other reasons, such as more often improper metered-dose inhaler technique and reduced inspiratory muscle strength, may further explain this difference (206, 207). However, women with asthma more often seem to have a primary-care physician, are more likely to use peak flow meters regularly and have a written asthma action plan, and are more likely to go for regular follow-up visits for asthma than men (208-210).

An analysis of the 1994 Canadian National Population Health Survey indicated that females had a lower level of education and more often reported being unemployed, employed part-time, or employed in jobs with higher work stress, such as jobs with low control, high psychological demands and high job insecurity, than males. Females were reported to have lower household incomes than males, were less often home-owners, and tended to have lower scores of self-perceived control (an index score reflecting their belief that their life chances were under their control) than males (211).

Behavioural factors do play a major role, as shown with cigarette smoking: globally, a difference between men and women can be

demonstrated in the incidence and mortality of lung cancer. At present, more men than women die from lung cancer each year. However, in the developed world, the incidence and mortality of lung cancer among women has sharply increased while the same parameters decline slowly among men, a finding that has been attributed to increased cigarette consumption by females in recent years (212). Males seem to have higher rates of alcohol use disorders than females (213), and the same is true for illegal substance abuse (214). Females tend to have higher rates of suicidal ideation but males have higher suicide rates (215). Another reason for the difference in mortality and life expectancy could be that men are more likely to work in high-risk manual jobs than females, making them prone to more severe occupational injuries and diseases.

Several studies have reported that men are at higher risk for several types and severities of work-related injuries in different workplace settings than women (216-219). However, these differences are almost entirely explained by differences in men's and women's involvement in tasks with a high risk of injury. Once that difference is taken into account, women may even have a higher risk than men for occupational injuries (217, 220).

Eng and co-workers conducted a telephone interview survey in New Zealand to investigate whether men and women working in the same occupation were equally exposed to known workplace hazards. Their analysis suggests that males are more likely to report exposure to welding fumes, herbicides, wood dust, solvents, tools that vibrate, irregular hours and night-

shift work than females. By contrast, women are more likely to report repetitive tasks, working at high speed, and working in awkward or tiring positions than do men (48).

1.2.2. Housing and neighbourhood conditions

It is more likely that housing reflects rather than creates socio-economic gradients. The neighbourhood we live in depends on our socio-economic status (221). Clearly, disease and mortality rates vary across areas, as has been demonstrated many times (222); however, less is known about whether differences are due to a clustering of individuals with similar risk profiles in the neighbourhood, or whether there are additional effects of the neighbourhood, over and above individual risk factors (195). Residency in deprived areas has been identified as a risk factor for diminished perceived general and mental health (223, 224), coronary heart disease (225), violence and murder (226, 227) and all-cause mortality (226, 228). The physical environment may increase illness: air pollution, measured as total particulate concentration and sulphur dioxide levels, has been demonstrated to increase mortality (229). This was confirmed in a meta-analysis of studies that investigated air pollution and mortality: Schwartz reported that airborne particle concentration was a significant risk factor for elevated mortality (230).

Other studies have investigated the effect of poor housing conditions on respiratory health. Strachan reported an increased risk of developing wheezing and chesty coughs in children living in homes with damp and mould exposure in the Edinburgh area (231). Another study found an increased prevalence of respiratory symptoms in adults and children living in damp and mouldy homes compared to adults and children living in dry dwellings (232). Among inner-city children with sensitization to cockroaches, exposure to high levels of this allergen at home was associated with increased health-care use (233). Results of a subsequent study indicate that housing deterioration and instability were associated with increased cockroach allergen concentrations in kitchens and bedrooms (234). Further studies have shown a negative effect of housing deprivation in childhood on increased mortality in adulthood (235).

1.2.3. Immigration status and health of ethnic minorities

There are various reasons why subjects leave their country of usual residence and move abroad. Most subjects move to developed countries to improve their socio-economic conditions, while others are forced to flee their country as refugees (236). Nevertheless, not all migrants leave their country because of poverty, nor are these migrants less educated (236). We must be cautious about using the term “immigrant” to refer to individuals from various

countries who settle in developed countries. These individuals differ in reasons for leaving their home country, prior exposure to workplace allergens and genetic backgrounds (237).

These migrants often have better health status when they arrive in their new country than the general population of the host country, mainly because only migrants in good health complete the strenuous journey and pass comprehensive medical screening before gaining entry to the host country (238, 239). This may lead to the selection of healthy immigrants, as those who are unfit to travel and work abroad are likely not to take such risks or will not be allowed to enter the country due to health restrictions.

Immigrants who come to an industrial country such as Canada are leaving communities where there is a relatively high mortality rate from infectious diseases as well as maternal causes, and limited access to health care, and going to a community with a high prevalence of cardiovascular diseases but also better access to health care (240). After years of living in the new environment and adapting to the local lifestyle, their level of mortality from cardiovascular disease approaches the level for the host population (241).

The distribution of the prevalence of atopy and asthma is not uniform throughout the world and seems to be higher in developed and affluent countries than in developing and less affluent countries (242-244). Several studies have shown that immigrants from Central and South America who settle in the United States or Italy often have less sensitization and less

history of allergies than the general population of the host country. However, these individuals seem to be more vulnerable than immigrants from other ethnic backgrounds to developing allergies in the early phases of living in their new host country (245-247). Sensitization to allergens and subsequent asthma results from the interaction of environmental factors with the genetic susceptibility of individuals (248). A history of asthma in the family, viral infections in early childhood, prematurity, exposure to outdoor or indoor pollutants and allergens at home or in the workplace, as well as living in an urban area have been identified as risk factors for the development of asthma (248). In a review, Rottem and co-workers suggest that in Western industrialized countries, lifestyle and environmental factors facilitate atopy and the development of asthma, and that 1) this effect is time-dependent; and 2) it especially affects individuals who immigrate in early childhood (under 2 years of age), since they are more prone to develop atopic disorders such as asthma, hay fever and eczema (244, 249). In Sweden, migration from a low- or median-income region of the world has been related to an increased risk of asthma medication in children of immigrant families; this risk declines with increasing age at immigration (250). In the ECRHS, a vast and important study that assesses the prevalence and incidence of atopy and asthma in several European countries, participants were divided into three groups according to their immigration status: 1. immigrants, defined as individuals who immigrated from a country outside Europe or one of the participating countries; 2. emigrants, defined as immigrants from another country where

the ECRHS took place; and 3. non-immigrants, or the host population in the ECRHS participating countries. In this study, the rates of asthma symptoms were higher in immigrants and emigrants compared to non-immigrants after adjustment for smoking status, age, sex and study area, but atopy and bronchial hyperresponsiveness were not more common in immigrants or emigrants compared with non-immigrants (251).

Self-reported health tends to worsen after some time in the host country and converge with the self-reported health of the host population (238, 252). Self-perceived health among migrants and ethnic minorities may even tend to be lower when compared with the majority populations in Europe (253). When they arrive in the host country, migrants need to adapt to a new physical and socio-economic environment and establish new social contacts. They may face discrimination, which has been shown to be associated with declining health (254). Furthermore, their past work experience or degrees may not be recognized in the host country. The migrant's only chance of earning money may be to work in an unskilled, poorly paid job. They are at risk for precarious employment, and may need to work overtime or in workplaces where their rights are not respected (236). A study conducted in the Montreal area suggests that immigrants may be particularly vulnerable to community unemployment, and that being unemployed is associated with adverse outcomes such as psychological distress, obesity and poor self-rated health status (255).

In Australia, it has been shown that migrant workers are at higher risk for work-related fatalities, especially in the first five years after immigration (256). In several countries, immigrants' access to health care may be reduced due to political, administrative and cultural reasons (257). It has been shown that immigrants may also have a lack of knowledge about the health-care system and may therefore overuse emergency room services (258). Furthermore, ethnic minorities are often underrepresented in research studies without identifiable justification (259).

In conclusion, immigrants often present fewer health problems than the host population when entering their new country of residence, due to a natural and political selection of fit and healthy individuals who are able to undertake the often long journey of migration. However, self-reported health can rapidly decline when these individuals have to adapt to local conditions, work in mainly manual occupations with a higher risk for occupational injuries or diseases, and face discrimination. Furthermore, access to health care and compensation might be more difficult for these individuals due to cultural or language barriers. In the host country, it seems that these individuals are at risk for developing asthma and that this risk is highest among those who migrate during early childhood.

1.2.4. Social exclusion and social support

Social exclusion can result from unemployment, discrimination, racism and stigmatization. At particular risk are subjects with a low income, those who are unemployed, belong to an ethnic minority, have just arrived in the country as an immigrant and are disabled or have left institutions such as psychiatric hospitals, prisons or children's homes. Social exclusion may preclude finding a decent job and housing and participation in social activities in the community (260). Being ill can also lead to social exclusion. Subjects with HIV or AIDS may be stigmatized or marginalized (261). The longer the social exclusion lasts, the more the subject is exposed to the deleterious factor of stress and the higher the risk of getting a stress-related illness, as discussed above. Illness, increased risk of addiction, divorce and separation may form a vicious cycle in subjects who are socially excluded.

There is good evidence that having social support has a positive effect on physical and mental health. Zunzunegui and co-workers have shown that individuals living in a Montreal neighbourhood and in the city of Moncton in the Province of New Brunswick who reported a high level of social integration and a strong network of friends also self-reported better health status (262). Social support has been defined by Cobb as "information leading the subject to believe that he is cared for and loved, is esteemed and valued and belongs to a social network of communication and mutual obligation" (263). Being engaged in a good marital relationship has been shown to be negatively

associated with depression in males and females (264). However, the opposite is also true: very close relationships such as an unhappy marriage may have a negative effect on mental health, as indicated by Coyne and Downey (265). The effect of marital status has been examined in studies of cardiovascular morbidity and mortality. Being married seems to be beneficial in terms of cardiovascular morbidity and mortality, mainly for males, whereas females seem to benefit more from support by friends or relatives (266). In the Whitehall study carried out in the UK, being married was associated with better mental health, especially in men, while in women mental health was best when support was provided by up to four close friends (266, 267). Singles seem to have better health outcomes when compared to those in low-quality marriages, as shown in hypertension research studies; therefore, being married per se is not universally beneficial and "… rather the satisfaction and support associated with such a relationship is important", as noted by Holt-Luntstad and co-workers (268). Further, it is important to consider that having poor health can be a barrier for individuals to maintaining or participating in social relationships, as seen with US veterans (269).

Social support can act on health via two types of mechanisms. Social support can have 1. direct effects on health; or 2. buffering effects on stressors that lead to ill health (266). An example of the direct effects of social support on health is if the subject is encouraged to change health-related behaviours, such as stopping smoking or eating healthier food. An example of the buffering effects on stressors would be if a woman discusses a potential

threat (for example a violent husband) with a supporter who counsels her on how to avoid situations and react if she is threatened (266).

Berkman and Syme conducted a survey in a population sample of adults in California and reported that males and females with fewer social ties had an increased relative risk for all-cause death during a nine-year follow-up period, even after controlling for several co-variables, including socio-economic status (270). Absence of social support has been shown to be associated with the onset and relapse of depression, as shown by Paykel (271). Kawachi and co-workers found a reduced incidence of stroke in subjects with strong social networks (272), whereas the effect on myocardial infarction was inconsistent (273, 274). It is important to mention that social networks mainly made up of family members rather than friends or civic engagement may actually increase individuals' stress and disease, as such support may lead to social isolation and role engulfing, as seen in South Asian women living in Canada (275). Furthermore, severe psychosocial problems caused by family relationships were shown to be important risk factors for the development of angina among men in Israel (276).

In civil servants living in the UK, emotional support by the closest person was associated with better mental health in men and women (277, 278). In the Netherlands, ten Have and co-workers reported that individuals who were already suffering from mental illness and had low self-perceived social support were two to three times more likely to use primary or mental

health care than those who had high self-perceived positive social support (279).

There is also good evidence to support the association between low social support and a poorer prognosis for cardiovascular and some other diseases. Social support can have a positive influence on the prognosis of disease by helping individuals to deal with stress caused by a disease. Social isolation increases the risk of death after myocardial infarction (280, 281). Social support may help people dealing with rheumatoid arthritis by limiting depressed moods or disability caused by the disease (282). In melanoma-cancer patients, social support by a structured psychiatric intervention, including group therapy, reduces psychological distress and significant immunological changes, leading to a lower recurrence and mortality rate (283-285). In a study investigating the effects of social relationships on the use of outpatient health services in adults in the US, Kouzis and Eaton reported that the combination of high distress measured with the General Health Questionnaire and low social support resulted in a fourfold increase of health-care utilization (286).

Social support also plays a role in the length of time individuals are away from work on medical leave. In British civil servants who participated in the Whitehall study, a high level of negative aspects in a close relationship with a person outside work was associated with increased rates of medical leaves for psychiatric diseases (287); in the same cohort, similar findings applied for sick leave for other conditions (288).

As mentioned above, migrants may have problems gaining access to the host country's health system and need to establish new social contacts. Migration to remote countries often destroys or disrupts established networks with social interactions and support, which has been shown to increase the risk of unfavourable stress and health behaviour such as smoking and prenatal care in women from Puerto Rico moving to the USA (289).

Importantly, the socio-economic position of the individual seems to be associated with self-perceived social support: Larger networks, more frequent contact with network members and better quality of support were all consistently associated with higher income and higher socio-economic status in several investigations (266, 290, 291).

In this chapter, I have presented the argument that good social support is in general beneficial for mental and overall health and is an important prognostic factor in how individuals can deal with disease. Poor support is associated with increased health-care use and absenteeism. However, we should remember that poor health per se can hinder individuals from maintaining social contacts and forming new contacts. Research shows that social support is in general worse in individuals with lower socio-economic status and income; this must therefore be considered an additional negative factor leading to worse health in these populations.

1.2.5. Single parenthood

In 2001, Statistics Canada estimated the number of families with a father and mother to be 7,249,010, with a median revenue of $61,200 CAD$, and the number of single-parent families to be 1,404,260 with a median revenue of $28,100 CAD$ (292). The National Council of Welfare in Canada estimated that 85% of these single-parent families were headed by the mother and that about 90% of these families were living in poverty (293). It has been shown that single low-income mothers experience less social support, more psychological distress and difficulties in caring for their infants, as reported by Armstrong and co-workers (294). Single mothers were shown to be more socially isolated, receive less emotional and parental support and have more unstable social networks compared to married mothers (295). Mothers of single-parent families with low incomes are less likely to believe in or seek help than those with higher incomes, as shown by Keller and McDade (296).

1.2.6. Social gradient and personal or family income

Poverty has a major impact on health and premature death. The risk for poverty may be even higher in ethnic minority groups, guest workers, disabled people, refugees and homeless people. Poverty means less access to health care, decent housing, education and safe transportation (260). For example, in Quebec, Pampalon and co-workers showed that premature death rates for different diseases differ when comparing subjects in the most materially deprived groups with subjects in the least materially deprived groups. Men in the most materially deprived group had a premature mortality rate for inferior respiratory tract infection that was 2.38 times higher than men in the least materially deprived group (297).

Another possibility is to compare life expectancy in different occupational groups. Saurel-Cubizolles and co-workers compared all-cause mortality rates in different occupational groups in France. After adjusting for age, the relative risk of all-cause mortality was higher in lower-status occupational groups compared with the reference group, which included wealthy professionals and managers. In this study, unskilled male manual workers had a relative risk of 2.5 compared to 1.0 for professionals and managers (298).

Having access to a car or occupying one's own home may be "surrogate markers" for socio-economic status. Subjects who live in social

housing or rented dwellings seem to have higher age-standardized rate ratios for premature death compared to subjects who own their home, as do subjects who do not have access to a car in their household compared to subjects with access to one or more cars (299). In the Almeda Country Study, residents of a federally designated poverty area were shown to have a higher age-, race- and sex-adjusted mortality rate over a follow-up period of nine years compared with residents of non-poverty areas (300).

1.2.7. Education and access to retraining schemes

Education is a very important parameter that can influence health and life expectancy. Having a good education helps subjects to get jobs with higher salaries and more job control. Subjects with a good educational background find jobs more easily after a period of unemployment. Education is also important because individuals can judge whether their behaviour is harmful for their health or not. Education is a major predictor of smoking status. The rate of smoking has been shown to decline with higher education, a correlation that seems to have increased in recent times (301). Adolescents with a lower socio-economic status have higher rates of marijuana use and alcohol risk behaviour than adolescents with a higher socio-economic status (302).

Education can also influence what subjects choose to eat. Malnutrition can contribute to obesity, cardiovascular disease, diabetes, cancer and dental caries. In general, a healthy diet that contains vegetables and fruits is more common among subjects with a higher education (303).

1.2.8. Workplace and job insecurity

Many factors encountered in the workplace may influence an individual's health. Men with a migratory background most often find jobs in sectors such as mining, construction or agriculture, where they are more prone to injuries and exposure to potentially toxic substances (236). Workers may be exposed to lead (e.g. lead smelting) that can cause hematologic abnormalities, neuropathy and nephropathy (304), or asbestos, with an increased risk of developing lung cancer or mesothelioma (305, 306). Further, there is a tendency for the labour market to be polarized according to workers' qualifications. There is a demand for workers with high levels of education and skills in new high-technology industries, whereas workers without advanced education and training may be hired in so-called "Mac-jobs" such as those in the service and sales industry (307).

Work may aggravate pre-existing disease. Psoriasis may worsen when the skin is irritated by mechanical, chemical or physical agents. Asthma may

be exacerbated when subjects are exposed to airway irritants such as dust, fumes or cold air (308). The workplace may offer easy access to potential dangers, as reflected by an increased risk in liver cirrhosis in innkeepers and bartenders (309), or suicide due to drug overdoses in medical personnel, such as pathologists (310). More recently, the social organization of work, management styles and social relationships in the workplace have been identified as predictors for health, sick leave and premature mortality (260). It has been shown that men and women with a low level of job control do have higher risks for coronary heart disease compared to those with a high level of job control (311).

Having a secure job can increase the subject's health, well-being and job satisfaction. In a large population study in Denmark consisting of subjects aged 20-64 years, those who were unemployed had a significantly increased death rate after adjusting for occupation, housing category, geographical region and marital status. Specific relative death rates were elevated for all causes, but especially for accidents and suicide (312). The increased mortality rate was interpreted by the authors as being the result of a selection of unhealthy workers who lost their jobs and increased susceptibility associated with the psychosocial stress of unemployment (312).

Subjects who are unemployed or insecurely employed are at increased risk for physical disease and premature death (307). Many studies show that individuals' psychological health can be impaired, leading to a less integrated and active life, and that this effect takes place regardless of pre-existing

mental illness (313). Support in the workplace by colleagues and supervisors has been shown to be associated with less frequent short-duration medical leaves in general, and this applies even in individuals with high levels of negative aspects in close relationships away from the workplace (266, 287). However, psychological distress can go down again when the individual is re-employed (307, 314). Increased levels of psychological distress or mental illness increase the risk of job loss and impair the person's chances of subsequent re-employment (315-317).

The development of psychiatric disease is frequently associated with recent job loss. Studies suggest that the decline in psychological well-being is greatest in the first 12 months after leaving the workplace and plateaus afterwards, suggesting that intervention programs designed to address the development of psychiatric disease need to be implemented early for those who become unemployed (307, 318-320).

Work *per se* has a beneficial effect on health, and the loss of work must be considered a highly stressful life event. Being unemployed creates heightened vulnerability to other stressful life events (307, 321).The beneficial effects of regular work have been summarized by Bartley and co-workers (307), as reported in Table 7.

Structure of the day
Self-esteem
Respect of others
Stimulates physical and mental activity
Allows use of personal skills
Decision latitude
Interpersonal contact
Social status

Table 7: The beneficial effects of regular work

Prolonged job loss is associated with a loss in income if no compensation is received, which leads to significant financial strain for individuals and their families. Individuals may run up debts to cover expenses and care for their family. Meltzer and co-workers have shown that poor job security and being in debt were independently associated with depression even after controlling for age and sex (322). Jackson and Warr also found a strong association in working-class men between household income and scores indicating more distress on a common assessment of mental well-being, the general health questionnaire (GHQ) (323). In several studies, financial hardship was found to be an important intermediary between unemployment and psychiatric illness or self-reported health status (324, 325). Furthermore, longer unemployment increases the risk of getting divorced and losing the home (326-328). In Australia, women who were currently unemployed described themselves more often as being isolated than women engaged in household duties or those who were currently employed (329). There is evidence that employment status in workers with

long-term medical leave differs according to socio-economic position: the employment rate of groups of managers and professionals was about 75%, while it was less than 50% in groups of semi- or unskilled workers (330).

The feeling of job insecurity can cause health status to decline: Ferrie and co-workers investigated civil servants in a state department that was sold to the private sector. Subjects who reported feeling that their jobs were insecure or had lost their jobs had increased minor psychiatric morbidity and more health-care visits to their general practitioner than securely employed subjects (331). But this does not only apply to the affected workers, as demonstrated by Beale and Nethercott, who studied health-care use in families of workers who lost their jobs when a factory was closed. Health-care resource use had already risen before the factory closing, when management announced that production might have to stop, but increased significantly in the four years after production stopped and the factory was shut down (332).

Several studies have indicated that being dissatisfied with the current workplace has a negative effect on mental health (333, 334).It has been shown that workers who were forced to agree to work in lower-status jobs had scores similar to unemployed individuals in the general health questionnaire (GHQ) designed to assess psychological well-being (307). Even an unintended job interruption despite continuing to receive full salary can lead to increased psychological distress, as shown in Italian workers (330, 335).

As outlined in this chapter, some professional activities can be harmful to an individual's health if they are associated with risky exposures, especially

if individuals are more susceptible due to pre-existing disease. Regular work has several beneficial effects, while unemployment may lead to financial hardship and loss of socio-economic position, putting people at risk for physical or mental illness.

1.2.9. Labour union affiliation

A labour union is an organization of workers who band together to achieve common goals such as better working conditions, wages and benefits. In the United States, the Economic Policy Institute has estimated that union membership raises wages by about 20% (336). Unionized workers have been shown to receive better health-care coverage and pensions than their non-unionized co-workers. In Canada, it has been shown that 70% of unionized workers, but only 40% of non-unionized workers, have health-care coverage (337). Coverage is even lower for workers in small companies with fewer than 20 employees, and for those working part-time or with temporary jobs (337). Labour unions try to improve health and safety protection in the workplace (338). Some unions even ensure the rights of their most senior members to make sure that they remain employed once they get older and could be replaced by a younger worker with a lower salary (339). They defend their members against unjust firing, offering better job security. When

employers decide to cut wages, unions require them to partake in collective bargaining with the labour force. In collective bargaining, the union will represent the workers for the negotiations. Collective bargaining can also be used to advocate for changes in the workers' favour (339).

Grievances are concerns, problems or complaints that workers raise with their employer. Labour unions can present a formal means to communicate with the employer and institute the grievance process. If a worker is punished for the complaint, the union will protect the worker and punishment can be handled through the union (339).

1.2.10. Stress

According to Hans Selye (340), stress is a physiological response of the human body to the challenges of everyday life (which may be called "stressors")(340). It involves the neuroendocrine pathways, which can be divided into two systems. The body immediately acts over the sympathetic branch of the autonomic nervous system by releasing noradrenaline and adrenaline, whereas action via the hypothalamic-pituitary-adrenal axis usually takes minutes to hours and releases cortisol and other steroid hormones (195). The action of the neuroendocrine pathways will trigger the "fight or flight" response by causing the heart rate to rise, mobilizing stored energy,

diverting blood to muscles and increasing alertness (260). Living in social hardship with financial strain, less social support and having a high-intensity job with low job control can produce constant psychosocial stress. As shown by Bosma et al., workers in government offices with low control over their work environment are at increased risk of future coronary heart disease (341).

1.2.11. Substance abuse and addiction

Substance abuse is common among subjects with low socio-economic status (342). Consuming substances may be seen as a way to escape hardship and stress, particularly among men. This behaviour can lead to deprivation when an individual's daily routine is controlled by the desire to consume and procure the substance. Healthy habits as well as social contacts are neglected. Consumption of the substance may have a direct impact on the individual's health. Alcohol abuse may put the individual at risk of injuries and may cause diseases such as liver cirrhosis, while intravenous administration of substances increases the risk of acquiring hepatitis or human immunodeficiency viruses. Smoking cigarettes is known to be a major cause of lung cancer and COPD (343). Adolescent and adult smokers have been shown to be at increased risk for the development of asthma (344, 345). Asthmatics who smoke are more likely to have poorer asthma control

compared with non-smokers, and smoking cigarettes decreases the effectiveness of steroid therapy (346). There is a known gradient in the prevalence of cigarette smoking by occupational class, with higher rates of smoking among single parents, the unemployed and mentally ill individuals, as reflected in higher death rates among these smoking populations (347). Poor people have been shown to have higher nicotine dependency, to be more likely to have a partner who smokes, and to have less money to spend for nicotine replacement medication (347).

1.3. Asthma in the workplace and its association with socio-economic factors

1.3.1. The socio-economic and psychological consequences of having asthma while in the workforce

Asthma is an extremely common condition among working-age adults. The median prevalence of asthma in the working population 20-44 years of age in 22 countries in Europe has been estimated to be 4.5% (348), and about 5.2% in the 1994 US National Health Interview Survey (NHIS) (349). More or less severe exacerbations can reduce the worker's productivity and lead to more days off work due to sick leave and finally, work loss. Further, asthma is influenced by various environmental stimuli that may be present in the workplace, leading to a deterioration of asthma control.

Several studies have investigated the impact of asthma on work. In the US, Collins reported that among individuals with asthma included in the NHIS census, 21% reported some limitation of routine activities in their daily life, and 22% had at least one hospitalization for asthma per year (350). The rates were significantly higher when compared to individuals with hypertension (11% reporting activity limitation and 8% hospitalization) (350). In the census, work limitation was reported by 7.1% of asthmatics between 18-44 years of

age and ranked among the most common medical conditions associated with working-age disability (349, 350).

Sibbald and co-workers reported that young adults working in the UK with a current or past history of asthma do have a higher risk of unemployment and tend to have more job changes and less recent full-time employment than subjects without a history of asthma (351). In a study by Blanc et al. of 550 study subjects with a history of labour force participation, about 17% reported asthma-attributed work disability, and the prevalence of complete work cessation was 7% (352). Yelin and co-workers showed that in a follow-up study over almost five years, only 66% of asthmatics were continuously employed. Interestingly, the strongest predictors for continuity of employment over the follow-up period were demographic and employment characteristics, not asthma severity (353).

In New Zealand, almost half of the asthmatic participants in a study by McClellan and co-workers indicated that asthma had affected their working activities. About 14% of the asthmatics indicated that the disease was a reason for employer discrimination, job dismissal and lack of career advancement; 77% of asthmatics had not informed their employers of their asthma, which further emphasizes the stigmatizing nature of the disease (354).

In Spain, patients with asthma seen in an outpatient clinic reported a mean of over 22 lost work days in the previous six months due to asthma, while in Singapore, about 62% reported work or school absences of at least

one day, with 21% reporting absences longer than one week due to asthma (355, 356).

While absenteeism represents days/hours missed from work attributable to the illness, presenteeism refers to illness/condition-related reductions in productivity while the person is at work. It has been shown that workers with asthma can see a major decline in self-rated work-effectiveness (354, 357, 358) as well as limitations in quality of life and work ability (359).

Several asthma-triggering or aggravating factors present in a military environment can impair work performance in individuals with asthma. In the Israeli armed forces, it was shown that soldiers with new-onset asthma were more often transferred to a new job when they had more severe asthma than soldiers with mild asthma (360).

A change of job duties, a reduction in salary or a change in job or employment status attributed to asthma can be seen as surrogate markers of work disability. Using these criteria, Blanc and co-workers reported that 36% of outpatients with asthma had had a work disability due to asthma in the previous five years (361).

The impact of asthma on absenteeism is reflected in indirect disease costs, which have important implications for the economy (362). In Canada, Krahn and co-workers estimated the costs for asthma out- and inpatient care in the year 1990 at between $504 and $648 million CAD$. Their assumption for indirect costs ranged from $76 to $98 million CAD$ for lost work outside and inside the home, and $21 million CAD$ for workers' compensation and

disability insurance payments (363). In the US, Birnbaum and co-workers estimated the costs of asthma for a major employer. In employees who claimed for illness, total costs for claimants with asthma were approximately 3 times higher than for disability claimants for conditions other than asthma (364). In the claimants with asthma, wage-replacement costs for lost work days were almost as high as costs for medical care (364).

Work factors

Many factors in the working environment affect asthma in a complex manner, as reported by Blanc and co-workers (349) and shown in Figure 8.

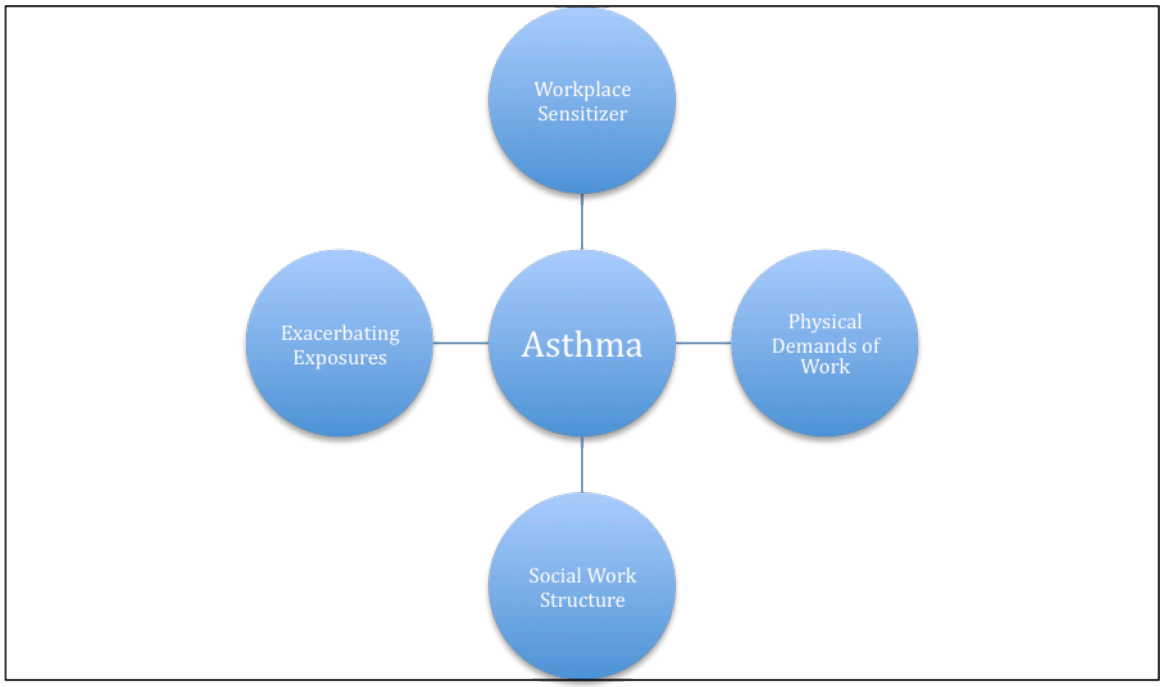

Figure 8: The working environment can interact with asthma in a complex manner

Workplace sensitizers such as LMW or HMW agents that may be present in an individual's workplace can lead to sensitization. Eventually, the workers develop symptoms and overt OA. However, besides substances that are known to cause OA, asthma-exacerbating factors such as exposure to frequent temperature changes, exposure to vapours, gases, dust and fumes may be present in the workplace and lead to a deterioration in asthma control. Asthma exacerbations may occur, for example, in a shopkeeper with asthma who needs to enter a refrigerated warehouse many times each day, where he may be performing work tasks with high physical demands. High physical job demands may exceed the respiratory capacity of an asthmatic subject. For

example, firefighters face high physical demands, especially when working with respiratory protection provided by a self-contained breathing apparatus (126).

The social characteristics of workplace personnel may affect an individual's ability to maintain employment by controlling the pace and schedule of work activities (365). Karasek and co-workers showed in a sample of the Swedish male working population that hectic and psychologically demanding jobs were associated with coronary heart disease symptoms and death. Low decision-making latitude, low intellectual discretion and a low personal schedule of freedom at work were also associated with coronary heart disease symptoms or mortality (366).

In patients with various chronic diseases, those who had greater autonomy and flexibility in the workplace were much less likely to stop working than those who had less control over their working schedule (349). Lack of flexibility may lead to work disability, for example when a worker who is having a more "symptomatic" day is not allowed to see a physician for medical care or to avoid certain exacerbating exposures in the workplace. There is evidence that lower socio-economic status and educational level are associated with less job autonomy and flexibility and workplaces at higher risk for sensitization to occupational agents (349).

As mentioned above, the individual's impairment in work capacity is unique to each job environment. An individual with asthma may be unable to work as a wild land firefighter with high physical work demands and airway

irritant exposure, but may work as an operator in a call centre, where he or she can work in a sitting position without exposure to irritants and be able to adapt the work schedule to suit his or her current state of health. Therefore, work disability in asthma must be considered multifactorial, as suggested by Blanc and co-workers (349) and shown in Figure 9:

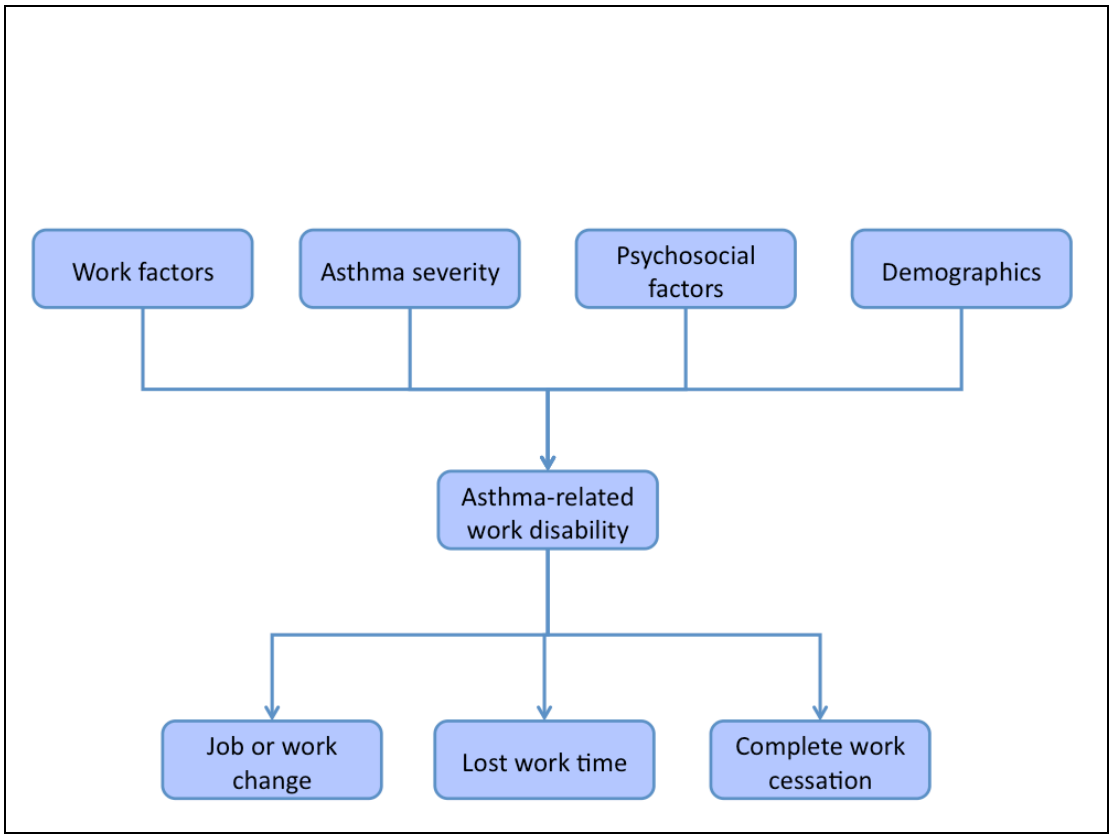

Figure 9: Predictive model of work disability among adults with asthma

This theoretical model was tested by the authors in a sample of adult asthma patients in the US. Among individuals with any history of labour force participation, work factors such as exposure to chemicals or dust, temperature changes and physical demands were all associated with partial

or complete work disability. In this sample, the strength of association between severity of asthma (incorporating symptoms, hospitalization and medication use) or general health status measured with the general quality of life SF-36 questionnaire was roughly the same (352). In Sweden, Balder and co-workers investigated asthmatics with new-onset asthma in the Göteborg area. In multivariate analysis, having respiratory symptoms in the workplace was significantly associated with asthma-related work disability, while having a physically demanding occupation and having exposure to respiratory irritants at work showed a borderline association when the model was controlled for asthma severity, bronchial hyperresponsiveness to methacholine and atopy (357). In the validation study of the Perceived Control of Asthma Questionnaire (PCAQ), asthma control status was associated with asthma severity, health-care use and work disability (367).

Psychological Impact

There is a link between asthma and psychiatric disorders: Anxiety disorders (e.g. panic disorder, generalized anxiety disorder and social phobia) have been shown to affect 16% to 52% of asthmatics, and mood disorders (e.g. depression) have been shown to affect 14-41% of asthmatics (368, 369). By comparison, the one-year prevalence rate for depression in the French-

speaking population of Quebec has been estimated at 4.6%, and for anxiety disorders, 3.9% (370).

There is increasing evidence on how emotional factors and psychological distress affect airway function in healthy and asthmatic adults. Several studies by Ritz and co-workers indicate that respiratory resistance measured with forced oscillation technique rises in asthmatic and non-asthmatic individuals during laboratory sessions when shown films that are known to induce various emotions (anxiety, anger, depression, happiness, elation, contentment and neutrality) (371-373), whereas the increased resistance mainly affects the expiratory portion of the breathing cycle, suggesting that the upper airways contribute to this response (374). These reactions seem to be stronger in asthmatics in response to specific stimuli with medical slides depicting injuries, mutilation and corpses compared to non-asthmatics (375). In asthmatics investigated over three weeks with self-assessments of spirometry and mood, an association between negative and, to a lesser extent, positive mood states with FEV1 values was reported (372). There is, however, a study in which active psychological laboratory tasks produced a decrease in airway impedance in asthmatic and non-asthmatic participants, while passive response to watching films depicting accidents and thoracic surgery procedures did not change respiratory impedance (376).

Further data are accumulating to indicate that mood states and psychological distress can influence the allergic reaction of the human body to an allergen challenge. Liu and co-workers investigated college students

with mild asthma during a low-stress phase and during a stress phase during final school examination week. The students' anxiety and depression scores were significantly increased during the stress phase compared to the low-stress phase. Interestingly, an allergen challenge during the stress phase led to significantly increased sputum eosinophils and eosinophil-derived neurotoxin levels reflecting increased allergic airway inflammation when these markers were obtained after a challenge during the low-stress phase (377). In another study investigating asthmatic individuals with bronchial challenge tests, Rosenkranz and co-workers performed functional magnetic resonance imaging of the anterior cingulated cortex and insula to determine the effect of asthma-relevant emotion, compared with neutral stimuli presented during measurement of activity in that brain region. Further, they measured several inflammation markers in the blood of participants. In multivariate analysis, they reported that activation of these brain regions due to emotional stimuli accounted for ≥40% of variance in the peripheral inflammation markers, suggesting a neural basis for emotion-induced modulation of airway disease in asthma (378).

Lavoie and co-workers investigated 504 outpatients with asthma seen in a consecutive manner in a tertiary-care asthma clinic with a brief structured psychiatric interview using the Primary Care Evaluation of Mental Disorders Questionnaire (Prime-MD). The authors found that 31% met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for one or more psychiatric disorders. In the same sample, 20% met criteria for a current

mood disorder and 23% met criteria for a current anxiety disorder (379). In the ECRHS, Janson and co-workers investigated a sampling of subjects between the ages of 22 and 44 using the Hospital Anxiety and Depression Scale questionnaire (HADS) (380). They found a significant correlation between anxiety and depression on the one hand and reports of asthma-related symptoms, such as attacks of breathlessness after activity and waking with attacks of breathlessness, on the other hand. However, there was no evidence that patients with diagnosed bronchial asthma had more anxiety and depression than those who did not have asthma (380). In Dutch patients, the length of hospitalization was significantly correlated with anxiety symptoms, as reported by Kaptein (381). Subjects with asthma and comorbid anxiety showed marked differences in their asthma self-management knowledge and their actual behaviour compared to asthmatics without anxiety, particularly in terms of potentially life-saving actions such as medication use and seeking help (e.g. calling an ambulance) (382). In the same study, asthmatics identified as having a psychiatric disorder were more likely to have poorly controlled asthma and higher drop-out rates from asthma management programs (382). Goldney and co-workers investigated a representative sample of the South Australian population in respect to doctor-diagnosed asthma and assessed depression using the Primary Care Evaluation of Mental Disorders Questionnaire (PRIME-MD) self-report questionnaire. In this sample, major depressive disorders were associated with worse nocturnal and waking asthma symptoms, as well as worse asthma-related quality of life

(383). Lavoie and co-workers evaluated the prevalence of psychiatric disorders in 406 adult asthma patients seen in an asthma outpatient clinic using the PRIME-MD brief structured psychiatric interview and found evidence of an association between psychiatric disorders and higher asthma morbidity, such as worse asthma control and quality of life (384). High job-specific stress is common and associated with worse health outcomes in patients with several chronic illnesses: job stress is positively associated with cardiovascular risk factors (385-387) and non-fatal myocardial infarction (388). Subjects with chronic illnesses (e.g. musculoskeletal diseases, cancer) but who had greater autonomy and flexibility in the workplace were much less likely to stop working (365, 389-391).

1.3.2. Socio-economic consequences of work-related asthma

The workplace can trigger or induce asthma. Therefore, individuals' asthma must be considered work-related if asthma control or symptoms are influenced by the workplace. In work-exacerbated asthma, workplace exposure leads to a worsening of pre-existing or coincident asthma. If asthma is caused by a specific agent encountered only or mainly in the workplace, it is called OA.

In order to prevent further deterioration of OA, it is essential to remove the person from exposure to the offending agent. Individuals with OA have worse outcomes, such as increased respiratory symptoms, airway obstruction and non-specific AHR, when they remain in their workplace by comparison with workers who leave exposed workplaces (122). Lemière and co-workers have shown that health-care use such as seeing a physician, visiting the emergency room and being hospitalized for asthma were more frequent compared to individuals without work-related symptoms (392). However, this finding contradicts the results of an earlier study by Liss and coworkers in Ontario, in which workers with OA were shown to have a lower rate of hospitalizations for asthma than those with asthma not related to the workplace (393).

Workers with OA are more likely to change their workplace compared with workers who have asthma that is not worsened at work (394). Unfortunately, many studies in various countries have shown a relatively high proportion of workers with OA who were not working and who had significant loss of income at the time of evaluation (Table 9), as reviewed in a book chapter by Vandenplas and D'Alpaos on the social consequences of WRA (395).

Country	Number of subjects	Duration of follow-up (years)	Rate of unemployment (%)	Loss of income (% of workers)
UK (396)	112	Median 1.4	35%	Exposed: 44% Unexposed: 74%
British Columbia/Canada (180)	128	Mean: 4.8	41%	
Quebec/Canada (397)	134	Range: 2-5	25%	
UK (398)	87	5	39%	55%
France (399)	209	Mean: 3.1	34%	46%
USA (400)	55	Mean: 2.6	69%	
UK (401)	770	Range 1.5-5.5	37%	
Belgium (160)	86	Median 3.3	38%	62%
Norway (402)	496	Range 2-6	49%	51%
Finland (403)	213	Mean: 10	14%	

Table 8: Impact of OA on major socio-economic outcomes

Workers who avoid exposure to the offending agent suffer from more pronounced loss of income compared to those who remain exposed. In the UK, Gannon reported that 74% of workers who had changed their jobs reported reduced income as opposed to 44% of those who kept their jobs (396). In France, Ameille and co-workers reported that 84% of workers who left their employers saw a loss of income compared to 19% of those who remained exposed (399). In Belgium, 20% of workers who continued to work suffered a loss in income, compared to 32% of workers who experienced a reduced exposure and 78% of workers who were not exposed any more, as reported by Larbanois and co-workers (160). This may be one reason why workers choose to continue working without seeking medical advice or

choose to remain exposed if a diagnosis has been assigned. Moscato and co-workers prospectively studied the clinical and socio-economic outcomes of workers with a diagnosis of immunological OA. After one year, the patients with more severe asthma had stopped their exposure, probably because their asthma was too severe to continue with the exposure. In all the subjects who stopped exposure, the severity of asthma declined, as did their monthly expenses for asthma medication. Nevertheless, 69% of those who had stopped their exposure, compared to 17% of those who remained exposed, reported a deterioration in their financial condition. Those who had to stop working had a mean decline in annual income of 27% (range 12-50 %) (178). Vandenplas and co-workers have shown that complete cessation of exposure as well as reduction of exposure to latex can lead to a similar improvement in lung function and bronchial hyperresponsiveness, but with fewer socio-economic consequences such as work disruption due to OA and loss of income in those with reduced exposure (183).

Studies of workers in the UK, Belgium and Quebec/Canada indicate that workers with a work exacerbation of asthma had similar adverse socio-economic outcomes to individuals with OA (160, 164, 398).

As discussed above, gender may be a risk factor for OA and there is evidence that women – due to less job security and lower salaries – may remain exposed for a longer time even when they are having respiratory symptoms and may have more difficulty qualifying for compensation, since they are hired in temporary or part-time contracts or work in jobs without

workers' compensation coverage. In the UK, where a surveillance scheme for OA is in place (Surveillance of Work-related and Occupational Respiratory Disease (SWORD)), reported medico-legal cases are more common in men than in women (401). Dimich-Ward and co-workers have shown that the perception of respiratory symptoms is different in men and women in various occupations, such as hospitality workers, radiographers and respiratory therapists, and that women are more likely to report shortness of breath while men report more phlegm (404).

In Quebec, when the Workers' Compensation Board accepts claims for OA, individuals with asthma can receive compensation not only for medical expenses but also for loss of income. If a worker who had to leave the workplace because of asthma now earns less than he or she was earning in the workplace at the time the diagnosis was made, the worker can claim for a compensation payment to boost that income back to what he or she was earning at the time of diagnosis. The Quebec Workers' Compensation System provides at the current time income replacement for up to 90% of net salary for insurable earnings of up to CAD$ 60,500/year.

Nevertheless, the proportion of individuals who receive some kind of compensation for OA varies significantly in studies conducted in Europe and Canada (395). The reported median loss of salary compared to the income the individual earned in the causing workplace was 22% and 41% in workers in Belgium and France respectively (160, 399).

It has been estimated that about one-third of workers in studies conducted in the United Kingdom, British Columbia/Canada, France and Belgium remain exposed at the workplace after a diagnosis of OA (177). Studies show that the loss of income is more pronounced when an individual has to leave the workplace even when she/he is hired by another employer (399). Many studies, however, indicate that relocation to a workplace without exposure can be achieved in fewer than 20% of workers with OA (395). It is more difficult to relocate a worker in a small-sized company where job opportunities are limited and where the workers are confined to small premises, increasing the risk of job change or unemployment (399).

Effective retraining and re-integration programs, as offered in Quebec/Canada and Finland, are considered an important tool for bringing down rates of unemployment in individuals with OA (395).

For health-care workers in Belgium, harm reduction by providing personal respiratory equipment or reducing exposure – as discussed above - has been shown to have a similar short-term impact on health outcomes with less adverse socio-economic impact (183). However, this management approach is not considered standard care for patients with OA (3, 172).

Individuals with OA hired in unskilled jobs or with lower levels of education have been shown to be at higher risk of becoming unemployed after the diagnosis (160, 396, 399). It seems likely that subjects with lower education levels are more limited in their job selection, and it is therefore more difficult for them to find a new job without the risk of exposure to the

offending agent or to irritating substances. In workers who process Western red cedar, Marabini et al. reported that workers with a higher number of dependent family members were less likely to be unemployed compared to those with smaller families and fewer dependent individuals in the household (180).

In order to avoid financial hardship, workers with OA who have to take care of family members without income are forced to continue to work and to be exposed. Younger age has been associated with unemployment in France; this is suggested to be the result of poor and limited possibilities for re-training in individuals under 40 years of age (399). However, in Belgium and British Columbia/Canada, the findings were contrary, with unemployment associated with older age (160, 180). While Piirilä and co-workers reported an association between asthma severity and employment status, suggesting that those with night-time asthma symptoms and increased peak-flow variability were more likely to be unemployed (403), most other studies have not shown such strong and significant associations (160, 178, 180, 396-399, 405).

In a cross-sectional study carried out by Caldeira and co-workers in 1,922 subjects who were randomly selected from a birth cohort in1978/79 in Brazil, individuals 23 to 25 years of age had a prevalence of work- related asthma of 4.2%. Work-related asthma was associated with low education level after adjusting for gender, smoking, atopy and rhinitis. The adjusted OR for work-related asthma in the entire population was 6.82 (95% CI 2.99 to 15.57) for those individuals with one to eight years of education compared to

those with more than 12 years. When analyzing the data only in those with hyperresponsiveness to methacholine, the OR was 2.99 (95% CI 1.32 to 6.76) (406). It is likely that individuals with lower education levels are more limited in choosing a profession and therefore are diverted towards lower-paid manual working professions with more risk of exposure to asthma-causing substances. Their lack of education may have prevented participants from being aware of the danger to their health and how to effectively limit exposure, for example by using respiratory protection. However, the duration of exposure to asthma-causing substances may differ as well. The authors did not provide data on exposure duration, and it is likely that individuals with one to eight years of education had started to work earlier than individuals with more than 12 years of education, who had probably just finished their university studies. It is also possible that exposure may be limited during job training as respiratory protection is applied or individuals spend more time in the classroom than in their workplace.

1.3.3. Quality of life, psychological distress and psychiatric disease in individuals with work-related asthma

1.3.3.1. Impact on quality of life

Once OA is confirmed, subjects should perhaps avoid contact with the causing allergen and stop working at their workplace. However, up to 70% of subjects with OA experience persistent respiratory symptoms and non-specific AHR when evaluated years after cessation of exposure (154). This directly influences patients' quality of life, as shown by Malo and co-workers in subjects with OA who had been off exposure for more than two years (407). In this study, subjects were investigated by using a disease-specific QOL questionnaire originally developed by Juniper and co-workers (408). The authors found that subjects had significantly reduced quality of life in the four domains of activity limitations, asthma symptoms, management of environmental triggers and emotional distress (407). Interestingly, quality of life of subjects with OA was even more affected than in the control population of subjects with asthma not related to the workplace, matched for disease severity. Al-Otiaibi evaluated a small group of health-care workers with different types of natural rubber latex allergies at a mean interval of 24.4 months (SD ±11.1 months) post-diagnosis and found only marginally impaired disease-specific quality of life, despite the fact that some of the subjects had

not changed their workplace. However, most of the subjects avoided wearing latex gloves and their co-workers mainly used non-powdered latex gloves (409).

Satisfaction with life and perception of asthma symptoms are related to employment status and asthma control, as shown by Piirila and co-workers: Those who indicate more impairment in quality of life are more likely to be unemployed and have greater PEF variability and a greater need for medication to control asthma (403). In a retrospective study, Vandenplas and co-workers compared asthma-specific quality of life impairment in health-care workers who completely avoided exposure to latex with those who reported reduced ongoing exposure. Individuals who reported having reduced ongoing exposure tended to have more impairment in QOL than those who were no longer exposed to latex, although the difference was not statistically significant (183). Henneberger and co-workers have shown that individuals with WEA report more impairment of quality of life, measured with the Marks' asthma quality of life questionnaire, than control subjects whose asthma is unrelated to the workplace (166). It has recently been reported that quality of life impairment was in the same range for workers with OA and WEA who had left their workplace and were evaluated approximately three years after diagnosis (164).

1.3.3.2. Psychological distress and Psychiatric disease in individuals with work-related asthma

Psychological distress may persist after withdrawal from the workplace, as demonstrated by Yacoub and co-workers, who evaluated subjects with OA two years after the diagnosis. They found a prevalence of 35% for anxiety disorders and 22.5% for dysthymia (410). Interestingly, that is higher than the rate of 25% for anxiety disorders and 4% for dysthymia found in subjects with confirmed non-OA, as shown by Lavoie and co-workers for asthma outpatients (384). The difference can be explained in part by the fact that Lavoie and co-workers used a standardized psychiatric interview to assess psychiatric disorders, while in the study by Yacoub and co-workers, a self-report questionnaire was used, which may overestimate the true rate of psychiatric illness (410).

There is an important knowledge gap regarding the prevalence of psychological distress and psychiatric disease in the population of patients with OA. Currently, the prevalence of these conditions is unknown at the time individuals develop asthma-like symptoms in the workplace and at the time a diagnosis of OA is made (167).

1.3.4. Possible interactions between socio-economic factors and objective measures of asthma

Questionnaires

One of the main obstacles in patient–health care worker communication is linguistic differences, especially when the patient's native language is not the language spoken in the health care system at which he/she is consulting (411, 412). Therefore, whenever possible, health care providers should try to use questionnaires that are translated and validated in the patient's native language (413).

Individuals with illiteracy have never learned or cannot read and write in their native language, whereas those with functional illiteracy have reading and writing skills that are inadequate to cope with the demands of everyday life. The Expert Panel on Health Literacy of the Canadian Public Health Association (414) defined health literacy as the ability to access, understand, evaluate, and communicate information in such as way so as to promote, maintain, and improve health in a variety of settings during the course of life.

Various questionnaires have been developed to measure health literacy and numeracy (415). Although health illiteracy is more prevalent among minority groups, such as the poor, ethnic minorities, immigrants, elderly, and those with limited education, it is a common problem even in

industrialized countries (416). In a study of working age Canadians, approximately 55% of the participants had low health literacy by scoring below the threshold of skills needed to manage one's health without compensatory help (414). Importantly, health illiteracy often coincides with asthma in poor urban communities and certain minority groups (415, 416). Furthermore, a study conducted in the US showed that physicians commonly overestimate literacy levels of patients; this apparently occurs more often with minority patients, particularly, African Americans (417).

Low health literacy and low numeric skills have been shown to be associated with adverse asthma-related quality of life. Apter et al. examined individuals with asthma using the Asthma Numeracy Questionnaire and Mini-Asthma Quality of Life Questionnaire. They found that low numeracy was associated with decreased levels of asthma-specific quality of life (418). Mancuso and Rincon studied adults with asthma who were seen in primary care practices in New York City. They reported that low health literacy was associated with less satisfaction with asthma status, worse results from asthma care, and a lower likelihood of participating in asthma management programs, even after adjustments were made in a multivariate model for asthma and demographic characteristics (419). In their longitudinal follow-up study, low health literacy was associated with worse asthma-related quality of life, although associations became statistically insignificant after adjustments were made to their model (420).

The Australian Health Omnibus Survey investigated individuals ≥15 years of age, and found that those who had inadequate health literacy more often reported nighttime awakenings, hospitalizations, and days lost from usual daily activities than those with better health literacy (421).

One method to overcome health illiteracy might be to offer short, easy to administer questionnaires that use pictures rather than words. Ghiassi et al. translated a questionnaire to measure daytime sleepiness, the Epworth Sleepiness Scale, into a pictorial version for use with those with normal or diminished literacy skills. They showed that this new questionnaire provided similar results but was rated as more easy to fill than the traditional questionnaire (422).

Lung function assessments

To perform lung function measurements, an individual must perform respiratory maneuvers according to the instructions given by a lung function technician. It might be difficult to follow these instructions if they are given in a foreign language. To have reliable spirometry results, acceptability and reproducibility criteria formulated by the American Thoracic Society must be fulfilled (111). Individual spirograms are considered acceptable if they are free from artifacts, such as cough or glottis closure during the first second of

exhalation, early termination, variable effort, leakage, or obstructed mouthpieces. The spirograms must show a good test start and have a satisfactory exhalation time. Regarding criteria for reproducibility, the two highest FVC and FEV1 values should have measured values within 200 ml of each other.

Lung volumes are gender dependent. Adult males have greater lung volumes than females (423). Lung function increases with body size and declines at both the high and low extremes of weight (423). Race has also been shown to be an important determinant of lung volume (423). Normal lung development is characterized by an increase in lung function (expressed as FEV1) during childhood and adolescence until peak lung function is reached by 18–20 years of age. Subsequently, lung function plateaus before it begins to decline due to normal aging (424). Several factors can influence the growth and plateau phases or lead to an accelerated decline in lung function Figure 10.

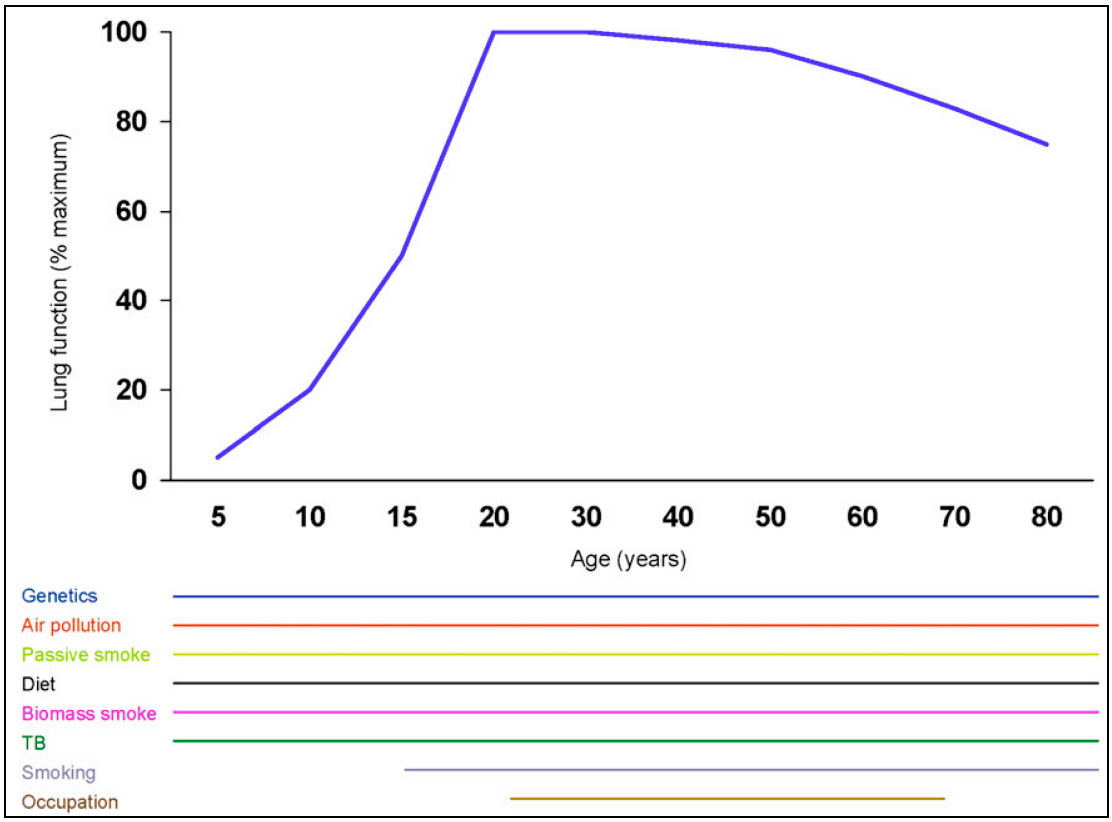

Figure 10: Theoretical model of how exposures affect lung function throughout the life

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Therefore, lung function at any one point in time not only reflects the health of the individual at that time but also is a result of insults and injuries and how the body dealt with exposures in the past.

Social and environmental factors may influence the development of peak lung function and influence its rate of decline. There is evidence that children with lower socio-economic status attain lower peak levels of pulmonary function in early adulthood, and they experience earlier, faster declines compared to children with higher socio-economic status (425).

Socio-economic factors such as education level and poverty have been shown to explain only a small proportion of the racial differences in lung function as suggested by an analysis of data from the Third National Health and Nutrition Examination Survey (426). In this same cohort, Van Sickle et al. showed that completing high school was associated with improved FEV1 in men and women and that there was a significant interaction based on racial differences in the effects of completing high school on FEV1 (427).

Peak Flow measures

The availability of portable, inexpensive devices allows physicians to monitor and record PEF when at and away from work. There are physiological diurnal variations in PEF values for most healthy individuals and these rhythms are exaggerated in those with asthma. The lowest PEF values are usually recorded around the time of waking. Then, there is an improvement for 6–8 h, followed by a subsequent decline until going to sleep, with a further decline overnight (428). This relationship can be substantially altered by shift work. The effects of an intermediate reaction can dampen the increase in peak flow rather than causing any decline, and thus renders PEF recordings less sensitive for diagnosis of asthma (428).

Workers should record their PEF at least four times daily and the minimum period of recording should be at least 2 weeks both at and away from work to be able to draw any conclusions (428). It is very important to instruct the worker on when and how PEF measurements need to be performed. This is best demonstrated by personal instructions from a health care worker with experience in PEF measurements. Huggins et al. noted that after sending written instruction by post, only 56% of patients investigated in a specialized occupational lung clinic returned their PEF diary compared to 85% of those who were personally instructed (429).

However, there are some limitations to this method of investigation. Records from less compliant workers are more difficult to interpret and sensitivity and specificity decline with less frequent readings (430). In a study of 12 workers who were investigated for OA with an electronic PEF meter, Gannon et al. showed that peak flow readings taken when unsupervised were lower and that a learning curve was needed for PEF values to increase in the first few days of a recording period (428, 431). Additional evidence suggests that electronic PEF meters should be used instead of mechanical PEF meters and written diaries. Quirce et al. studied individuals who used electronic PEF meters and asked the study participants to record their measured PEF values in a diary. They found that only 55% of the PEF records were completely accurate in terms of the recorded values and the timing of measurements. About 23% of the results were inaccurate either in terms of the recorded values or the timing of measurements. The remainder of the recorded

readings were fabricated results because no such measurements were stored in these electronic devices (432). Similar findings were reported by Malo et al. in which only 80% of the requested measurements were either recorded in the electronic peak flow monitor memory or in the written diary. Only 52% of the recordings corresponded accurately with the stored values, and only 71% of the recordings were made within 1 h of the requested time slot for measurement. Interestingly, PEF recording compliance was the worst among those individuals who were referred for investigations by the Workers' Compensation Board (121).

Even when PEF measurements are performed with electronic devices, varying treatments, intermittent use of bronchodilatators, or non-compliance with treatments can result in variations in PEF recordings that are difficult to interpret (428). Individuals who are unable to keep an adequate manually transcribed record often fail to produce adequate recordings with an electronic device (428). In some workplaces where the use of complete respiratory protection is required, it might be difficult to measure peak flow because the worker will need to leave his workplace to remove the personal protective device and perform measurements.

Exhaled biomarkers

Several factors can influence exhaled biomarker values like ENO. For example, relationships exist among ENO values, age, and sex (433). In females, ENO is associated with the menstrual cycle and pregnancy (434, 435). Smoking has been found to acutely and chronically reduce ENO levels in adults (433). In addition, upper and lower respiratory tract infections may lead to higher ENO levels (436, 437).

In a clinic study population, Dressler et al. derived predicted values for ENO considering smoking status, respiratory tract infections during the last 4 weeks, allergic rhinitis, height, and sex (438).

Specific Inhalation Challenge

SIC is considered to be the gold standard for diagnosis of OA. However, if some substances are used in high concentrations during SIC determinations, they can provoke irritating reactions and give false-positive results (439). In addition, SIC determinations can have false-negative results for individuals in whom the wrong substance is tested. Therefore, knowledge of work conditions and the ability to report exposures at the workplace can be influenced by education and language skills of the individual worker.

There are reports of workers with asthma who became sensitized to a product that was used in a different factory and not to products used in their workplace (440). Thus, proximity to other workplaces and company size can be factors that need to be considered when workers are scheduled for SIC and in decisions on what substances should be tested.

Individuals frequently suffer from respiratory symptoms for years before they present to a physician or a diagnosis is finally made (397, 441). Often, when these individuals are scheduled for specialist investigations they are no longer employed at the workplace that caused their problems or have been away from work for a prolonged period of time. Several studies have shown decline in specific AHR after being removed from exposure for a long time (59, 442). Nevertheless, most individuals with OA retain their specific bronchial reactivity despite being removed from the causative workplace for a long time (175). When these individuals are examined, one also needs to consider the changes in NSBH levels or inflammation markers in sputum after exposure to the allergen during SIC (443, 444).

1.4. The medico-legal system for workers' compensation in Quebec

The CSST is entirely funded by employers' contributions to insurance rates. The amount of the insurance rate is set by the CSST and depends on the risk of the workplace, the number of employees and workers' salaries.

In 2007, $1,700 million CAD$ was paid by the CSST in benefits for occupational injuries. That includes such costs as the income replacement indemnity (IRR) and rehabilitation (medical expenses, expenses for rehabilitation, benefits for death) and permanent disability indemnity (DAP). $1,062.5 million CAD$ was allocated for the IRR; of that amount, $565.4 million CAD$ was paid to workers during the period of consolidation and rehabilitation and $497.1 million CAD$ in the post-rehabilitation period (445).

OA is currently among the most frequently compensated occupational respiratory diseases in Quebec, after diseases related to exposure to asbestos dust, including pleural and bronchial cancers. The number of accepted claims for some occupational respiratory diseases in Quebec is shown in Figure 11.

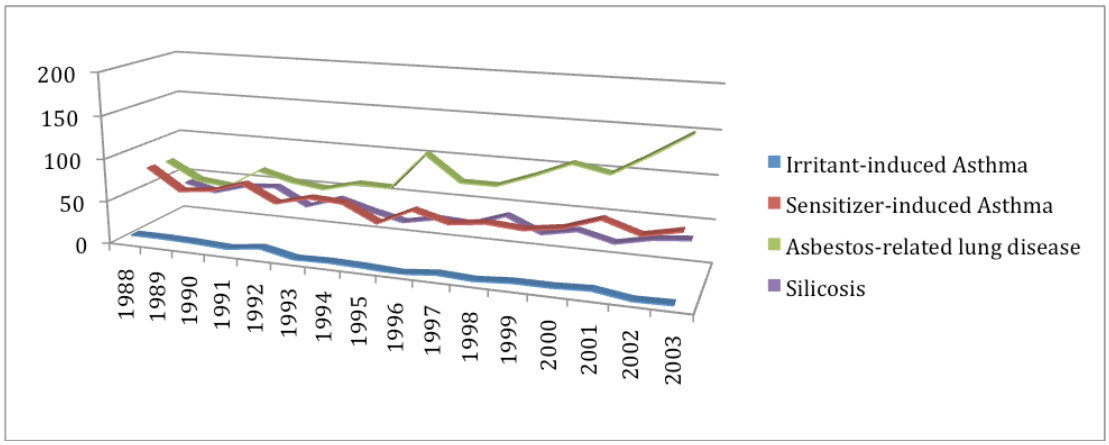


Figure 11: Number of cases of compensated occupational lung diseases in the province of Quebec from 1988-2003

1.4.1. The claims process

In Quebec, workers who are insured with the CSST through their employer are eligible for compensation for OA. There are several possible ways of filing claims for compensation. A worker who suspects that he or she suffers from OA can file a claim for compensation at the regional office of the CSST. Alternatively, the employer can file a claim for compensation. Also, when a link between the health symptoms and the workplace is suspected or established, a physician can issue a medical leave certificate and advise the worker to go to the regional CSST office to file a claim for compensation. The claim is then handled by the central medical department of the CSST. All claims for respiratory diseases are sent for evaluation to one of the four provincial committees responsible for assessing occupational pulmonary

diseases (the *comité des maladies pulmonaires professionnelles* or CMPP). Three respiratory specialists sit on each of these committees. There are two committees in Montreal (McGill University and the Université de Montréal), one in Quebec City (Université Laval), and one in Sherbrooke (Université de Sherbrooke). The committees assess each worker by collecting a structured history, performing medical examinations and pulmonary function and biological testing. If OA is suspected, the committee refers the claimant for a specialist investigation of OA to one of the two centres in Quebec (Hôpital du Sacré-Coeur de Montréal and Hôpital Laval) where experienced physicians and trained personnel offer specific expertise and where specific inhalation challenges can be performed. In order to be accepted by the CSST, OA must be confirmed by objective means. The dossier is then re-evaluated by the CMPP, at which the results of specific tests are appraised and a suggestion for the acceptance or rejection of OA is formulated. That suggestion is then reviewed by the chairperson of one of the four medical committees (*Comité des présidents*) and a decision is made to accept or reject the suggestions made by the CMPP. Finally, in case of a dispute, the decision of *the Comité des présidents* can be appealed by the claimant or the employer. If this is the case, a medico-legal court, the *commission des lésions professionnelles* (CLP), is required to make the final decision that is mandatory for all the parties involved.

Compensation for accepted claims includes income and the cost of rehabilitation, such as expenses for medical treatment and the permanent disability indemnity.

1.4.2. Income replacement indemnity and rehabilitation

In general, workers whose OA is confirmed by objective means and whose claim is accepted will stop working at their workplace if the offending agent cannot be removed. The IRR covers a maximum of 90% of net annual income for the previous year. An IRR is usually paid for one to two years, until the worker has found a new job, but there is no time limit and it is theoretically possible to receive the IRR up to the age of retirement (65). If a worker whose claim is accepted is over 55 years of age, he or she is eligible to receive the IRR until the age of 65. All costs for diagnostic evaluation or re-evaluation, if the condition worsens, as well as medical treatment, are reimbursed by the CSST. Rehabilitation costs also include the cost of counselling to find a new job and the cost of retraining (studies to complete another degree and studies at vocational schools).

1.4.3. Permanent disability indemnity

Impairment is defined by the WHO as a weakening, damage or deterioration of a body function, especially as a result of injury or a physiological disorder. A *disability* is an inability to execute some class of movements, or pick up sensory information of some sort, or perform some cognitive function, that typical unimpaired humans are able to execute or pick up or perform. A *handicap* is an inability to accomplish something one might want to do, that most others around one are able to accomplish (http://www.who.int/classifications/icf/en/).

In the case of OA a loss in FEV1 measured by lung function can be considered as impairment. If the loss in FEV1 causes some exercise limitation it can be considered a disability. If individuals with loss of FEV1 are unable to climb more than one fleet of stairs the individual can be considered handicapped due to the loss of lung function.

In subjects with OA, the rate of improvement in lung function and decline in bronchial hyperresponsiveness declines significantly two years after exposure has ended (152). In Quebec, all claimants are re-evaluated by the CSST two years after the initial assessment in order to determine the DAP. The criteria used are: the level of bronchial obstruction, measured as the FEV1 in %predicted and the ratio FEV1/FVC in %predicted, the level of bronchial responsiveness determined by the concentration that causes a drop in FEV1 of 20% (PC20) and the need for medication to treat asthma.

Sensitization to the agent, as well as impairment of quality of life, increases the percentage of impairment. The evaluation scheme that is currently used is shown in Figure 12.

Évaluation fonctionnelle pulmonaire – asthme professionnel

Classe	**Obstruction Bronchique (degré)**	**Excitabilité Bronchique (degré)**	**Besoins en medicaments**	**DAP**
1	0	0	Aucun	0
2	0	1	Aucun	5
	0	1	Bdt au besoin (PRN)***	8
	0	1	Bdt sur une base rég ****	10
	0	2	Aucun	10
	0	2	Bdt prn ou rég	13
	0	3	Bdt prn ou rég	15
3	1	1	Bdt prn ou rég	18
	1	2	Bdt prn ou rég	20
	1	3	Bdt prn ou rég	25
4	2	1-2	Bdt prn ou rég	28
	2	3	Bdt prn ou rég	33
5	3	1-2	Bdt prn ou rég	50
	3	3	Bdt prn ou rég	60
6	4	1-2-3	Bdt prn ou rég avec stéroïdes inhalés	100
Le cas échéant, s'ajoutent pour stéroïdes inhalés				3
pour stéroïdes oraux avec ou sans stéroïdes inhalés				10
Facteurs additionnels de sévérité				
Sensibilisation				3
Hyperexcitabilité bronchique non allergique				
- À l'effort physique important ou au froid				2
- À La marche par beau temps ou lorsque le travailleur est exposé à des irritants tes que la fumée et les odeurs fortes				4
- Aux activités normales à domicile				6
- De façon continue, incluant la nuit				10
Degrés d'obstruction bronchique*			**Degrés d'excitabilité bronchique****	
0 VEMS* et/ou VEMS*/CVF>85% (%pred)			0 CP 20>16mg/ml	
1 VEMS et/ou VEMS/CVF=71%-85% (%pred)			1 CP 20=2-16mg/ml	
2 VEMS et/ou VEMS/CVF=56%-70% (%pred)			2 CP 20=0.25-2mg/ml	
3 VEMS et/ou VEMS/CVF=40%-55% (%pred)			3 CP 20<0.25mg/ml	
4 VEMS et/ou VEMS/CVF<40% (%pred)				
* VEMS, VEMS/VCF (pourcentage exprimé par rapport aux valeurs prédites). Des épreuves de fonction respiratoire plus élaborées telles que les volumes pulmonaires, la diffusion de l'oxyde de carbone, les échanges gazeux au repos et à l'effort, la boucle débit-volume et l'étude de la résistance des voies aériennes pourraient être effectueées, le cas échéant.				
** Selon les résultats du test à l'histamine ou à la méthacholine. Ce test est fait selon la méthode standardisée de Cockcroft et coll.				
*** Bronchodilatateurs (bdt) comprend des dérivés Beta-2 adrénergiques, théophylines et bromure d'iprotropium.				
**** Sur une base régulière (rég.) signifie quotidiennement.				

Figure 12: Table for calculation of permanent disability indemnity used by the "CSST" in Quebec/Canada

Before this scale was used, determination of impairment and disability for individuals with asthma was performed according to the method suggested by the American Medical Association (AMA), which incorporated

information on dyspnoea severity, spirometry (FEV1, FVC and the ratio FEV1/FVC), as well as exercise capacity, expressed as maximal oxygen consumption during exercise (446). Unlike other occupational respiratory diseases, occupational asthma does not typically present with radiological changes, and airflow obstruction is variable. The guidelines suggested that due to the variability of airflow obstruction, periodic evaluation should be considered and the degree of impairment should be determined by recording post-exercise spirometry (446). However, the prevalence of post-exercise airway obstruction or exercise-induced AHR in individuals with OA is unknown, and so these guidelines were considered insufficient and even inappropriate for the evaluation of impairment/disability in individuals with OA (447). Subsequently, scales incorporating information on spirometry, non-specific AHR to BPTs and medication needed to control symptoms of asthma were suggested or introduced (447-449). This led to a new scale for the evaluation of patients with asthma in the AMA's fifth edition of the Guides to the Evaluation of Permanent Impairment (450).

1.4.4. Costs of occupational asthma and effectiveness of the compensation system

Leigh and co-workers attempted to estimate the costs of OA in the USA. For this analysis, the population-attributable risk for an occupational case of asthma was set at 15% and the lower age limit at 20. To calculate costs, the authors used the human capital method, which separates costs into direct categories, such as medical expenses, as well as indirect categories, such as lost earnings and lost home production. The proposed model suggested that this PAR leads to costs of USD $1.6 billion and that the major contributor to that sum is direct costs (74% direct and 26% indirect costs) (451).

Malo and co-workers evaluated the direct costs of OA in Quebec by evaluating a sample of claims that were filed between 1988 and 2002. They estimated the median costs of compensation for IRR, DAP and total direct costs at $40,700, $7,600 and $ 61,300 respectively. In their study, direct costs were higher for older subjects, men, workers exposed to LMW allergens and workers with more severe asthma reflected by use of steroids, lung function impairment and bronchial hyperresponsiveness (162). In a subsequent analysis, using socio-economic factors as predictors of cost for compensation, the authors showed that IRR was directly and positively related to the length of time for which compensation was received. Again, the

IRR was shown to be higher in older, married individuals and those to whom early retirement was offered. Older individuals whose claim is accepted are eligible to get the IRR until the age of 65. These workers are often earning higher salaries due to their seniority and experience in the workplace. Individuals with OA to low-molecular-weight agents also had higher IRR costs, which were only associated with the duration of compensation but not with other socio-economic factors in multivariate analysis (452).

Although this compensation program is among the most extensive for workers affected by OA, it seems that a significant proportion of subjects with probable OA do not receive compensation. In the PROPULSE sentinel physician-based study by Provencher and co-workers, 121 highly likely cases of OA asthma were reported by sentinel physicians during the one-year study period in 1992-1993 (453). However, in the 1991-1994 period, only a mean of 60 cases were compensated for OA, suggesting that a significant proportion of subjects with highly probable OA do not submit a claim to the CSST and do not receive compensation. To get compensation from the CSST for immunological OA, a worker needs to be exposed to a product that is specific to the workplace and does not aggravate pre-existing asthma through a non-specific (irritant) mechanism, which is considered to be WEA (397). Occasionally, workers with WEA may be compensated if they had to be away from work due to the unusual presence of ubiquitous allergens (moulds in the case of water leaks) or irritants (renovation with dusts at work). The IRR allocation is offered for a short interval in these circumstances.

It is possible that workers do not file a claim. Some workers may change their workplace, stop being exposed, and have fewer symptoms or even become asymptomatic; they therefore feel it unnecessary to file a claim, whereas others continue to work in order to avoid stigmatization, loss of income or diminished personal status.

Subjects with OA who have left the workplace do have persistent sequelae, measured as lung function impairment, bronchial hyperresponsiveness, inflammatory cells in the sputum or quality of life, as demonstrated by Yacoub and co-workers (410). One reason for this unfavourable outcome is that individuals remain exposed to the causal agent despite having respiratory symptoms for too long a time. Assigning a diagnosis of OA has significant consequences for the worker and the compensation system. Therefore, it needs to be precise. Specialized centres with experience in the diagnosis and treatment of subjects with OA are needed. Moreover, the wait for referral should be reasonably short. In Quebec, once a claim is submitted to the CSST, there is a delay of 2-3 months for the claimant to be assessed by a CMPP. It has been estimated that the medico-legal process for examining claims and making an initial decision takes an average of eight months, including the 2-3 months' interval for referral to the CMPP (397).

The cause of the delay in diagnosing OA was investigated in Ontario/Canada by reviewing charts of patients referred to a tertiary asthma centre for a diagnosis of WRA. In a sample of 42 patients, it was found that

common reasons for a delay in investigation and referral to a specialist centre were that the physician did not inquire about workplace association and that workers feared losing their job. The mean interval to diagnosis was longer for those with a lower level of education: for those with primary education, it was 7.4 years ± 6.7 years, versus 3.1 years ±1.6 years for those with post-secondary education. Patients whose household income before diagnosis was less than $30,000 CAD$ had a mean interval to diagnosis of 6.4 years ±6.5 years, compared to 2.7 years ±1.8 years for those with a household income of $80,000 CAD$ or more (441, 454).

1.5. Measuring health with questionnaires

Measurement is an essential component of scientific research, and measurements in the laboratory disciplines present no inherent difficulties. It is relatively easy for intervention studies to measure clear endpoints such as death. However, there is an increasing awareness of the impact of health and health care on the quality of human life. Many interventions in the various fields of medicine are directed equally, if not primarily, to improving the quality and not the “quantity” of life (455).

As in the laboratory disciplines, there is need for reliable and valid quality of life measures. In the field of psychiatry, it has been shown that when unpublished measurement scales are used, studies are more likely to report that treatments are effective compared to those in which validated instruments are used (456).

The impact of disease on a patient’s health and well-being differs among individuals. According to Paul Jones, “A patient’s health-related quality of life is the result of a generic disturbance to health common to all patients with the disease, modulated by factors that are internal and unique to the individual.” (457). Health-related quality of life questionnaires should include items that evaluate the physical, psychological, and social domains; in general, the items of a questionnaire should be derived from patients rather than health care professionals (458).

Questionnaires can use open-ended questions for which respondents can record what they have to say in their own words. These types of questions are often used in the exploratory phases of question design and allow researchers to formulate more structured and perhaps more closed-ended questions at a later phase. These require qualitative methods for coding and analyzing data (459).

Closed-ended questions are much more common in questionnaires, which ask respondents to choose from one or more preselected answers. Closed-ended questions are generally faster to answer and data are easier to manage and analyze (459). However, there are disadvantages. The questions may lead respondents in certain directions and the answers that can be chosen may not be the most appropriate for a particular respondent because the set of answers is not exhaustive (459).

A variation in the option to answer closed-ended questions is to provide respondents with visual analog scales. The individual is asked to mark a line at a spot along a continuum from one extreme to the other that best represents his characteristics. The ends of these scales are anchored with words that describe the most extreme responses (e.g. “none” and “unbearable”). The advantage of these answering options is that individuals can create their characteristics on a continuous scale, which has a higher sensitivity to detect changes.

Questionnaires can be administered either by the respondent or by an interviewer. Often, questionnaires are self-administered because this option is

cheaper and there is no risk of introducing bias in such a way that the response might be influenced by the relationship between the interviewer and respondent. However, interviews are considered to be the better option if long, complicated questions that require explanation or guidance are asked. Further, an interviewer can assure that the respondent answers all the questions in the questionnaire.

Validation and testing

Questionnaires should be assessed for their validity (i.e., accuracy) and reproducibility/reliability, which is the same as precision. This is analogous to validating laboratory tests. Questionnaires should have face validity, which is a subjective judgment that the items in the instrument seem to measure the desired characteristics. Validity can be assessed by comparing measurements of the questionnaire with a reference or gold standard measure. Predictive validity can be assessed by examining the correlations of the questionnaire measurements with the future outcomes of interest. If the questionnaire is intended to measure change, its responsiveness should be examined by using it for patients both before and after receiving known effective treatments (459). Reliability, or the degree to which an instrument is free from random error, is assessed by evaluating the

homogeneity of the scale's items at one point in time, whereas test–retest reliability assesses the stability of an instrument over time (460).

Generic versus disease-specific health measurement scales

Generic instruments are broad-based instruments that can measure quality of life with regard to different disease states and conditions, treatment interventions, and populations (460). These measures are specifically designed to detect differences between individuals and a general population (461). One of the most widely used generic health measurement scales is the Short Form Health Survey (SF-36) (94). This questionnaire incorporates eight domains. Each domain explores a different aspect of health-related quality of life: physical functioning; physical role; bodily pain; general health; vitality; social functioning, emotional role; and mental health.

Disease-specific instruments include items that are more relevant to a particular condition and have been shown to be more sensitive for assessing changes within patients (460-462). When most of the marks are clustered in only a few boxes at one extreme, the scores are very close to the top of the scale. In population studies that might include many individuals with mild forms of disease, this effect can occur and is called a ceiling effect. For asthma studies, Puhan reported that general health measures like the SF-36

are less influenced by this phenomenon compared to disease-specific measures like AQLQ. Thus, SF-36 should be considered a more valid measure of HRQL than AQLQ in cross-sectional studies in general populations (463).

Most of the currently available asthma-specific quality of life questionnaires were developed in the 1990s. Some of these can be used for different age groups, for individuals with asthma or COPD, and one was developed specifically for individuals with asthma and concomitant rhinitis (Table 9) (460).

	AQLQ-Juniper	AQLQ-Sydney	LWAQ	SGRQ	QOL-RIQ	Rhinasthma
Country of origin	Canada	Australia	United Kingdom	United Kingdom	Netherlands	Italy
Target group	Adults with asthma	Adults with asthma	Adults with asthma	Adults with chronic airflow obstruction	Adults with mild to moderate chronic nonspecific lung disease	Adults with rhinitis and/or asthma
Items	32	20	68	50	55	30
Domains	-Activity limitation -Symptoms -Emotional functioning -Exposure to environmental stimuli	-Breathlessness -Concerns -Mood -Social	-Social/leisure -Sport -Holidays -Sleep -Work & other activities -Colds -Mobility -Effects on others -Medication usage -Sex -Dysphoric states & attitudes	-Symptoms -Activities -Impacts	-Breathing problems -Physical problems related to chest problems -Emotions related to chest problems -Problems with general activities -Situations that might trigger or enhance breathing problems -Daily & domestic activities -Social activities, relationships & sexuality	-Upper airways symptoms -Lower airways symptoms -Respiratory allergy impact
Recall period	2 weeks	4 weeks	Current time point	Past 12 months, past 3 months, “these days”	12 months	2 weeks
Response format	7-point Likert scale	5-point Likert scale	3-point Likert scale, Not applicable option	Mostly binary or up to five response options	7-point Likert scale. Not applicable option	5 point Likert scale
Burden of administration	10-15 min	5 min	15-20 min	10 min	Not reported	5-10 min
Cultural and language adaptations	79 languages	4 languages	3 languages	73 languages	2 languages	2 languages

Table 9: Comparison of different asthma-specific quality of life questionnaires

For this study, we selected AQLQ developed by Juniper et al. The English version of this questionnaire was developed in Canada. Malo et al. conducted a formal validation study of the French version of this questionnaire at the Sacré-Coeur Hospital in Montreal (407). It is the most widely used asthma-specific quality of life questionnaire with the most available validated translations. This questionnaire was routinely used by our

research group in previous studies of individuals with OA, which allowed easy comparison with results of prior studies conducted by us and researchers worldwide.

This questionnaire was originally developed at McMaster University in Hamilton, Canada in 1991 (408, 464). After generating 152 items from a wide range of sources, Juniper et al. reduced it to 32 items. Patients rated the importance of each item and those items with the greatest importance were selected. The items can be grouped into four domains: activity limitation; symptoms; emotional function; and exposure to environmental stimuli. Each question is scored from one (extremely severe impairment of quality of life) to seven (no impairment). The total score is the mean of the four domain scores.

AQLQ(S) used in our study and the original questionnaire distinguish themselves on one point: in AQLQ(S), five generic activities (strenuous exercise, moderate exercise, work-related activities, social activities, and sleep) replaced specific activities that could be chosen by the patient in the original questionnaire (465).

Construct validity was investigated and reported by correlating the questionnaire scores with lung function test results and generic health-specific quality of life questionnaires, such as the Sickness Impact Profile and the shortened version of the Rand General Health Survey (408). The questionnaire's responsiveness was shown by comparing asthmatics with stable disease and asthmatics in which asthma had changed. A change in

score of around 0.5 has been reported as being the minimal important difference for the sub-scores and the total score (466).

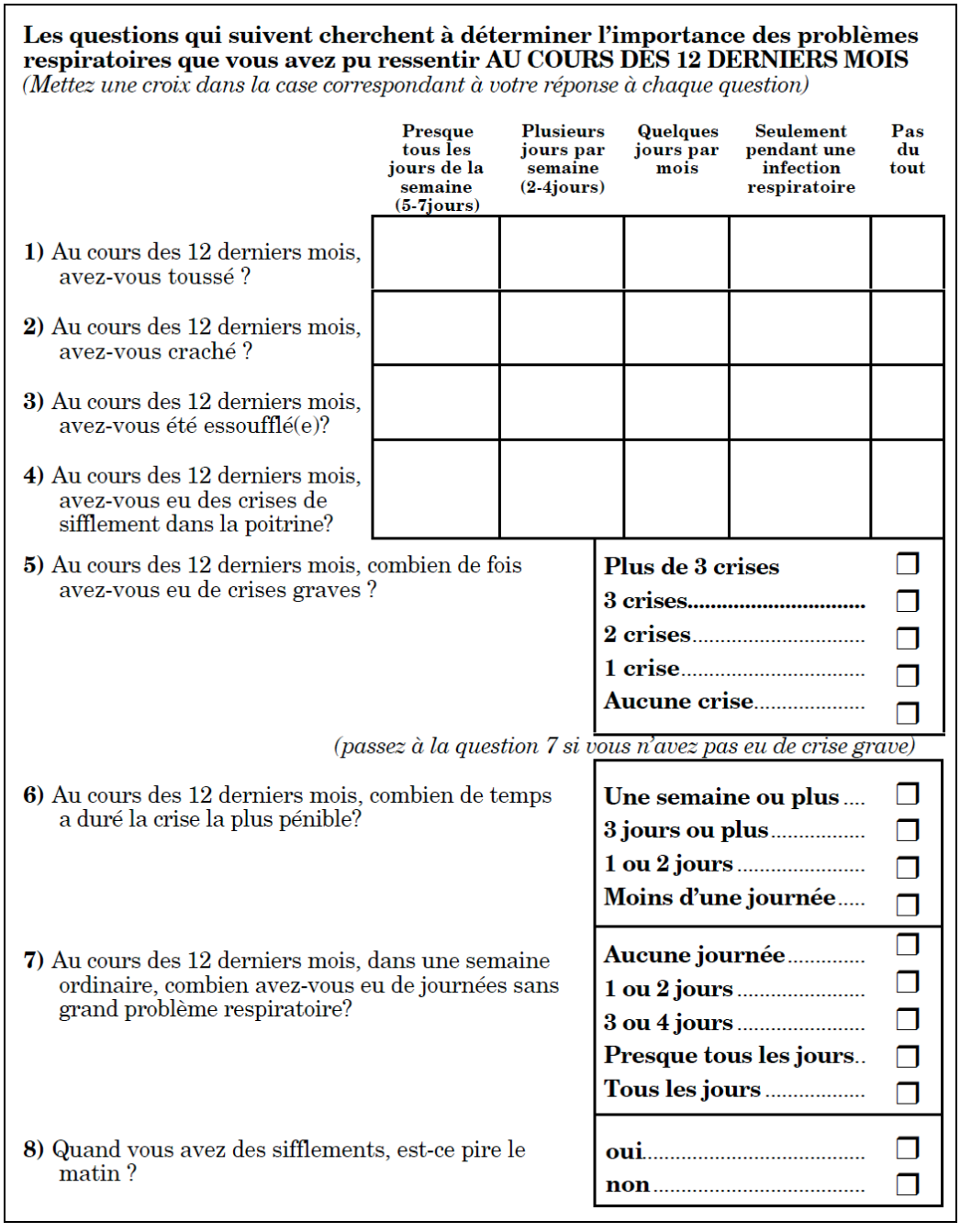
Therefore, we selected the AQLQ(S) questionnaire developed by Juniper et al. for the following reasons:

1. It is the best validated questionnaire currently available to measure asthma-specific quality of life;
2. The French translation has been validated in Quebec;
3. It is the most widely used asthma-specific quality of life questionnaire worldwide;
4. It has often been used in various studies conducted at our laboratory;
5. The administration burden is only about 10 min.

St. Georges Respiratory Questionnaire (SGRQ)

In our study, we used the symptoms domain of SGRQ only. SGRQ was developed in the United Kingdom in 1991 by Jones et al. It was intended to be used for adults older than 20 years of age who had chronic airflow obstruction (467, 468). The unabridged measure consists of 76 items, and each item has an empirically-derived weight (range: 0–100). The scores are calculated as the percentage of the summed weights of positive items relative to the summed weights of all items for each component, and in total (460). In

the symptoms domain, respondents are asked to report the intensity of their symptoms during the last 12 months, for which they respond to eight items (Figure 13).



Les questions qui suivent cherchent à déterminer l'importance des problèmes respiratoires que vous avez pu ressentir AU COURS DES 12 DERNIERS MOIS
(Mettez une croix dans la case correspondant à votre réponse à chaque question)

	Presque tous les jours de la semaine (5-7jours)	Plusieurs jours par semaine (2-4jours)	Quelques jours par mois	Seulement pendant une infection respiratoire	Pas du tout
1) Au cours des 12 derniers mois, avez-vous toussé ?					
2) Au cours des 12 derniers mois, avez-vous craché ?					
3) Au cours des 12 derniers mois, avez-vous été essoufflé(e)?					
4) Au cours des 12 derniers mois, avez-vous eu des crises de sifflement dans la poitrine?					

5) Au cours des 12 derniers mois, combien de fois avez-vous eu de crises graves ?

- **Plus de 3 crises** ☐
- **3 crises** ☐
- **2 crises** ☐
- **1 crise** ☐
- **Aucune crise** ☐

(passez à la question 7 si vous n'avez pas eu de crise grave)

6) Au cours des 12 derniers mois, combien de temps a duré la crise la plus pénible?

- **Une semaine ou plus** ☐
- **3 jours ou plus** ☐
- **1 ou 2 jours** ☐
- **Moins d'une journée** ☐

7) Au cours des 12 derniers mois, dans une semaine ordinaire, combien avez-vous eu de journées sans grand problème respiratoire?

- **Aucune journée** ☐
- **1 ou 2 jours** ☐
- **3 ou 4 jours** ☐
- **Presque tous les jours** ☐
- **Tous les jours** ☐

8) Quand vous avez des sifflements, est-ce pire le matin ?

- **oui** ☐
- **non** ☐

Figure 13: Symptoms domain of the SGRQ questionnaire

Psychiatric diseases

The concept of a syndrome is fundamental to the diagnostic classifications used for mental disorders. Without the concept of a syndrome, a disorder would be defined by a single symptom or a simple symptom count. A syndrome is a special collection of symptoms that cluster in a peculiar manner, which is determined by the underlying pathophysiology (469). For this, we rely on certain essential or core symptoms that commonly occur in individuals with the disease, but rarely occur in those without the disease.

Some symptoms are diagnostically more important than others. In mental disorders, there are rarely any symptoms that are entirely unique only to a specific disorder and not to another (469). Diagnostic checklists can be used to define psychiatric disorders. Some of these have been developed by the World Health Organization in the form of the International Classification of Diseases or by the American Psychiatric Association Committee on Nomenclature and Statistics in the form of the Diagnostic and Statistical Manual: Mental Disorders (DSM).

Despite the availability of these checklists, there is no universally accepted gold standard for diagnosis of mental disorders. As with asthma, clinically-based assessment is purportedly a reference standard in psychiatry if the clinician has adequate time and resources available for diagnosis (469). Longitudinal evaluation performed by Expert Clinicians who utilize All available Data (LEAD) approach was proposed by Spitzer (470). In this

approach, physicians have to incorporate information on collateral history, hospital records, psychological evaluations, and laboratory results to make a diagnosis. Semi-structured diagnostic interviews were developed to allow lay interviewers to obtain a diagnosis in mental disorders. However, they are considered time-consuming and are often not well accepted by patients and interviewers (471).

It is estimated that about one-third of patients in a primary care setting suffer from relevant psychiatric disorders, but only a small proportion of these are recognized and subsequently receive treatment (472, 473). It has been shown that primary care physicians encounter difficulties with accurately diagnosing mental disorders in their practices (474, 475).

Questionnaires to screen for depression and anxiety

The American College of Psychology Consultants lists 220 psychologically oriented scales with variable validation and reliability data (http://www.mentaltests.com/cms/mentaltests_list). I will only discuss those tests that have been previously used in the field of OA and that are available at the Sacré-Coeur Hospital.

Hospital Anxiety Depression Scale (HADS)

HADS is a brief, self-administered rating scale of symptoms and functioning. Anxiety and depression are assessed as separate components (sub-scale HADS-A for anxiety and HADS-D for depression). Each of these has seven items that are rated from 0 (no problem) to 3. Thus, a person can score between 0 and 21 for either anxiety or depression. The scale used is a Likert scale. A cut-off of >8 in the HADS-D and HADS-A sub-scales has been suggested to provide an optimal balance between sensitivity and specificity (476, 477). A limitation of this scale might be the reverse rating of some items along with the random sorting of anxiety and depression questions, which can create confusion. This questionnaire has not yet been used in studies that investigated patients with OA, but it is one of the most frequently used questionnaires in hospital settings in North America.

Psychiatric Symptom Index (PSI)

PSI is a shortened version of the Hopkins Symptom Distress Checklist that was constructed for use in a survey of stress and coping in 1972 in the US (478). It is a 29-item questionnaire elaborated to assess the presence and intensity of psychological distress during the 2 weeks preceding evaluation

(479). Items are scored using a four-point Likert scale from 0 (never) to 3 (very often). Total and sub-scale scores (depression, anxiety, anger, and cognitive disturbance) are calculated as a percentage of the total possible score out of 100. Illfeld at al. considered a score of >20 as clinically significant distress for all of the sub-scores (479). This questionnaire has been validated using a large urban sample that included a significant subset of minority inner-city residents (480). A total score on the PSI of ≥30 indicates a high likelihood of major depression diagnosed by a structured psychiatric interview (478).

Therefore, for this study, we selected the PSI questionnaire for the following reasons:

1. The administration burden is only about 10 min;
2. This questionnaire covers domains such as anger-related distress and cognitive disturbances in addition to anxiety and depression related distress;
3. It has been validated with a large cohort that included individuals belonging to minority groups;
4. It has often been used in various studies conducted at our laboratory;
5. A validated French version of the questionnaire is available.

Millon Clinical Multiaxial Inventory I-III (MCMI-III)

MCMI-III is a psychological assessment tool intended to provide information on psychopathology, including specific disorders outlined in DSM-IV. It is a 175-item, true–false inventory with 24 clinical scales designed to assess personality disturbances (e.g. avoidant personality) and psychiatric syndromes (e.g. anxiety disorders). Scores of <75 are considered to be within the normal range, scores of 75–85 identify those with a possible psychiatric syndrome, and scores of >85 identify those with a high probability of a psychiatric syndrome (481). MCMI was developed and standardized specifically with clinical populations (i.e. patients in psychiatric hospitals or people with existing mental health problems). It is intended for adults (18 years and older) with at least an 8^{th} grade reading level who are currently seeking mental health services (481). This questionnaire was used in the only study to date at our clinic that investigated psychiatric disease in patients with OA (410).

The Primary Care Evaluation of Mental Disorders (PRIME-MD)

PRIME-MD is a validated, brief screening instrument that is designed to detect some of the most common psychiatric disorders seen in community

and medical settings. It assesses four domains of mental disorders that are commonly observed in the general population: mood; anxiety; somatoform; and alcohol disorders. It consists of a 27-item patient self-report section followed by a structured clinical interview, which is used to follow-up on patient responses. The structured clinical interview assists the physician in either ruling in or ruling out psychiatric disorders and can be completed in approximately 8 min. PRIME-MD has been shown to be an acceptable surrogate for the reference standard in diagnosis by a structured psychiatric interview with a sensitivity of 83%, a specificity of 88%, and an overall accuracy of 86% for any mental disorder (482).

In this study, we selected the PRIME-MD questionnaire that diagnoses mental disorders based on the diagnostic criteria from DSM-III-R. This questionnaire was used in several ongoing studies at the Sacré-Coeur Hospital. Therefore, the team administrating this questionnaire had already gained experience with it. The administration time is much shorter, compared to MCMI-III. Because other questionnaires on quality of life and socio-economic factors were presented to study participants, we wanted to keep the total number of questions to a certain limit.

By comparison, the HADS questionnaire is much shorter. However, it only offers two dimensions (anxiety and depression) and, for depression, seven of nine DSM criteria are not covered in HADS. Categorical questionnaires, such as PRIME-MD, do not allow rating of disease severity. This is better accomplished by using a dimensional approach with continuous

measures, such as PSI. Using this approach, even “normal” individuals (no mental disorder diagnosed with PRIME-MD) may have measureable levels of depressive symptomatology. Those diagnosed with depression, for example, can have depressive symptomatology and higher levels of anxiety in the PSI questionnaire.

Therefore, for this study, we selected PRIME-MD for the following reasons:

1. The administration burden is relatively short compared to other investigational tools;
2. This instrument was developed for use by non-psychiatrists in a general practice setting;
3. It diagnoses mental disorders based on criteria from DSM-III-R;
4. It evaluates a broad spectrum of mental disorders (mood, anxiety, somatoform, alcohol, and eating);
5. It has often been used in various studies conducted at our laboratory;
6. A validated French version of this questionnaire is available.

1.6. Study aims

In this research study, we hoped to identify socio-economic factors that can influence the delay in submitting a claim to a medico-legal agency with removal from exposure after the onset of asthmatic symptoms. We wanted to confirm that this delay is associated with worse respiratory prognosis and examine whether the delay generates higher direct costs when combined with others. Further, we wanted to examine the association between anthropometric, clinical, functional and socio-economic variables, assessed at the time of the OA diagnosis and two years later, on quality of life and psychological outcomes in patients with OA. We also wanted to determine whether quality of life and psychological distress assessed at follow-up were associated with higher compensation costs for OA. Finally, we wanted to assess the correlation between asthma-specific quality of life and both levels of psychological distress and psychiatric disorders assessed by standardized tools in patients with OA. Specifically, we examined the correlation between general and different subscale scores on the Juniper Asthma Quality of Life Questionnaire (AQLQ(S)) on the one hand and, on the other hand, levels of psychological distress and rates of psychiatric disorders, and the extent to which responses on the emotion subscale of the AQLQ(S) allowed for the identification of individuals with significant psychological distress or

psychiatric disorders (i.e. patients who met diagnostic criteria for depressive and anxiety disorders).

2. Methods and Results

2.1. Article 1: Factors influencing duration of exposure with symptoms and costs of occupational asthma

European Respiratory Journal 2010; 36(4): 728-734.

L’article peut être consulté en suivant le lien suivant:

http://www.ncbi.nlm.nih.gov/pubmed/20150200

2.2. Article 2: Quality-of-life, psychological, and cost outcomes 2 years after diagnosis of occupational asthma

Journal of Occupational and Environmental Medicine 2011; 53(3):231-238

Quality of life, psychological and cost outcomes two years after diagnosis of occupational asthma

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Competing interest

None of the authors has competing interest to declare.

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Abstract

Objective

To examine the association between clinical and socioeconomic variables and their influence on psychological and cost outcomes in patients with occupational asthma (OA).

Methods

Longitudinal study of 60 subjects who claimed compensation for OA in Quebec. Beside clinical markers of asthma, quality of life (QOL), psychological distress (PD) measures and an instrument to diagnose mental disorders were used.

Results

QOL and PD parameters had moderate correlations with clinical markers of OA. Asthma severity, employment and marital status, income, and the length of employment with the employer showed the strongest associations with QOL and PD. More impaired QOL was associated with higher direct costs for compensation.

Conclusions

Impaired QOL and PD are frequent among subjects with OA receiving compensation and are associated with clinical markers of OA and socioeconomic factors.

Introduction

Psychiatric disorders such as mood (depressive) and anxiety disorders are frequently associated with asthma, and patients with depressive disorders have been shown to have worse asthma control, impaired quality of life, and tend to use more healthcare than patients without psychiatric comorbidity(1-3).

Only a handful of studies have attempted to assess quality of life impacts and the prevalence of psychological and psychiatric disorders in patients with OA as stated in a recent review article(2). One can hypothesize that patients with OA would have a more impaired quality of life because of being removed from their workplace, resulting in lost income and personal status. We have shown that patients with OA have a significantly decreased quality of life compared to asthma patients without OA(4).

In a study assessing participants with OA two years after removal from exposure from the causal agent, we reported that 35% of patients with OA had anxiety disorders and about 23% had dysthymia (a chronic form of depression). We also found that patients with OA had elevated psychological distress and moderately impaired disease-specific quality of life(5). However, this study only examined psychological morbidity and disease-specific quality of life two years post-diagnosis; therefore, we could not examine the risk factors that might influence the psychosocial and quality of life outcomes of OA.

The aim of this study was to examine the association between anthropometric, clinical, functional, and socio-economic variables assessed at the time of the OA diagnosis and two years thereafter, on quality of life and psychological outcomes in patients with OA. We expected that factors such as sex, age, the time interval since diagnosis, asthma severity and being employed at follow-up would be associated with worse psychological outcomes, particularly the prevalence of mood and anxiety disorders. We also wanted to determine whether or not quality of life and psychological distress assessed at follow-up were associated with higher compensation costs for OA.

Methods

The interested reader will find a detailed account of all aspects of the methodology used in this study by consulting the supplemental digital content section.

Study design, setting and participants

This was a cross-sectional study investigating patients who claimed compensation for occupational asthma (OA) at the Workers' Compensation Agency of Quebec (Commission de la santé et sécurité du travail du Québec; CSST) in the years 2004 to 2006. Patients who were no longer exposed to the offending allergens causing OA for two years or more were evaluated by two of the four Quebec CSST medical committees in Montreal (Montreal Chest Institute and Hôpital du Sacré-Coeur) for a permanent disability indemnity. In Quebec, all patients who claim compensation for OA undergo specific inhalation testing to confirm a diagnosis of OA. The methods used for specific challenge testing using different work related allergens have been described before (6) and this method is considered to be the reference standard for the diagnosis of OA (7). Therefore in all of the patients included in this study showed a positive response to a specific inhalation test. In this study the definition of asthma is therefore based on workplace associated respiratory symptoms and a positive result in the specific inhalation test. All claimants scheduled for evaluation by the committees were asked to participate in this study on a voluntary basis.

Patients were assessed on two occasions: when the initial OA diagnosis was made and the claim filed with the Workers' Compensation Board (WCB) (diagnosis), and when the participants were re-evaluated to determine compensation for permanent disability approximately two years later. Patients underwent the same testing protocol on both occasions, with the exception of skin prick testing, which was only performed at diagnosis (see details below). Further, questions regarding patients' employment status at the time, participation in rehabilitation programs, socio-economic factors as well as validated psychological and quality-of-life questionnaires, were added to their investigation at the two-year re-evaluation point.

Patients were assured that the medical committee would not be informed of participation or decline of participation in this study nor of the test results. They were given compensation for their study participation to cover expenses like loss of salary and transportation or parking fees. All study participants gave written consent for their participation. The research protocol was approved by the Research Ethical Committee of our hospital (CER de l'Hôpital Sacré-Coeur, Montreal).

Measures at diagnosis

All patients investigated underwent standard spirometry, methacholine challenge testing and induced sputum analysis. The type of agent causing OA, medication use, smoking status, and data on socio-economic status such as income, employment status, and company size were recorded from the WCB's report (Figure 1).

Measures at re-evaluation

Approximately two years after receiving their initial diagnosis, all patients investigated underwent standard spirometry, methacholine challenge testing and if patients could produce sputum on induction examination, induced sputum analysis (Figure 1). All patients completed a questionnaire on chest and upper airway symptoms, medication use, home allergen exposure, and smoking status. Patients also completed a questionnaire assessing whether they were still exposed to the offending agent, as well as a questionnaire assessing socio-economic factors including their employment at time, salary, education history, country of origin, number of children and family members dependant on the household income, and the nature of their participation in social rehabilitation programs offered by the WCB (e.g., full or part-time participation in job education, use of the employment agency, etc.). In addition, participants completed the validated French versions of the following questionnaires:

Asthma Quality of Life Questionnaire (AQLQ(S))

The standardized version of the AQLQ(S) includes 32 items and evaluates asthma quality of life across four life domains that may be negatively affected by asthma. The life domains include 1) asthma symptoms 2) activity limitations 3) emotional function and 4) exposure to environmental stimuli. Every question is scored from one (extremely severe impairment of quality of life) to seven (no impairment at all) and the total score is the mean of the four scores (8).

St-Georges Respiratory Questionnaire (SGRQ)

For this study we only used the section on respiratory symptoms from the St-Georges Respiratory Questionnaire which includes eight questions and the total score represents the sum of these elements. The total score ranges from 0 to 100 and a higher score indicates a worse HRQoL (9).

Psychiatric Symptom Index (PSI)

The PSI is a 29-item questionnaire elaborated to assess the presence and intensity of psychological distress in the two weeks preceding the evaluation (10). Items are scored using a four-point scale from 0 (never) to 3 (very often). Total scores and subscale scores (depression, anxiety, anger and cognitive disturbance) are calculated as a percentage of the total possible score out of 100. Scores of >25 are considered to indicate clinically significant distress (10).

Primary Care Evaluation of Mental Disorders (Prime-MD)

The PRIME-MD is a validated screening instrument designed to detect some of the most common Diagnostic and Statistical Manual of Mental Disorders (DSM) disorders seen in community and medical settings (11). It consists of a 27-item patient self-report section followed by a structured clinical interview that is used to follow-up patient responses. The PRIME-MD evaluates 5 groups of mental disorders (mood, anxiety, somatoform, alcohol, eating), and items were developed on the basis of criteria from the DSM-3rd edition revised (DSM-III-R) (12) It has demonstrated very good sensitivity (83%) for

any psychiatric diagnosis and excellent specificity (88%) across diagnostic modules (11).

Spirometry and Methacholine Provocation Testing

All patients underwent standard spirometry according to ATS guidelines(13), using the reference values derived by Knudson(14). Methacholine challenge testing was performed according to a previously published protocol(15). Normal responsiveness was set at a concentration of methacholine causing a 20% fall (PC_{20}) in FEV_1 of greater than 16 $mg*mL^{-1}$(16).

Allergy Testing

Skin prick tests were performed at diagnosis of OA to assess atopic status according to the method described by Pepys(17). Atopy was defined as having at least one positive result to an aeroallergen.

Induced Sputum Analysis

Patients underwent sputum induction by inhaling increasing concentrations (3%, 4%, and 5%) of hypertonic saline at diagnosis and at re-evaluation(18). The samples were processed according to a previously published protocol(19).

Compound Asthma Severity Score

Asthma severity was assessed at diagnosis and at re-evaluation. The asthma severity at diagnosis, at re-evaluation and the proportion of permanent disability that was allocated were calculated according to the Quebec Workers' Compensation Board Scale for OA: 0% low severity, 100%

maximum severity(20). This scale incorporates three factors in the same way as the one proposed by the American Medical Association(21): level of bronchial calibre, degree of bronchial responsiveness and need for medication to control asthma(22).

Direct Costs of OA

We consulted the patients' files at the Québec WCB to determine the costs of compensation for OA at the time of the re-evaluation. We reported the compensation for loss of income (CLI) and functional impairment (CFI) in this study. CLI corresponds mainly to compensation for lost wages during the rehabilitation period (up to two years) after the worker is removed from the workplace. CFI is allocated at the time of re-evaluation by the WCB, about two years after confirmation of the initial diagnosis and subsequent removal from the workplace, and is calculated according to the WCB scale for OA.

Statistical analysis

Continuous data is reported as mean ±standard deviation or median and 25 and 75 percentiles. Proportions were compared by using Chi–Square or Fisher's exact test if the expected cell count was <5. Continuous variables were compared by using the Mann-Whitney U test. We calculated Spearman's rho for correlation analysis between two continuous variables, and we conducted point-biserial correlations between continuous and categorical variables, but we did not correct the p-values for multiplicity. Prior to performing linear regression, we performed logarithmic transformation and then, applied the second power of the dependent variables AQLQ(S) and the

PSI total scores. Presence of psychiatric mood and anxiety disorders was assess by the PRIME-MD and coded as a dichotomous variable (yes, no).

Two models were fitted for each dependant variable. First, an a-priori model which included factors set in our hypotheses as likely associated with psychological outcomes (AQLQ(S), SGRQ and PSI): sex (male vs female), age at re-evaluation, time intervals since diagnosis, the asthma severity composite score at re-evaluation and the current employment status (working vs. not working). Second, a full model that we have named “a posterior” which included all significant covariates identified in the a priori model in whom the coefficients had a p-value of <0.2 and new socioeconomic covariates gathered at the time of diagnosis as well as at the time of re-evaluation. Linear regression was used for continuous dependant variables and logistic regression for the presence of mood and anxiety disorders according to the PRIME-MD. For all data analyses, we used the statistical software package SPSS V.16 (SPSS Inc., Chicago, USA). We considered a p-value of <0.05 as significant.

Results

Seventy-three subjects were eligible to participate as their claims were reviewed by the two committees in Montreal for a permanent disability indemnity during the study's recruitment period. Out of these eligible individuals, we were unable to contact five subjects and eight subjects refused to participate, yielding a final sample of 60 subjects and a participation rate of 82%. Participants did not differ from non-participants with respect to sex, age at diagnosis, atopy, smoking status, lung function, hyper-reactivity to methacholine, proportion of subjects with OA caused by low molecular weight agents, and the number of years at the workplace with symptoms (see results in the supplemental digital content section of this journal).

Characteristics of the study sample at the time of their initial diagnosis and at re-evaluation can be seen in Table 1. Fifty-five percent of participants were working at the time of re-evaluation, 20% were retired, 20% were unemployed and 5% were currently on re-training for another job. Thirty-one percent reported their overall health status as being fair or poor.

Disease-specific quality of life, psychological distress, and the frequency of psychiatric (mood and anxiety) disorders assessed at the re-evaluation are shown in Table 2. Disease-specific quality of life measured with the AQLQ(S) was moderately impaired and participants had a score in the medium range of the SGRQ symptom subscale. Forty-seven percent of the participants had a total score of ≥25 on the PSI, indicating a clinically

significant level of psychological distress. Thirty-two percent of patients screened positive for a mood disorder, and 15% screened positive for anxiety disorder according to the PRIME-MD. Twelve percent had comorbid mood and anxiety disorders concomitantly and 35% had mood and/or anxiety disorder(s).

As shown in Table 3, FEV_1(%predicted) was positively correlated with all the AQLQ(S) subscale scores and total score, and negatively correlated with the SGRQ symptom subscale score and the PSI total score. Furthermore and not shown in Table 3 change in FEV1%predicted (FEV1%predicted at diagnosis – FEV1%predicted at re-evaluation) was negatively correlated with the symptom and emotional function subscale score (r=-0.266, p=0.042 and r=-0.273, p=0.036 respectively) and positively with the SGRQ symptom score (r=0.256, p=0.050). Not shown in Table 3 inhaled steroid dose was positively correlated with the SGRQ symptom score (r=0.398, p=0.013), and the asthma severity compound score was negatively correlated with the AQLQ(S) total and subscale scores, the SGRQ symptom score and all PSI subscale scores (with the exception of cognitive disturbances). For the induced sputum analysis, the total sputum cell count was negatively correlated with all the AQLQ(S) total and subscale scores (with the exception of environmental stimuli), and positively correlated with the SGRQ symptom score (Table 3). Not shown in Table 3, the proportion of eosinophils was negatively correlated with having a diagnosis of mood disorder and having a mood and/or anxiety disorder according to the PRIME-MD (r=-0.312, p=0.035 and r=-0.368,

p=0.012 respectively). The proportion of neutrophils was negatively correlated with the AQLQ(S) activity limitation subscale score and positively correlated with the SGRQ symptom score (r=-0.389, p=0.008 and r=0.375, p=0.010 respectively).

Participants receiving no treatment for asthma or taking only short-acting bronchodilators as needed, had significantly less impaired disease-specific quality of life (total AQLQ(S) 5.9 (4.9;6.4) vs. 3.9 (2.9;5.1), p<0.001 and a lower SGRQ symptom score 35.2 (21.1;40.8) vs. 64.1 (36.8;81.7), p<0.001) as well as less psychological distress (total PSI 17.5 (6.0;27.0) vs. 28.5 (15.0;39.5), p=0.028) compared to those on regular (daily) anti-asthma treatment.

Total asthma disease-specific quality of life was significantly different according to employment status at re-evaluation: participants who were working at the time had better disease-specific quality of life (AQLQ(S) 5.3 (Q1:Q3:4.2;6.3) and SGRQ: 38 (26;53)) than those who were unemployed (AQLQ(S) 3.9 (3.1;4.4) and SGRQ 68 (40;86)) or retired (AQLQ(S): and 2.9 (2.3;5.3), p=0.001 and SGRQ 69 (39;79), p=.0.008) at the time of re-evaluation. For psychological distress levels, there was a similar trend for the PSI anxiety and depression scores: participants who were working at the time had less psychological distress (anxiety 21.0 (Q1; Q3: 9;36) and depression 17.0 (3;3)) than those who were unemployed (anxiety 36.0 (21;48) and depression 28.5 (23;33)) or retired (anxiety 30 (10.5;43.5), p=0.067 and depression: 26.5 (11.8;47), p=0.088) at the time of re-evaluation.

In the multivariate linear regression analysis, the AQLQ(S) total score was significantly negatively correlated to the compound asthma severity score at re-evaluation in the a priori model (Table 4). After applying stepwise linear regression, the compound asthma severity score at the time of re-evaluation and being married at diagnosis of OA were associated with worse quality of life in the AQLQ(S) score; however, the p-values derived after applying stepwise regression modelling are only approximate values. The SGRQ symptom score was significantly positively associated to the compound asthma severity score in the a priori model. After applying stepwise linear regression to other socio-economic variables, and retaining asthma severity within the model, being married, having low income and being employed for more than five years with the same employer at the time of diagnosis were related to poorer QOL scores according to the SGRQ.

The total PSI score had no significant association with the covariates in the a priori model; however, being a labour union member at the time of diagnosis was associated with the PSI score at re-evaluation in the “a-posteriori” model (Table 4).

The median CLI cost was $55.6*10^3$ CAD (Q1;Q3:$25.3*10^3$CAD;$124.1*10^3$CAD), the median CFI cost was $12.0*10^3$ CAD ($2.5*10^3$CAD;$18.6*10^3$CAD) and the median total cost for compensation was $69.2*10^3$ CAD ($36.6*10^3$CAD;$135.5*10^3$CAD). The correlation of the asthma severity, disease-specific quality of life, and psychological distress scores to direct costs for compensation are shown in Table 5. All AQLQ(S)

subscale scores and the total score had a significant negative correlation with CLI costs and this correlation remained significant with total costs for the total score and all the subscores with the exception of the emotional function score. The activity limitations sub-scale score had a small negative correlation to the CFI costs. The SGRQ symptom score had a small to medium positive correlation to the CLI and total cost. The PSI total and sub-scales scores did not correlate to costs for compensation, with the exception of the anger score (rho=0.285, p=0.028).

Discussion

Our study shows that an high proportion of patients with OA have moderate impairment in disease-specific quality of life, elevated levels of psychological distress and a high prevalence of psychiatric (mood and anxiety) disorders two years after their initial diagnosis.

Despite the fact that most of the study participants were no longer working at the workplace that caused OA at the time of re-evaluation, participants had moderately impaired quality of life measured according to the AQLQ(S). This is in accordance with past studies showing that more than 70% of subjects continue to have symptoms and use asthma medication despite being removed from the workplace for more than two years(23). Airway hyperresponsiveness to methacholine tends to improve more rapidly in the first 2.5 years, but slows down afterwards(24). In workers with different allergic manifestations due to natural latex, Al-Otaibi reported a decrease of disease specific quality of life impairment with increasing time since the diagnosis was made and symptoms duration(25). In our study we did not investigate a control group and therefore we cannot compare the level of quality of life impairment with individuals without OA, however as shown in the past despite matching for disease severity, subjects with OA seem to be significantly more impaired in quality of life than control subjects without OA(4).

In our study, between 35% and 47% of participants had clinically significant levels of psychological distress and 35% met criteria for one or

more current mood or anxiety disorders according to the PRIME-MD. Without considering asthma severity, in non-OA patients seen in our hospital asthma clinic, the prevalence of anxiety or mood disorder is similar, that is 31%(26). Suffering from a chronic illness is known to be associated with higher psychological distress in cross-sectional population studies(27) and in patients attending primary care. In a WHO Study, the prevalence of depressive disorder was reported to be between 10.4% and 7.9% for generalized anxiety disorder(28). It has been demonstrated that physical disability is a risk factor for the development of depressive disorders whereas other studies have shown in healthy cohorts at baseline, that individuals with depression have an increased risk of developing a new disabilities in the following years(29).

Our study shows that the principal factor associated with impact on quality of life and psychological outcomes was the severity of asthma. There are conflicting findings concerning the correlation between objective parameters of asthma severity and anxiety levels. Some studies show significant correlations between peak expiratory flow variability and self-reported anxiety in the Beck Anxiety Symptom Inventory(30) whereas other studies could not report a correlation between psychological distress and lung function(31, 32). Depression does not appear to be associated with objective measures of asthma severity. In a pilot study, asthmatics with a history of mood disorder seemed to have less severe airway obstruction and less severe asthma(33). Elevated depression scores were associated with

perceived asthma severity and risk, but not with intubation history, number of hospitalizations or asthma medication history(34). Interestingly, we found a correlation between the proportion of sputum eosinophils and mood disorder. It has been shown that eosinophilic airway inflammation is more pronounced following antigen challenge during final examinations among college students and is associated with higher self-reported psychological stress(35).

In the multivariate linear regression a priori model, the asthma severity compound score was the only factor significantly associated with the AQLQ(S) total score. Other covariates such as sex, age, current employment status, and the time since diagnosis of OA and consequent removal from the causal allergen, all factors found significant at a $p<0.2$ level in the univariate analysis, were not significantly associated with disease-specific quality of life. However, in the a posteriori analysis, some socio-economic factors were significantly associated with AQLQ(S) but not with psychological outcomes. Being married at the time of diagnosis was associated with more severe quality of life impairment, measured as the total AQLQ(S) and in the SGRQ symptom score. In general, married individuals often have better health status than their unmarried counterparts(36). However, singles seem to have better health outcomes when compared to those in low-quality marriages, as shown in hypertension research studies(37). Job loss due to OA and resultant income and social status losses might influence quality of life; this might be even more important in individuals who have a dependent spouse. Participants being labour union members at the time of diagnosis had lower

psychological distress levels at re-evaluation. The mission of a labour union is to defend the economic, professional and social interests of workers, especially in the workplace. Workers may thereby benefit from labour union help in terms of complying to the requirements of filing a claim for compensation. Moreover, they may receive support during the rehabilitation phase (e.g. in finding a new workplace, exploring possibilities for re-education programs, receiving legal support, etc.) thereby explaining lower levels of psychological distress at the time of re-evaluation. Although employment status at the time of re-evaluation was significantly related to quality of life and psychological outcomes in the univariate analysis, this was not the case in the multivariate analysis, in contrast to asthma severity that was significantly correlated to quality of life and psychological outcomes both in the univariate and multivariate analysis. Asthma severity has been shown in other studies to be a weak although significant determinant for employment status (38).

Another important finding of this study is the association between direct costs and psychological outcomes. We found small to medium significant correlations between quality of life measures and the anger subscale of the PSI questionnaire and compensation costs. The relation was strongest with the CFI compensation component, which reflects disease severity. As many factors influence CLI costs (age and income at the time of diagnosis being the most important ones), it is not surprising that we could not find any association between quality of life, psychological distress and costs for CLI.

We did not collect information about disease-specific quality of life and psychological distress, and psychiatric morbidity (mood and anxiety disorders) at the time of diagnosis, and therefore have no information about the interaction of OA with psychological distress/psychiatric disorders and the progression of both conditions. Furthermore, we did not systematically collect information on medication used in treating psychiatric disorders. It is possible that some individuals were treated successfully for psychiatric disorders, and that the results of our study underestimate impairment in quality of life and psychological distress in individuals with OA. In Quebec, a broad compensation system for OA is in place. Even when compensation systems appear to be effective, not all subjects with a high probability of asthma claim compensation from the WCB or change workplaces to avoid the causal agent(s)(39). In countries such as the United States, where disputes about compensation are usually settled through litigation in an adversarial setting, the impact on quality of life and psychological distress might be even more pronounced. Compensation claims and costs for occupational injuries have shown to be influenced by economic cycles. Compensation claims tend to decline in recessions and increase in times of economic recovery(40). How these factors influence quality of life and psychological distress in individuals with OA is unknown.

A large proportion of patients with OA have significant impairment in disease-specific quality of life with elevated levels of psychological distress and psychiatric (mood and anxiety) disorders. Quality of life, as well as some

psychological distress parameters at re-evaluation, correlate well with objective measures of disease activity which seems to be the principal determinant. However, besides the current asthma severity, socio-economic factors, such as employment status, marital status, income, the number of years of employment at the time of diagnosis also influence, though to a lesser degree, disease-specific quality of life and psychological outcomes. Finally, disease-specific quality of life correlates with the direct costs for compensation by the WCB. Therefore, our findings underline the importance of psychological distress and comorbid psychiatric disorders in patients with OA. However, further studies are needed to prospectively investigate patients in terms of the evolution of their quality of life, psychological distress levels and psychiatric morbidity from the time of diagnosis to when patients are removed from the workplace and undergo rehabilitation. Furthermore, future studies are needed to investigate if intervention programs can reduce psychological distress and/or prevent the development of psychiatric morbidity in patients with OA and if the same factors influence quality of life and psychological distress in countries with different medical and compensation systems.

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Table 1: Selected baseline characteristics of participants at the time of diagnosis and re-evaluation (n=60)

At diagnosis	
Sex (male/female)	45 (75%)/15 (25%)
Atopy	42 (70%)
Causal agent (HMW/LMW/unknown)	26 (43%)/33 (55%)/1 (2%)
Length of exposure to causal agent (years)	10.5 (3.1;22.8)
Duration of symptoms prior to claim (years)	1.4 (0.1;7.5)
Time interval between diagnosis and re-evaluation (years)	2.8 (2.5;4.3)
Asthma severity compound score (%)	24 (16.0;32.5)
At re-evaluation	
Age (years)	47.2 ±11.7
Medication	
- No medication for asthma	5 (8%)
- Short acting Beta-agonists	17 (28%)
- Long acting Beta-agonists	12 (20%)
- Inhaled steroids	38 (63%)
- Dose of inhaled steroids (equivalent of budesonid in mcg)	800 (800;1600)
Smoking habit	
- Non-smoker	10 (16%)
- Ex-smoker	25 (42%)
- Smoker	25 (42%)
Type of rehabilitation program	
- No Program	42 (70%)
- Program without studies	9 (15%)
- Program with studies	9 (15%)
Employment status	
- Without job	12 (20%)
- Retraining	3 (5%)
- Retired	12 (20%)
- Other employer	20 (33%)
- Same employer	13 (22%)
Self reported overall health status	
- Excellent	2 (3%)
- Very good	15 (25%)
- Good	24 (40%)
- Fair	8 (13%)
- Poor	11 (18%)
FEV1% predicted	83 ±2
FEV1/FVC% predicted	92 ±2
Bronchial hyperresponsiveness to methacholine	
PC 20 $mg.mL^{-1}$	16 (31%)
- >16	19 (37%)
- 2-16	14 (27%)
- 0.25-<2	3 (6%)
- <0.25	
Asthma severity compound score (%)	16 (10.3;31)

Legend: Data are presented as n, mean ±standard deviation, median (1.Quartile; 3.Quartile) exposure times are presented as median (1.Quartile; 3.Quartile) or n (%). HMW=High molecular weight allergen. LMW=Low

molecular weight allergen. Mcg=microgram. FEV1=Forced expiratory volume in one second. FVC=Forced vital capacity. PC20=Concentration of methacholine to provoke a fall of 20% or more in FEV1. The asthma severity compound score included objective parameters such as spirometry, methacholine reactivity, and current medication use (0% low severity, 100% maximum severity). Self reported overall health status according to the question in the PRIME-MD (Primary Care Evaluation of Mental Disorders) questionnaire.

Table 2: Distribution of Quality of Life, Psychological Distress and Psychiatric Syndromes at re-evaluation

	Frequency (n (%))	Score (median (Q1;Q3))
Juniper AQLQ		
Symptoms Domain		4.5 (3.5;6.0)
Activity limitations Domain		4.6 (3.3;5.7)
Emotional function Domain		5.0 (3.6;6.6)
Exposure to environmental stimuli Domain		4.8 (3.3;5.8)
Total		4.6 (3.6;5.9)
SGRQ Asthma Symptom Score (%)		45 (32;71)
Psychological distress	**(PSI score >25)**	
Depression	27 (45%)	23.0 (10.0;33.0)
Anxiety	28 (47%)	24.0 (12.8;39.0)
Anger	21 (35%)	19.0 (8.0;33.0)
Cognitive disturbance	24 (40%)	24.5 (8.0;39.8)
Total	28 (47%)	24.5 (10.8;37.8)
Prime-MD		
Mood disorders	19 (32%)	
- Major depression	8 (13%)	
- Dysthymia	3 (5%)	
- Minor depression	11 (18%)	
Anxiety disorders	9 (15%)	
- Panic disorder	1 (2%)	
- Generalized anxiety	1 (2%)	
- Unspecified anxiety disorder	7 (8%)	

Legend: AQLQ(S)=Standardized version of the Juniper Asthma Quality of Life Questionnaire; SGRQ : St. George Respiratory Questionnaire; PSI=Psychiatric Symptom Index, PRIME-MD= Primary Care Evaluation of Mental Disorders questionnaire

Table 3: Cross-sectional correlation of QOL, psychological distress and psychiatric syndromes with selected clinical, functional and inflammatory parameters at re-evaluation

	AQLQ(S)					SGRQ	PSI					PRIME-MD		
	Symptoms	Activity limitations	Emotional function	Exposure to environmental stimuli	Total	Symptom Score	Anxiety	Anger	Depression	Cognitive disturbance	Total	Mood disorder	Anxiety disorder	Anxiety and or mood disorder
FEV1% predicted at re-evaluation	0.431, 0.001	0.429, 0.001	0.409, 0.001	0.455, <0.001	0.475, <0.001	-0.463, <0.001	-0.338, <0.001				-0.275, 0.035	0.262, 0.045		
Asthma severity	-0.582, <0.001	-0.611, <0.001	-0.627, <0.001	-0.561, <0.001	-0.650, <0.001	0.597, <0.001	0.434, 0.001	0.298, 0.021	0.371, 0.003		0.418, 0.001	-0.279, 0.031		
Total sputum cell count	-0.391, 0.007	-0.407, 0.005	- 0.419, 0.004		-0.392, 0.007	0.351, 0.017								

Legend: Correlation reported as r with p-value. The p-values presented were not corrected for multiplicity. Blank scales are considered p>0.05. AQLQ(S)=Standardized version of the Juniper Asthma Quality of Life Questionnaire; SGRQ : St. George Respiratory Questionnaire; PSI=Psychiatric Symptom Index, PRIME-MD= Primary Care Evaluation of Mental Disorders questionnaire. Asthma severity=Asthma severity score at re-evaluation.

Table 4: Multivariate analysis of quality of life, psychological distress and psychiatric syndromes according to different socioeconomic factors

		AQLQ(S) Total		SGRQ		PSI Total		Prime-MD
		A priori	A posteriori	A priori	A posteriori	A priori	A posteriori	A priori
Information collected at diagnosis	Sex	-0.045 (0.051), 0.388		6.535 (7.430), 0.383		-0.064 (0.307), 0.836		0.538 (0.763), 0.481
	Not married		0.084 (0.038), 0.034		-13.414 (5.266), 0.014			
	Other than low income				18.067 (7.377), 0.018			
	With employer for less than 5 years				11.166 (5.338), 0.042			
	Not a labour union member						0.492 (0.233), 0.039	
Information collected at re-evaluation	Age (years)	-0.002 (0.002), 0.331		0.258 (0.305), 0.402		0.000 (0.013), 0.964		0.057 (0.035), 0.107
	Time since Diagnosis (years)	-0.002 (0.007), 0.834		0.729 (1.071), 0.499		0.037 (0.047), 0.432	0.058 (0.033), 0.083	0.023 (0.109), 0.836
	Asthma severity (%)	-0.004 (0.001), 0.007	-0.004 (0.001), <0.001	0.483 (0.192), 0.015	0.713 (0.126), <0.001	0.003 (0.009), 0.718		-0.35 (0.022), 0.118
	Not employed	-0.069 (0.050), 0.173	-0.076 (0.045), 0.095	5.509 (7.283), 0.453		0.299 (0.303), 0.329		-0.783 (0.746), 0.294
	R2	0.404	0.440	0.349	0.471	0.105	0.144	0.176

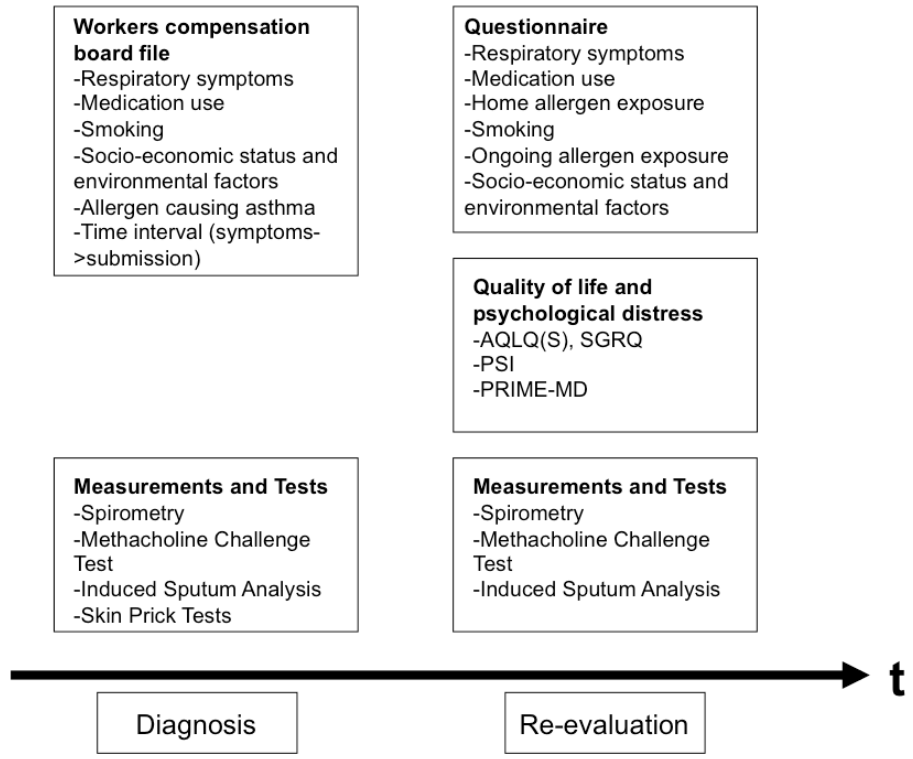
Legend: Data presented as β (SE), p-value. For the a-posteriori model the following variables were considered AQLQ(S)=Standardized version of the Juniper Asthma Quality of Life Questionnaire; SGRQ : St. George Respiratory Questionnaire; PSI=Psychiatric Symptom Index, PRIME-MD= Primary Care Evaluation of Mental Disorders questionnaire

Table 5: Correlation of QOL and psychological parameters with costs for compensation

		CFI costs	CLI costs	Total costs
AQLQ(S)	Symptoms		-0.309, 0.017	-0.290, 0.039
	Activity limitations	-0.279, 0.045	-0.353, 0.006	-0.337, 0.015
	Emotional function		-0.424, 0.001	
	Exposure to environmental stimuli		-0.358, 0.005	-0.282, 0.045
	Total		-0.381, 0.003	-0.325, 0.020
SGRQ	Symptom score		0.357, 0.005	0.283, 0.044
PSI	Anger		0.285, 0.028	

Legend: Correlation reported as r with p-value. The p-values presented were not corrected for multiplicity. CFI: compensation for income loss, CLI: compensation for impairment. Correlation reported as r with p-value. AQLQ(S)=Standardized version of the Juniper Asthma Quality of Life Questionnaire; SGRQ : St. George Respiratory Questionnaire; PSI=Psychiatric Symptom Index, PRIME-MD= Primary Care Evaluation of Mental Disorders questionnaire

Figure 1:



Legend: AQLQ(S)=standardized version of the Asthma Quality of Life Questionnaire; SGRQ= St-Georges Respiratory Questionnaire; PSI=Psychiatric Symptom Index; PRIME-MD=Primary Care Evaluation of Mental Disorders

Supplemental Digital Content

Methods

Study design, setting and participants

This was a cross-sectional study investigating patients who claimed compensation for occupational asthma (OA) at the Workers' Compensation Agency of Quebec (Commission de la santé et sécurité du travail du Québec; CSST) in the years 2004 to 2006. Patients who were no longer exposed to the offending allergens causing OA for two years or more were evaluated by two of the four Quebec CSST medical committees in Montreal (Montreal Chest Institute and Hôpital du Sacré-Coeur) for a permanent disability indemnity. In Quebec, all patients who claim compensation for OA undergo specific inhalation testing to confirm a diagnosis of OA. The methods used for specific challenge testing using different work related allergens have been described before (1) and this method is considered to be the reference standard for the diagnosis of OA (2). Therefore in all of the patients included in this study showed a positive response to a specific inhalation test. In this study the definition of asthma is therefore based on workplace associated respiratory symptoms and a positive result in the specific inhalation test. All claimants scheduled for evaluation by the committees were asked to participate in this study on a voluntary basis.

Patients were assessed on two occasions: when the initial OA diagnosis was made and the claim filed with the Workers' Compensation

Agency (diagnosis), and when the participants were re-evaluated to determine compensation for permanent disability approximately two years later. Patients underwent the same testing protocol on both occasions (see details below). However, questions regarding patients' employment status at the time, participation in rehabilitation programs, socio-economic factors as well as validated psychological and quality-of-life questionnaires, were added to their investigation at the two-year re-evaluation point.

Patients were assured that the medical committee would not be informed of participation or decline of participation in this study nor of the test results. They were given compensation for their study participation to cover expenses like loss of salary and transportation or parking fees. All study participants gave written consent for their participation. The research protocol was approved by the Research Ethical Committee of our hospital (CER de l'Hôpital Sacré-Coeur, Montreal).

Measures at diagnosis

All patients investigated underwent standard spirometry, methacholine challenge testing and if participants could produce sputum on induction examination, induced sputum. The type of agent causing OA, medication use, smoking status, and data on socio-economic status such as income, employment status, and company size were recorded from the WCB's report.

Measures at re-evaluation

Approximately two years after receiving their initial diagnosis, all patients completed a questionnaire on chest and upper airway symptoms, the interval

of time between the onset of symptoms and the submission of their claim to the WCB, medication use, home allergen exposure, and tobacco consumption. Patients also completed a questionnaire assessing whether they were still exposed to the offending agent, as well as a questionnaire assessing socio-economic factors including their employment at time, salary, education history, country of origin, number of children and family members dependant on the household income, and the nature of their participation in social rehabilitation programs offfered by the WCB (e.g., full or part-time participation in job education, use of the employment agency, etc.). In addition, participants completed the validated French versions of the following questionnaires:

Asthma Quality of Life Questionnaire (AQLQ(S))

The standardized version of the AQLQ(S) includes 32 items and evaluates asthma quality of life across four life domains that may be negatively affected by asthma. The life domains include 1) asthma symptoms 2) activity limitations 3) emotional function and 4) exposure to environmental stimuli. Every question is cored from one (extremely severe impairment of quality of life) to seven (no impairment at all) and the total score is the mean of the four scores (3).

St-Georges Respiratory Questionnaire (SGRQ)

For this study we only used the section on respiratory symptoms from the St-Georges Respiratory Questionnaire which includes eight questions and the

total score represents the sum of these elements. The total score ranges from 0 to 100 and a higher score indicates a worse HRQoL (4).

Psychiatric Symptom Index (PSI)

The PSI is a 29-item questionnaire elaborated to assess the presence and intensity of psychological distress in the two weeks preceding the evaluation (5). Items are scored using a four-point scale from 0 (never) to 3 (very often). Total scores and subscale scores (depression, anxiety, anger and cognitive disturbance) are calculated as a percentage of the total possible score out of 100. Scores of >25 are considered to indicate clinically significant distress (5).

Primary Care Evaluation of Mental Disorders (Prime-MD)

The PRIME-MD is a validated screening instrument designed to detect some of the most common Diagnostic and Statistical Manual of Mental Disorders (DSM) disorders seen in community and medical settings (6). It consists of a 27-item patient self-report section followed by a structured clinical interview that is used to follow-up patient responses. The PRIME-MD evaluates 5 groups of mental disorders (mood, anxiety, somatoform, alcohol, eating), and items were developed on the basis of criteria from the DSM-3rd edition revised (DSM-III-R) (7). It has demonstrated very good sensitivity (83%) for any psychiatric diagnosis and excellent specificity (88%) across diagnostic modules (6).

Spirometry and Methacholine Provocation Testing

All patients underwent standard spirometry according to ATS guidelines(8) at diagnosis and at re-evaluation, using the reference values derived by Knudson(9). Methacholine challenge testing was performed according to a previously published protocol(10). Normal responsiveness was set at a concentration of methacholine causing a 20% fall (PC_{20}) in FEV_1 of greater than 16 $mg*mL^{-1}$(11).

Allergy Testing

Skin prick tests were performed at diagnosis of OA to assess atopic status according to the method described by Pepys(12). Atopy was defined as having at least one positive result to an aeroallergen.

Induced Sputum Analysis

Patients underwent sputum induction by inhaling increasing concentrations (3%, 4%, and 5%) of hypertonic saline at diagnosis and at re-evaluation(13). The samples were processed according to a previously published protocol(14).

Compound Asthma Severity Score

Asthma severity was assessed at diagnosis and at re-evaluation. The asthma severity at diagnosis, at re-evaluation and the proportion of permanent disability that was allocated were calculated according to the Quebec Workers' Compensation Board Scale for OA (Table 1) (15). This scale incorporates three factors in the same way as the one proposed by the American Medical Association(16): level of bronchial calibre, degree of bronchial responsiveness and need for medication to control asthma(17).

Table 1: Quebec system of compensation for occupational asthma: criteria used to determine permanent disability

Class	Level of bronchial obstruction*	Level of bronchial responsiveness$	Need for medication	Percentage disability
1	0	0	None	0
2A	0	1	None	5
2B	0	1	BDT if needed	8
2C	0	1	BDT regularly	10
2D	0	2	None	10
2E	0	2	BDT reg or if needed	13
2F	0	3	BDT reg or if needed	15
3A	1	1	BDT reg or if needed	18
3B	1	2	BDT reg or if needed	20
3C	1	3	BDT reg or if needed	25
4A	2	1-2	BDT reg or if needed	28
4B	2	3	BDT reg or if needed	33
5A	3	1-2	BDT reg or if needed	50
5B	3	3	BDT reg or if needed	60
6	4	1-2-3	BDT reg or if needed	100

Legend: Group with oral steroids and with or without inhaled steroids: add 3% for inhaled steroids, ad 10% for oral steroids. *: level of bronchial obstruction (FEV1 and/or FEV1/FVC) determined at least 8 h after inhaled beta2-adrenergic agent and 48 h after oral theophylline, as follows: 0 = >85% pred; 1 = 71–85% pred; 2 = 56–70% pred; 3 = 40–55% pred; and 4 = <40% pred. $: level of bronchial hyperresponsiveness determined as follows: 0 = PC20 >16mg·ml-1; 1 = PC20 2–16 mg·ml-1; 2 = PC20 0.25–2 mg·ml-1; 3 = PC20 ≤0.25 mg·ml-1. PC20 assessed by the method of Cockcroft and co-workers (10). BDT: bronchodilator therapy; PC20: provocative concentration producing a 20% fall in FEV1; reg: regularly (daily).

Direct Costs of OA

We consulted the patients' files at the Québec WCB to determine the costs of compensation for OA at the time of the re-evaluation. We reported the compensation for loss of income (CLI) and functional impairment (CFI) in this study. CLI corresponds mainly to compensation for lost wages during the rehabilitation period (up to two years) after the worker is removed from the workplace. CFI is allocated at the time of re-evaluation by the WCB, about two years after confirmation of the initial diagnosis and subsequent removal from the workplace, and is calculated according to the WCB scale for OA.

Statistical analyses

Proportions are reported as absolute numbers and relative frequencies. Continuous data is reported as mean ±standard deviation or median and 25 and 75 percentiles, if non-normally distributed. Distribution of continuous variables was verified visually by plotting histograms. Proportions were compared by using Chi – Square or Fisher's exact test where the expected cell count was <5. Continuous variables were compared by using the Mann-Whitney U test. We calculated Spearman's rho for correlation analysis between two continuous variables, and we conducted point-biserial correlations between continuous and categorical variables, but we did not correct the p-values for multiplicity. Prior to performing linear regression, we performed logarithmic transformation and then, the second power of the dependent variables AQLQ(S) and PSI overall scores. Presence of psychiatric mood and anxiety disorders was assessed by the PRIME-MD and coded as a dichotomous variable (yes, no).

First, we analysed the a priori model with factors set in our hypotheses as likely associated with psychological outcomes (AQLQ(S), SGRQ and PSI): gender (male vs. female), age at re-evaluation, time intervals since diagnosis, the asthma severity composite score at re-evaluation and the employment status at the time (working vs. not working). Secondly, we performed a univariate analysis of the dependent variables with different socio-economic covariates gathered at the time of diagnosis as well as at the time of re-evaluation. We then performed a linear regression analysis with covariates with a p-value <0.2 identified in univariate analysis, and covariates identified in the a priori model in which the coefficients had a p-value of <0.2 in the model. The same scheme was applied for the logistic regression analysis of the dichotomous variable. Similarly, we performed a logistic regression analysis for the dependent dichotomous variable having mood or anxiety disorder diagnosed, according to the Prime-MD. For analysis of the data, we used a statistical software package (SPSS V.16, SPSS Inc., Chicago, USA). We considered a p-value of <0.05 as significant.

Results

Recruitment and characteristics of study participants versus non-participants

Seventy-three subjects were eligible to participate as their claims were reviewed by the two committees in Montreal for a permanent disability indemnity during the study's recruitment period. Out of these eligible individuals, we were unable to contact five subjects and eight subjects

refused to participate, yielding a final sample of 60 subjects and a participation rate of 82%. The baseline characteristics of the study participants as well as the non-participants at the time of diagnosis of OA can be seen in Table 2.

Table 2: Characteristics of study participants versus non-participants at the time of diagnosis of occupational asthma

	Participants (n=60)	Non-participants (n=13)	p-value
Male gender	45 (75%)	12 (92%)	0.273
Age (years)	42 (15)	39 (21)	0.795
Atopy	42 (70%)	11 (85%)	0.491
Smoking habit - smoker - ex-smoker - non-smoker	 10 (16%) 25 (42%) 25 (42%)	 2 (15%) 9 (70%) 2 (15%)	0.153
FEV1% predicted	86 (25)	78 (35)	0.264
FVC% predicted	91 (15)	80 (21)	0.143
Bronchial hyperresponsiveness to methacholine PC 20 $mg.mL^{-1}$	0.87 (2.30)	0.32 (0.75)	0.155
Causal agent is a high molecular allergen	27 (45%)	5 (38%)	0.632
Duration of symptoms prior to claim (years)	1.4 (7.3)	3.6 (15.0)	0.141

Legend: Data are presented as n (%) or median (interquartile range). PC20= concentration of methacholine to provoke a fall in FEV1 of 20% or more. Atopy= presence of at least one immediate skin reaction to 15 ubiquitous aeroallergens.

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2.3. Article 3: Identification of clinically significant psychological distress and psychiatric morbidity by examining quality of life in subjects with occupational asthma

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Identification of clinically significant psychological distress and psychiatric morbidity by examining quality of life in subjects with occupational asthma

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Abstract

Background

The Juniper Asthma Specific Quality of Life Questionnaire (AQLQ(S)) is a questionnaire that allows measurement of disease specific quality of life. We wanted to examine correlations between the (AQLQ(S)) general and different subscale scores and both psychiatric morbidity and levels of psychological distress in individuals with occupational asthma (OA) and to determine if results in the emotional function subscale allow identification of individuals with clinically significant psychological distress or current psychiatric disorders.

Methods

This was a cross-sectional study of individuals with OA who were assessed during a re-evaluation for permanent disability, after they were no longer exposed to the sensitizing agent. Patients underwent a general sociodemographic and medical history evaluation, a brief psychiatric interview (Primary Care Evaluation of Mental Disorders, PRIME-MD) and completed a battery of questionnaires including the AQLQ(S), the St-Georges Respiratory Questionnaire (SGRQ), and the Psychiatric Symptom Index (PSI).

Results

There was good internal consistency (Cronbach alpha=0.936 for the AQLQ(S) total score) and construct validity for the AQLQ(S) (Spearman rho=-0.693 for the SGRQ symptom score and rho=-0.650 for the asthma severity score). There were medium to large correlations between the total score of the AQLQ(S) and the SGRQ symptom score (r=-.693), and PSI total (r=-.619) and subscale scores (including depression, r=-.419; anxiety, r=-.664; anger, r=-.367; cognitive disturbances, r=-.419). A cut-off of 5.1 on the AQLQ(S) emotional function subscale (where 0 = high impairment and 7 = no impairment) had the best discriminative value to distinguish individuals with or without clinically significant psychological distress according to the PSI, and a cut-off of 4.7 best distinguished individuals with or without a current psychiatric disorder according to the PRIME-MD.

Conclusions

Impaired quality of life is associated with psychological distress and psychiatric disorders in individuals with OA. Findings suggest that the AQLQ(S) questionnaire may be used to identify patients with potentially clinically significant levels of psychological distress.

Abbreviations

AQLQ(S) = Juniper Asthma Quality of Life Questionnaire

CSST = “Commission de la santé et sécurité du travail du Québec” translates as Workers’ Compensation Agency of Quebec

FEV1 = forced expiratory volume in one second

FN = false-negative

FP = false-positive

HAD = Hospital Anxiety and Depression Scale

OA = Occupational Asthma

LWAQ = Living with Asthma Questionnaire

PC_{20} = Concentration of Methacholine causing a 20% fall in FEV_1

PRIME-MD **=** Primary Care Evaluation of Mental Disorders

PSI = Psychiatric Symptom Index

ROC = Receiver Operator Characteristic Curve

SGRQ = St-Georges Respiratory Questionnaire

YI = Youden Index

Competing interest

None of the authors has competing interest to declare.

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Keywords

Occupational asthma, psychiatric disorder, psychological distress, screening, quality of life

Background

Asthma is a chronic inflammatory disorder of the airways. Occupational asthma (OA) is asthma that is caused and maintained by conditions attributable to the occupational environment and not to stimuli encountered outside the workplace [1]. The impact of a disease on a patient's health and well-being is individual. According to Paul Jones, "A patient's health-related quality of life is the result of a generic disturbance to health common to all patients with the disease, modulated by factors that are internal and unique to the individual." [2]. Health-related quality of life questionnaires should therefore contain items evaluating physical, psychological and social domains, and in general, the item content of a questionnaire should be derived from patients rather than health professionals [3].

There are a variety of different measures available to determine asthma-related quality of life according to a recent review [4]. One of the most commonly used measures is the Asthma Quality of Life Questionnaire (AQLQ) developed in Canada by Juniper and co-workers. This questionnaire is available in approximately 80 languages, and changes in AQLQ scores have been shown to have strong correlations with changes in asthma control and medication usage [5]. Juniper and co-workers found moderate cross-sectional correlations of the AQLQ subscales with the psychosocial function domain of the Sickness Impact Profile and the emotion subscale of the Rand General Health Survey [5]. The standardized version of the AQLQ(S) has

been shown to have a moderate cross-sectional correlation (r=0.48) with the mental component summary measures of the Short Form-36 questionnaire [5, 6].

Previous research has demonstrated a link between health-related quality of life and an increased risk of all-cause mortality and healthcare use in individuals with asthma [7, 8]. The goal of asthma treatment is therefore to gain control of symptoms, which relies upon various self-management behaviors such as daily symptom self-monitoring, adherence to medication, refraining from smoking, as well as managing environmental asthma triggers. Chronic negative mood states such as depressive or anxiety disorders may interfere with motivation to engage in these self-management behaviors, and have been linked to worse asthma-related quality of life [9]. Having depression has also been shown to be associated with medication non-adherence in patients suffering from different medical conditions,[10] and anxiety disorders have been shown to be related to increased use of bronchodilators (reliever medication) and decreased use of controller medication such as inhaled corticosteroids among asthmatics [9, 11]. Early diagnosis of chronic negative mood states therefore offers the opportunity to begin specific anti-anxiety or anti-depressive therapy (i.e., psychotherapy or pharmacotherapy), and has the potential to reverse these adverse disease outcomes.

The aim of this study was to assess the correlation between asthma-specific quality of life and both levels of psychological distress and psychiatric

disorders assessed by standardized tools, in patients with OA. Specifically, this study examined the correlation between general and different subscale scores on the AQLQ(S) on the one hand and, on the other hand, levels of psychological distress and rates of psychiatric disorders, and the extent to which the responses on the emotion subscale of the AQLQ(S) allowed for the identification of individuals with significant psychological distress or psychiatric disorders (i.e., patients who met diagnostic criteria for depressive and anxiety disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DSM-IV).

Methods

Study design, setting and participants

This was a cross-sectional study of patients who claimed compensation for OA at the Workers' Compensation Agency of Quebec ("Commission de la santé et sécurité du travail du Québec" ("CSST")) in the years 2004 to 2006. Patients who were no longer exposed to the sensitizing agents causing OA for two years or more were evaluated by two of the four Quebec CSST medical committees in Montreal (Montreal Chest Institute and Hôpital du Sacré-Coeur) for a permanent disability indemnity. In Quebec, all patients who claim compensation for OA undergo specific inhalation testing to confirm a diagnosis of OA. All claimants scheduled for evaluation by the committees were asked to participate in this study on a voluntary basis. Patients were assessed when the participants were re-evaluated to determine compensation for permanent disability. Patients were assured that the medical committee would not be informed of participation, nor of the assessment results. They were given compensation for their study participation to cover expenses like loss of salary and transportation or parking fees. All study participants gave written, informed consent for their participation. The research protocol was approved by the Research Ethical Committee of Hôpital du Sacré-Coeur de Montreal.

Measures

All patients underwent standard spirometry and methacholine challenge testing. All patients completed a questionnaire on chest and upper airway symptoms, medication use, home allergen exposure, and smoking status. Patients also completed a questionnaire assessing whether they were still exposed to the sensitizing agent, as well as a questionnaire assessing socio-economic factors. In addition, participants completed the validated French versions of the following questionnaires:

Asthma Quality of Life Questionnaire (AQLQ(S))

The standardized version of the AQLQ(S) includes 32 items and evaluates asthma quality of life across four domains that may be negatively affected by asthma. The domains include 1) asthma symptoms 2) activity limitations 3) emotional function and 4) exposure to environmental stimuli. Every question is scored from one (severe impairment) to seven (no impairment), and the total score is the mean of the four scores [6]. Information on psychometric properties of this instrument have been published [12].

St-Georges Respiratory Questionnaire (SGRQ)

For this study, patients completed the section on respiratory symptoms from the SGRQ to assess the patient's perception of their recent respiratory problems.

This section of the questionnaire includes eight items where individuals choose the appropriate answer on a 5-point Likert scale. Each item in the

questionnaire has an empirically derived weight. The total score is representing the sum of these items. The total score ranges from 0 to 100 and a higher score indicates a worse symptom-related HRQoL [13]. Information on psychometric properties of this instrument have been published [12].

Psychiatric Symptom Index (PSI)

The PSI is a 29-item questionnaire designed to assess the presence and intensity of psychological distress levels in the past two weeks [14]. Items are scored using a four-point scale from 0 (never) to 3 (very often). Total and subscale scores (depression, anxiety, anger and cognitive disturbance) are calculated as a percentage of the total possible score out of 100. Scores of >20 are considered to indicate clinically significant levels of psychological distress [14]. Information on psychometric properties of this instrument have been published [15].

Primary Care Evaluation of Mental Disorders (Prime-MD)

The PRIME-MD is a validated brief screening instrument designed to detect some of the most common psychiatric disorders seen in community and medical settings [16]. It consists of a 27-item patient self-report section followed by a structured clinical interview that is used to follow-up patient responses. The PRIME-MD evaluates 5 groups of mental disorders (mood, anxiety, somatoform, alcohol, eating), and items are based on the diagnostic

criteria from the DSM [17]. It has demonstrated very good sensitivity (83%) for any psychiatric diagnosis and excellent specificity (88%) across diagnostic modules [16]. We administered the mood (depressive) and anxiety disorder modules, given they are the most prevalent psychiatric disorders seen in asthma patients. We then classified individuals in two groups: either as having a mood and/or anxiety disorder (*any psychiatric disorder*) or not having either mood or anxiety disorder (*no psychiatric disorder*). Information on psychometric properties of this instrument have been published [18].

Spirometry and Methacholine Provocation Testing

All patients underwent standard spirometry according to ATS guidelines[19], using the reference values derived by Knudson[20]. Methacholine challenge testing was performed according to a previously published protocol[21]. Normal responsiveness was set at a concentration of methacholine causing a 20% fall (PC_{20}) in FEV_1 of greater than 16 $mg*mL^{-1}$[22].

Compound Asthma Severity Score

OA severity was calculated according to the Quebec Workers' Compensation Board Scale for OA: 0% = low severity, 100% = maximum severity[23]. This scale assesses three factors in the same way as the one proposed by the American Medical Association[24]: level of bronchial caliber,

degree of bronchial responsiveness, and need for medication to control asthma[25].

Statistical analyses

Continuous data are reported as means ± standard deviations or medians and 25 and 75 percentiles. Proportions were compared by using Chi–Square or Fisher's exact test if the expected cell count was <5. Continuous variables were compared by using the Mann-Whitney U test. For all data analyses, we used the statistical software package SPSS V.19 (SPSS Inc., Chicago, USA). A p-value of <0.05 was considered statistically significant.

Measures of reliability

Cronbach alpha's were calculated to assess the internal consistency of the AQLQ(S) total score and each subscale score. Cronbach's alpha is a numerical coefficient for reliability. The coefficient value ranges from 0 to 1, and the higher the score, the more reliable is the generated scale [26].

Measures of validity

We calculated Spearman's rho for correlation analyses between two continuous variables, and we conducted point-biserial correlations which allow measurement of the correlation between a continuous variable (AQLQ(S) or PSI total or subscale scores) and a dichotomous variable (*any*

psychiatric disorder or *no psychiatric disorder* according Prime-MD) [27]. The correlation was considered small for correlation coefficients between 0.1 and 0.3, medium between 0.3 and 0.5 and high between 0.5 and 1.

Receiver operator characteristic (ROC) curve and Youden Index (YI)

In order to determine the best cut-off level of the AQLQ(S) emotion subscale score for the diagnosis of clinically relevant anxiety and depressive symptoms according to the PSI, and mood and/or anxiety disorders according to the PRIME-MD, a ROC curve was plotted. The YI was calculated to capture the performance of the diagnostic test and to obtain the cut-off in the AQLQ(S) emotion subscale score. YI was calculated as follows: (Sensitivity+Specificity)-1 [28].

Linear and logistic regression models

As data of the dependent variable (PSI anxiety and depression subscale scores) were not normally distributed we performed logarithmic transformation and then, applied the second power to this data prior to performing linear regression. The presence of a *psychiatric disorder* (mood and/or anxiety) was assess by the PRIME-MD and coded as a dichotomous variable (yes, no). We used the presence of psychiatric disorder as dependent variable and entered the questions of the AQLQ(S) emotions subscale score as independent variables in the model. We used the

automatic stepwise procedure of the statistical package with a probability of F ≤0.05 to enter and the probability of F ≥0.10 to remove the co-variate.

Results

Patient characteristics

Seventy-three subjects were eligible to participate during the study period. We were unable to contact five subjects and eight subjects refused to participate, yielding a final sample of 60 subjects and a participation rate of 82%. Participants did not differ from non-participants with respect to sex, age at diagnosis, atopy, smoking status, lung function, hyper-reactivity to methacholine, proportion of subjects with OA caused by low molecular weight agents, and the number of years at the workplace with symptoms (data not shown).

The mean age of participants was 47.2 ±11.7 years, 75% (n=45) of which were male. The median duration of exposure to the causal agent was 10.5 years (Q1;Q3: 3.1;22.8 years). A total of 42% (n=25) were current smokers. Fifty-five percent (n=33) of participants were working at the time of re-evaluation, 20% (n=12) were retired, 20% (n=12) were unemployed, and 5% (n=3) were currently on re-training for another job. Thirty-one percent (n=19) reported their overall health status as being fair or poor.

Asthma-specific quality of life, levels of psychological distress, and the frequency of psychiatric disorders assessed at the re-evaluation are shown in Table 1. Thirty five percent (n=21) had one or more psychiatric disorder, 19 of whom had a mood disorder, 9 of whom had an anxiety disorder, and 2 of

whom had both a mood and anxiety disorder according to the PRIME-MD evaluation.

Psychometric properties of the AQLQ(S)

The internal consistency for the AQLQ(S) in this sample was high, with Cronbach alpha's of 0.934 for the emotion, 0.951 for the symptom, 0.922 for the activity, and 0.819 for the environment subscale scores, and 0.936 for the total score. The observed cross-sectional correlations between the AQLQ(S) total and subscale scores with the compound asthma severity score incorporating lung function, bronchial hyperactivity, and current medication support a discriminative validity of the AQLQ(S) and can be seen in Table 2.

Correlation between AQLQ and asthma severity

We investigated the construct validity of the AQLQ(S) and calculated correlation coefficients for the different AQLQ(S) scores with the compound asthma severity score according to the Quebec Workers' Compensation Board Scale for OA as well as the symptom score of the SGRQ. All combinations of scores between the continuous measures yielded significant medium to high correlations (Table 2).

Correlation between AQLQ and measures of psychological distress

We then calculated correlation coefficients for the different AQLQ(S) scores with the PSI total and subscale scores. All combinations of scores

between the continuous measures yielded significant medium to high correlations, which can be seen in Table 2. The highest correlation was found between the PSI anxiety subscale score and the AQLQ(S) total score and most of the AQLQ(S) subscale scores.

We then investigated the diagnostic properties of the AQLQ(S) emotion subscale for the detection of clinically significant levels of psychological distress according to the anxiety and depression subscales of the PSI. The highest Youden index of 0.53 was obtained when choosing less than 5.1 points as the cut-off for the diagnosis of clinically significant anxiety according to the PSI (Figure 1). Fifteen individuals were misclassified: Ten individuals had AQLQ(S) scores greater than 5.1 points but were classified as having scores greater than 20 points on the PSI anxiety subscale, whereas 5 individuals had scores than 5.1 points on the AQLQ(S) emotion subscale but had scores less than 20 on the PSI anxiety subscale (Figure 2). By using this cut-off sensitivity was 72%, specificity 79%, positive predictive value 84% and negative predictive value 66% for the diagnosis of clinically significant anxiety symptoms according to the PSI. The highest Youden index of 0.63 was obtained when choosing less than 5.1 points as the cut-off for the diagnosis of clinically significant depressive symptoms (Figure 1). Eleven individuals were misclassified: Six individuals had AQLQ(S) scores greater than 5.1 points but were classified as having scores greater than 20 points on the PSI depression subscale, whereas 5 individuals had scores less than 5.1 points in the AQLQ(S) emotion subscale but had scores less than 20 points on the PSI

depression subscale (Figure 2). By using this cut-off sensitivity was 81%, specificity 82%, positive predictive value 84% and negative predictive value 79% for the diagnosis of clinically significant depressive symptoms according to the PSI.

When performing linear regression on the PSI anxiety subscale score as the dependent variable, the questions “feeling concerned about having asthma” and “feeling afraid of getting out of breath” were significantly associated (ß=-0.222 S.E. 0.106, p=0.041 and ß=-0.220, S.E. 0.104, R2=0.040). The question “feeling afraid of getting out of breath” was associated with the PSI depression subscale score and the PSI total score (ß=-0.332 S.E. 0.084, p<0.001, R2=0.231and ß=-0.392, S.E. 0.078, R2=0.313, respectively).

Correlation between AQLQ and measures of psychiatric disorders

We calculated point bi-serial correlations with individuals having an anxiety disorder, mood disorder, or any psychiatric disorder according to the PRIME-MD. Having any mood or any psychiatric disorder showed significant correlations in the medium range for all the AQLQ(S) subscale scores and the AQLQ(S) total score. There was a small point-biserial correlation between having anxiety disorder and the AQLQ(S) emotional function subscale score, but not with the AQLQ(S) total score.

For classifying patients with any psychiatric disorder according to the PRIME-MD, a cut-off of less than 4.7 points in the AQLQ(S) emotion subscale

misclassified 17/60 individuals: Six individuals had AQLQ(S) scores of greater or equal 4.7 points but were classified as having at least one psychiatric disorder, whereas 11 individuals had scores less than 4.7 points but were classified as not having a psychiatric disorder according the PRIME-MD (sensitivity 71%, specificity 72%, positive predictive value 58% and negative predictive value 82%, area under the curve 0.736 (95% CI 0.609-0.863; data not illustrated)). When classifying patients with any psychiatric disorder according the PRIME-MD, 4 out of 21 individuals had scores of ≤20 points on the PSI anxiety subscale and/or AQLQ(S) scores of ≥5.1 on the emotion subscale. Five out of 21 individuals with a psychiatric disorder had scores of ≤20 points on the PSI depression subscale and/or had AQLQ(S) scores of ≥5.1 on the emotion subscale (Figures 2a and 2b).

After conducting stepwise logistic regression with any anxiety disorder according PRIME-MD as dependent variable, the question “feeling concerned about the need to use medication” was the only one with a marginal association (ß=0.346, S.E. 0.178, p=0.052, Cox&Snell R2: 0.062). When any mood disorder and any psychiatric disorder were used as dependent variables, the question “feeling afraid of getting out of breath” showed significant association with both (any mood disorder= ß=0.456, S.E. 0.165, p=0.006, Cox&Snell R2: 0.137; any psychiatric disorder = ß=0.508, S.E. 0.169, p=0.003, Cox&Snell R2: 0.166).

Discussion

We found high correlations between impaired asthma-specific quality of life and standard measures of psychological distress, and moderate correlations between impaired asthma-specific quality of life and psychiatric morbidity (i.e., mood and anxiety disorders) in individuals with OA. A cut-off value of <5.1 on the AQLQ(S)'s emotion subscale could reliably identify individuals with clinically significant levels of depressive and/or anxiety symptoms who need further evaluation by an validated psychiatric interview.

There is limited evidence about the association of psychological stress and asthma morbidity in individuals with OA [29]. When considering the available evidence about the impact of this stress on individuals with non-occupational asthma, we can imagine that an additional psychological burden is associated with OA. This is in accordance with past findings where subjects with OA had slightly but significantly higher impairment in asthma-specific quality of life than those with non-occupational asthma, even when controlling for asthma severity [30]. In a study of asthmatics affiliated with a health maintenance organization in the USA, patients with work exacerbated of asthma had lower quality of life measured according to the mood disturbance, social disruptions, and health concerns subscales of the Mark's Asthma Quality of Life questionnaire, compared to those individuals with no work exacerbated asthma [31].

Various and probably many unknown factors contribute to impairment of quality of life in individuals with asthma. Malo and co-workers have reported a weak but significant correlation between the original AQLQ with FEV1, bronchial responsiveness, and asthma severity in a more extensive sample of individuals with occupational and non-occupational asthma [30]. The AQLQ(S) used in our study and the original AQLQ questionnaires distinguish themselves on one point: in the AQLQ(S)'s five generic activities (strenuous exercise, moderate exercise, work-related activities, social activities, and sleep) replaced specific activities that could be chosen by the patient in the original questionnaire [6]. We could reproduce these findings and could find a larger correlation of the AQLQ(S) subscales and total score with the objective asthma severity score. We also found a large correlation between the symptom domain of a widely used quality of life questionnaire in chronic obstructive lung disease – the SGRQ, which provides support for quality of life being related to factors other than objective markers of disease severity.

It is currently unknown how treatment of psychological distress or psychiatric morbidity (either using psychotherapy or pharmacotherapy) might affect asthma and psychosocial outcomes in individuals with OA. Disease management programs for major depressive disorders have been shown to be beneficial in reducing the severity of the depression, maintaining employment, increasing short term adherence to medication and improving the individuals quality of life while being cost-effective [32]. It a recent

systematic review, Lerner and Henke have shown that individuals with depression have higher unemployment rates, more absenteeism and lower at-work performance than individuals without depression [33]. When on medical leave, individuals with poor mental health are at risk for prolonged work absence [34]. Co-morbid psychiatric disorders are one of the reasons for the adverse socioeconomic outcomes in regards of unemployment and income loss. As these disorders can influence the individual's adherence to medication, lifestyle behaviors such as smoking and managing environmental asthma triggers, it could at least partially explain the persistent symptomatology and bronchial hyperresponsiveness in many individuals with OA seen even years after termination of the exposure to a sensitizing agent [35, 36].

We found medium to large correlations between the individual AQLQ(S) and the PSI. In point-biserial correlations between AQLQ(S) and PRIME-MD outcomes such as having psychiatric disorder the correlations were in the range small to medium. In a population sample in Australia, major depression according to the PRIME-MD was associated with dyspnoea, wakening at night and morning symptoms in asthmatics and these symptoms were shown to have the greatest impact on decrease in quality of life scores in the SF-36 [37]. When using the Hospital Anxiety and Depression (HAD) scale, Rimington and co-workers found moderate correlation of the HAD depression subscale and a somewhat lower correlation of the HAD anxiety subscale with the AQLQ symptoms subscore in a sample of asthmatic

patients attending GP offices in the UK [38]. In that study, hardly any correlation of HAD anxiety and depression subscales on the one hand and lung function expressed as forced expiratory volume in one second (FEV1) or peak flow on the other hand could be demonstrated [38]. In contrast, Hommel and co-workers reported anxiety and depression to influence asthma specific quality of life measured with the Living with Asthma Questionnaire (LWAQ). When performing regression analysis, they demonstrated that anxiety had an independent main effect on LWAQ when the model was controlled for depression [39]. The impact of concomitant depression and anxiety seems to be even more deleterious for health-related quality in life in individuals with chronic obstructive pulmonary disease [40].

The AQLQ(S) has been used in a large variety of clinical therapeutic trials and many cross-sectional studies on patients with OA. Measuring quality of life with the AQLQ(S) allows us to determine the impact of asthma on respiratory symptoms, emotional function and activity limitation, as well as environmental stimuli. These factors are important to acknowledge in clinical practice when assessing a patient with asthma. In our sample of individuals with OA who have been removed from exposure to the sensitizing agent, using a cut-off point of 5.1 in the emotional function subscale most reliably distinguishes individuals with significant psychological distress, whereas a cut-off of 4.7 can be used to identify individuals who are at risk of relevant psychiatric disorder according to the PRIME-MD evaluation. It is not the intention of the authors to suggest that the evaluation of patients with the

AQLQ(S) emotional subscale can replace a structured diagnostic interview by a psychiatrist – which is considered to be the gold standard - for the diagnosis of psychiatric diseases. Questionnaires such as the Hospital Anxiety and Depression Scale (HADS) have been shown to have a sensitivity of 66-78% and specificity of 83-97% for the diagnosis of either depression or anxiety disorders in a general practice setting [41]. Therefore even administration of tools specifically designed to screen for psychiatric disorders would not allow making an accurate diagnosis and starting treatment without performing a structured psychiatric interview. The advantage of using the AQLQ(S) questionnaire is that it is widely available and regularly used in clinical practice and trials. It can therefore be used as a screening test. Considering the results of the emotional subscale will not only allow to measure the impact of asthma on quality of life but also to identify some individuals in whom a more extensive investigation such as a structured psychiatric interview is warranted. The diagnostic performance of the test using a cut-off of <5.1 in the emotional subscale score of the AQLQ(S) is modest for identification of clinically important psychological distress according to the PSI. But the performance is less for the diagnosis of current psychiatric disorders according to the PRIME-MD which relies on the diagnostic criteria for depressive and anxiety disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DSM-IV. In fact the positive predictive value for the diagnosis of current psychiatric disease by using a cut-off of 4.7 is close to the predictive value of flipping a coin and would even be lower

when this test would be performed in a population with a lower prevalence of psychiatric disorders. There is very limited data suggesting that anxiety and depression are more common in workers in whom the asthma is related to the workplace [42]. In our study all individuals were compensated for OA and one could expect that the prevalence of mood and anxiety disorders is more prevalent in this population than in most other populations of asthmatics. However there is currently no data available to conclude that the prevalence of psychiatric disorders is lower in individuals with uncompensated OA or in individuals with work-exacerbated asthma. Further studies are needed to compare the correlation of psychiatric disorders and psychological distress with asthma specific quality of life measures, such as the AQLQ(S), in individuals with OA, work-exacerbated asthma and asthma that is unrelated to the workplace. [41]

The AQLQ(S) emotional function subscale respondents report on different aspects that have been grouped in this domain by the developers of this questionnaire in which the items relate to three broad dimensions (concerns, anger and anxiety). When considering individual questions of this domain, the one about feeling afraid of getting out of breath was significantly associated with the PSI depression subdomain and PRIME-MD mood disorder whereas the questions about feeling concern about having asthma and about the need to use medication were significantly associated with PSI anxiety levels and PRIME-MD anxiety disorders respectively. Since our analysis was descriptive, we do not suggest to reduce items that have not

shown significant correlation with psychologic distress or psychiatric disorders from the emotions subdomain of the AQLQ(S) questionnaire.

Whereas the PSI is a continuous measure that provides information about the number and severity of psychological symptoms, PRIME-MD diagnoses are categorical: individuals are classified as having a particular disorder or not based on having fulfilled a defined number of diagnostic criteria. Therefore, the severity of psychiatric disorders as measured by the PRIME-MD cannot be quantified[43]. Clinically, anxiety and depressive symptoms (and disorders) overlap significantly, so it can sometimes be difficult to determine if these disorders are separate entities or different manifestations of the same disorder [39]. Due to the limited number of individuals with OA included in our study, we were not able to examine associations between AQLQ(S) scores and individual mood and anxiety disorders (e.g. panic disorder, generalized anxiety disorder). To demonstrate these associations, studies with larger samples of individuals with OA are needed. Further our sample consisted of manly male workers with OA and therefore one must be cautious when extrapolating our findings to a population of female workers as the prevalence of the different forms of psychiatric disorders might be different [9].

Our study does not allow us to determine the relation of causation. We did not have information available about psychological distress or any psychiatric disorder prior to the development of OA or at the time the diagnosis of OA was made. Furthermore, we did not gather information about

concurrent or past behavioural or medical therapy for psychiatric disorders in each individual. To our knowledge, the prevalence of psychiatric disorders at the time of diagnosis of OA and its devolution after removal from the causing agent or workplace is currently unknown and thus other studies are needed to investigate these factors in prospective investigations. It is unclear how interventions specifically targeted to decrease psychological distress or psychiatric disorders change the natural course of both conditions OA and concurrent mental disorders.

An important strength of the present study is that extensive objective assessments including spirometry, measurement of nonspecific bronchial hyperreactivity, and specific inhalation testing were performed in all individuals, the latter of which is considered the reference standard for a diagnosis of OA [44, 45].

Conclusions:

Our study suggests that it is important to consider concomitant psychological distress and psychiatric morbidity in individuals with OA, even when their exposure to the causing allergen has ended. By performing disease-specific quality of life assessment with the AQLQ(S), individuals with significant psychological distress or psychiatric disorder could be identified and more elaborative and conclusive investigations and if necessary treatment be offered.

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Table 1: Description of Quality of Life, Psychological Distress and Psychiatric Disorders

	Frequency (n (%))	Score (median (Q1;Q3))
Juniper AQLQ(S)		
Symptoms		4.5 (3.5;6.0)
Activity limitations		4.6 (3.3;5.7)
Emotional function		5.0 (3.6;6.6)
Exposure to environmental stimuli		4.8 (3.3;5.8)
Total		4.6 (3.6;5.9)
SGRQ Asthma Symptom Score (%)		45 (32;71)
Psychological distress	(PSI score >20)	
Depression	32 (53)	23.0 (10.0;33.0)
Anxiety	36 (60)	24.0 (12.8;39.0)
Anger	30 (50)	19.0 (8.0;33.0)
Cognitive disturbance	31 (52)	24.5 (8.0;39.8)
Total	34 (57)	24.5 (10.8;37.8)
Prime-MD		
Any psychiatric disorder	21 (35)	
Any mood disorder	19 (32)	
- Major depression	8 (13)	
- Dysthymia	3 (5)	
- Minor depression	11 (18)	
Any anxiety disorder	9 (15)	
- Panic disorder	1 (2)	
- Generalized anxiety	1 (2)	
- Other anxiety disorder	7 (8)	

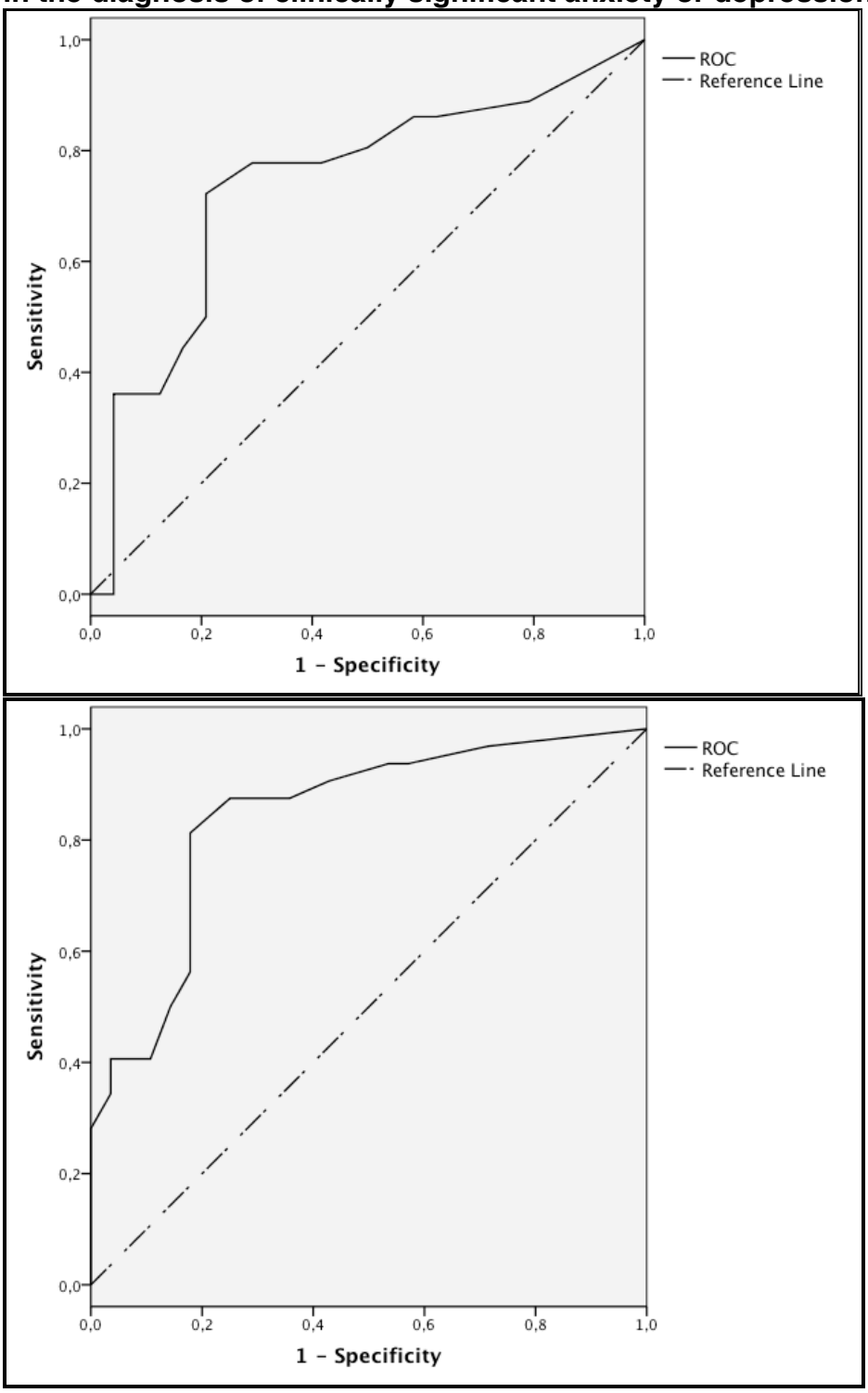
Legend: AQLQ(S)=Standardized version of the Juniper Asthma Quality of Life Questionnaire; SGRQ : St. George Respiratory Questionnaire; PSI=Psychiatric Symptom Index, PRIME-MD= Primary Care Evaluation of Mental Disorders questionnaire

Table 2: Correlation of the Asthma Quality of Life Questionnaire by Juniper with Psychiatric Symptom Index, the PRIME-MD evaluation, the St. George Respiratory Questionnaire and the Asthma Severity Compound Score

	AQLQ Symptoms	AQLQ Activity limitations	AQLQ Emotional functions	AQLQ Exposure to environmental stimuli	AQLQ Total Score
Asthma Severity Compound Score	-0.582*	-0.611*	-0.627*	-0.561*	-0.650*
SGRQ Symptom Score	-.686*	-.650*	-.610*	-.574*	-.693*
PSI Anxiety	-.623*	-.648*	-.609*	-.616*	-.664*
PSI Anger	-.331*	-.376*	-.344*	-.404*	-.367*
PSI Depression	-.558*	-.611*	-.507*	-.639*	-.605*
PSI Cognitive disturbance	-.426*	-.401*	-.373*	-.432*	-.419*
PSI Total Score	-.583*	-.613*	-.553*	-.622*	-.619*
PRIME-MD Anxiety	0.254	0.163	0.261§	0.213	0.236
PRIME-MD Mood	0.352*	0.381*	0.334*	0.402*	0.393*
PRIME-MD Psychiatric disorder	0.396*	0.361*	0.389*	0.427*	0.417*

Legend: * $p<0.01$, § $p<0.05$

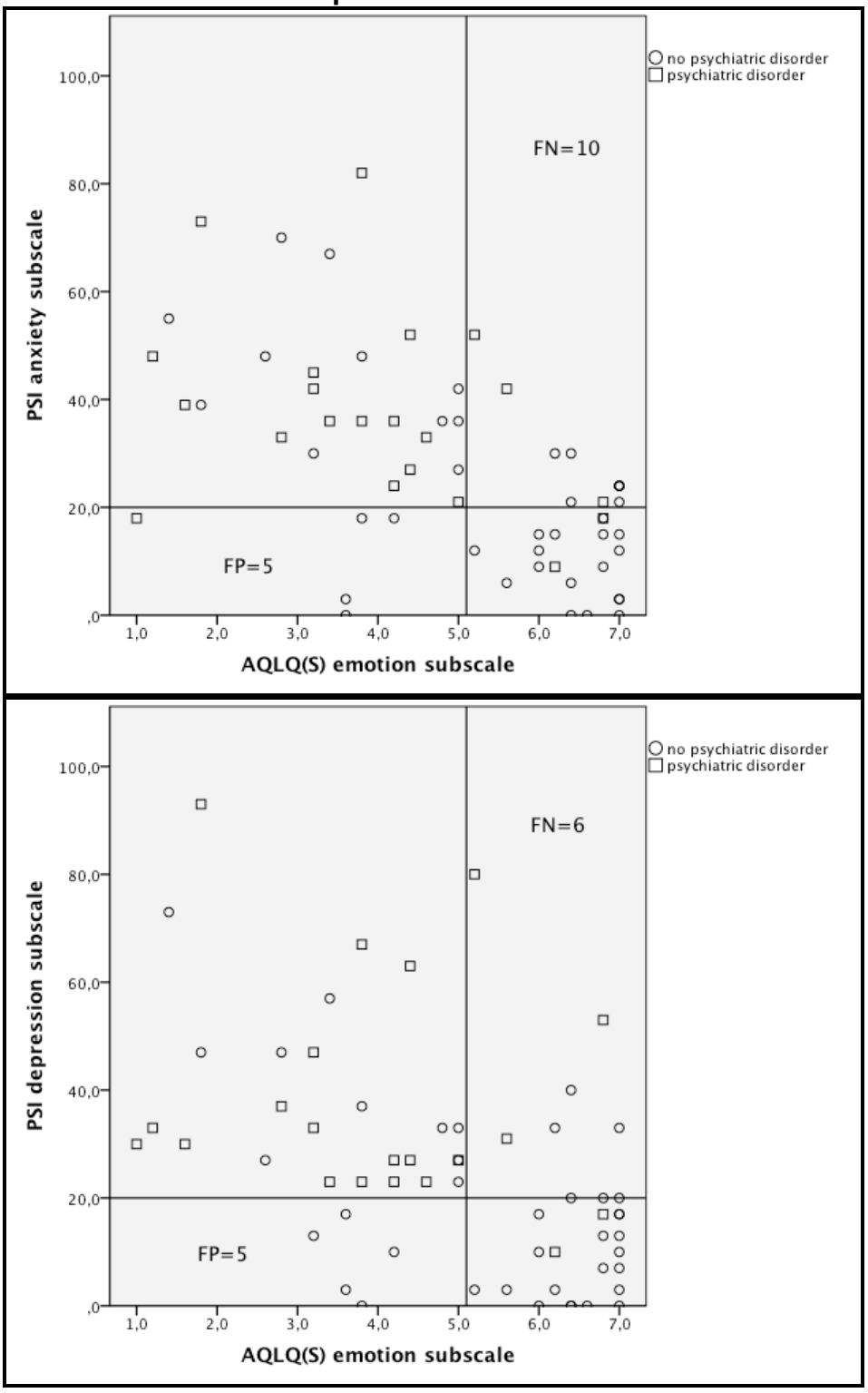
Figure 1. Receiver operator curves for the AQLQ(S) emotion subscore in the diagnosis of clinically significant anxiety or depression.



Legend: ROC=Receiver operator characteristic curve. ROC for AQLQ(S) emotion subscore in the diagnosis of clinically significant anxiety (>20 points in the PSI anxiety subscore; AUC 0.740 (95%CI 0.608-0.872)). ROC for AQLQ(S) emotion subscore in the diagnosis of clinically significant

depression (>20 points in the PSI depression subscore; AUC 0.843 (95%CI 0.741-0.945))

Figure 2. Scatterplots showing the correlation of the AQLQ(S) emotion with the PSI anxiety subscale and the correlation of the AQLQ(S) emotion with the PSI depression subscale.



Legend: PSI=Psychiatric symptom index; AQLQ(S)=Asthma Quality of Life Questionnaire; FP=false-positive; FN=false-negative

3. Discussion

In this research, we were able to show that:

1. in the first contribution: Socio-economic factors are associated with asthma-specific health outcomes in individuals with OA in Quebec. Individuals who were older, with income of >$30,000 CAD$ and OA to HMW allergens, were able to remain longer in their workplace with symptoms before removal of exposure. Such a delay was associated with more respiratory symptoms, a higher risk of persistent bronchial hyperresponsiveness and higher direct costs for compensation.
2. in the second manuscript: About half of the study participants had clinically significant levels of psychological distress, with a correlation between psychological distress and clinical markers of OA. Some socio-economic factors present at diagnosis of OA were associated with quality of life, symptoms and psychological distress measures at re-evaluation independently of asthma severity. Being married was associated with worse asthma-specific quality of life and worse asthma symptoms in the SGRQ symptoms score. Low income and being employed for more than 5 years with the same employer at the time of diagnosis were associated with worse asthma symptoms. Being a labour union member at the time of diagnosis was associated with less psychological distress.

3. in the third part of our work, measuring asthma-specific quality of life in individuals with OA using the Juniper Asthma Quality of Life Questionnaire (AQLQ(S)) demonstrates high internal consistency, good construct validity when compared with other quality-of-life measures such as the symptom subdomain of the SGRQ and asthma severity parameters such as lung function, bronchial hyperreactivity and asthma medication use. Considering the results of the emotional subscale of the AQLQ(S) not only allows us to measure the impact of asthma on quality of life, but also helps to identify individuals with clinically significant psychological distress for whom a more extensive investigation, such as a structured psychiatric interview, is warranted.

In this general discussion, I will:

1. Present the strengths and limitations of our study

2. Extend the discussion of points raised in the discussion sections of the specific papers

3. Outline and emphasize the originality and the possibility for generalization of our results.

3.1. Strengths and limitations of this study

Strengths

Confirmation of diagnosis

For this project, we were able to recruit over 80% of individuals whose diagnosis of OA had been confirmed using objective measures, including the gold standard for the diagnosis of OA, i.e. specific inhalation testing. For all of our participants, the diagnosis of OA led to compensation from the Workers' Compensation Board of Quebec. This is extremely important, since in most studies in the field of OA the diagnosis is not confirmed by specific inhalation testing, and therefore the studies also include workers with work-exacerbated asthma, leading to misclassification of cases. There are very few countries for which a sample of subjects with OA confirmed by SIC would have been available for study. To our knowledge, in addition to Quebec, only Finland and Belgium use SIC, considered as the gold standard for confirming a diagnosis. These tests are mandatory in these countries to establish a diagnosis of OA for compensation agencies.

The study participants agreed to undergo extra testing in addition to the usual information requested by the Workers' Compensation Board. To ascertain DAP two years after diagnosis, the worker is interviewed by a

physician on current respiratory symptoms and medication use. He then undergoes evaluations using lung function tests and BPT with methacholine. Additional investigations, such as sputum induction, filling out study questionnaires, and a PRIME-MD evaluation, can easily take one to two hours in addition to the time already required for the compulsory investigations.

Characteristics of participants and non-participants

We were able to show that those who refused to participate had similar baseline characteristics such as gender, age, atopy status, smoking behaviour, lung function, types of causal agents for OA and time with symptoms prior to filing a claim with the Workers' Compensation Board. Similar to the statistics reported by the Workers' Compensation Board of Quebec, diisocyanates and flour were among the most frequent causes of OA in our study sample (483). It is therefore unlikely that significant selection bias affected the results when considering the population of individuals with compensated OA in Quebec/Canada.

The variety of functional and socioeconomic information obtained

In the field of OA, many other studies investigated their participants only by recording basic respiratory symptoms, lung function, AHR, and medication use. However, the impact of OA on an individual is far greater. Thus, the evaluation of these patients requires a multidimensional approach (410). We have attempted to characterize the type of inflammation present by investigating induced sputum. We have also added an extensive standardized evaluation of respiratory symptoms, such as the SGRQ and, equally importantly, an extensive assessment of quality of life and psychological outcomes.

Regarding quality of life, we used a disease-specific quality of life measure, the AQLQ(S) questionnaire developed by Juniper et al., which is surely the most widely disseminated quality of life questionnaire used in the field of asthma (460, 465). Because there is evidence that patients have increased levels of psychological distress, which mainly derives from studies that investigated individuals with asthma unrelated to the workplace, we used the PSI to measure psychological distress levels. To diagnose the most frequent mental disorders in primary care, we used the PRIME-MD evaluation.

Previous studies have paid little attention to socioeconomic factors and OA

As discussed in the Introduction section of this thesis, various socio-economic factors are associated with the development, course, and outcome of many medical conditions. With regard to OA, previous studies have focused on mainly two issues: employment status and loss of income (65, 160, 177, 178, 180, 183, 396, 398-403, 405, 406, 441, 454). Other important factors were often not considered. These included being born either in Canada or abroad, salary at the time of onset of OA, employment status at the time of re-assessment, marital status, having dependent children to support, or specific factors at work, such as company size, number of years employed, or being unionized. Additionally, we could obtain individual objective data from the Workers' Compensation Board records.

Referring to these data provided information on important issues that were not previously analyzed: 1. if the individual was assisted with finding a new job, had occupational counseling, or was granted support for re-education; 2. precise information on the costs that the Workers' Compensation Board had to spend on IRR and DAP for each participant. The latter information was unique and has not been previously published.

Limitations

Sample size

The relatively small number of individuals included in our analysis (N = 60) is an important limitation. Small sample sizes increase the risk that the sample is not representative of the population one wishes to study and can lead to erroneous inferences. A small sample size increases the risk of Type I and II errors: A Type I error occurs if we reject a null hypothesis that is actually true for the population, whereas a Type II error occurs if we fail to reject a null hypothesis that is actually not true for the population (484). Non-participants might differ from participants regarding various asthma-related and socio-economic outcomes.

One can hypothesize that individuals who have lower socio-economic status, who are migrants, and who have difficulty understanding and speaking the local language are more reluctant to participate in this kind of study. Yet, we had a relatively small proportion (20%) of non-participants. Moreover, we showed that the characteristics of non-participants were similar to those of participants.

To increase the sample size, one might extend the inclusion criteria or the time during which individuals can be included in the study. In our case, including workers with OA examined by other Workers' Compensation Board

committees (B committee of Montreal, Sherbrooke and Quebec City) might have been a possibility. According to our estimates, including these workers might have increased the sample size by approximately one third. However, performing sputum induction and analyzing these specimens require specialized equipment and experience and are not routinely available in hospitals where the Workers' Compensation Board committees meet and examine claimants. Indeed, examination of induced sputum is not routinely performed in Sherbrooke or during investigations by the other Workers' Compensation Board committee in Montreal (Montreal Chest Hospital) and Quebec City (Hôpital Laval).

In addition, despite the fact that the PRIME-MD was designed for use in general practice, the people who administer this questionnaire should have acquired some experience with this instrument before using it for a research study. To limit the inter-observer variability, we decided that all of the additional tests required for this study should be performed by members of our research team at the Sacré-Coeur Hospital. Because the compulsory investigations already take half a day and due to distance constraints, we thought that only a few individuals with OA who were investigated in Sherbrooke and Quebec would have come to Montreal to participate in our study if they were offered the chance to participate. Finally, as alluded to before, we did not want to recruit participants in other study centers outside of the province of Quebec because the criteria and tests used for diagnosing OA

are less stringent and the eligibility criteria for compensation differ substantially.

For this investigation, we studied workers who had made claims for compensation for OA to the Quebec CSST between 2004 and 2006. These individuals were recruited for this study at the time of their re-evaluations for DAP about two and a half years after their diagnoses. Extending the inclusion criteria and including individuals who made claims after 2006 was not possible, as this would have precluded analyzing the data obtained during the candidate's studies in Montreal. Extending the criteria to include individuals who made claims before 2004 would have required contacting these individuals and repeating all measures that were done during the past investigation for the settlement of DAP. This "excess" information would not have been in synchrony with the routine information obtained at the time of assessment by a Workers' Compensation Board committee.

Recall bias

In immunological asthma, the appearance of respiratory symptoms is often gradual, and recall bias is possible for the time of appearance of symptoms and therefore the interval a subject reported being symptomatic in the workplace. We tried to minimize that bias by consulting the most reliable

documented source of information, the official Workers' Compensation Board report.

Study design

The study design used was partly longitudinal (for clinical and functional data) and partly cross-sectional (for other outcomes). We did not collect information about disease-specific quality of life and psychological distress, and psychiatric morbidity (mood and anxiety disorders) at the time of diagnosis, and therefore have no information about the interaction of OA with psychological distress/psychiatric disorders and the progression of both conditions. Furthermore, we did not systematically collect information on medication used in treating psychiatric disorders. It is possible that some individuals were treated successfully for psychiatric disorders, and that the results of our study underestimate impairment in quality of life and psychological distress in individuals with OA. However, we assume that the number of individuals with treatment for psychiatric disorders in the study sample was small. Furthermore, we figure out that information about current or past psychotherapy and medical treatment for psychiatric disorders was not recorded with the same precision and details as treatment for asthma, since the individuals were claiming compensation for a pulmonary disease. To our knowledge, the prevalence of psychiatric disorders at the time of

diagnosis of OA and its devolution after removal from the causing agent or workplace is currently unknown; further studies are therefore needed to investigate these factors in prospective investigations.

Due to the limited number of workers with OA included in our study, we were not able to examine associations between AQLQ(S) scores and individual mood and anxiety disorders (e.g. panic disorder, generalized anxiety disorder). To demonstrate these associations, studies with larger samples of individuals with OA are needed. Furthermore, our sample consisted of mainly male workers with OA; we must therefore be cautious when extrapolating our findings to a population of female workers, as the prevalence of different forms of psychiatric disorders may be different (379).

3.2. Interpretation of study findings

Some of the issues discussed in the following section were included in the discussion sections of specific manuscripts, although not sufficiently extensively, which justifies the following discussion.

Manuscript no. 1

Eligibility for compensation for OA as well as compensation processes differ depending on the country or even province. Individuals with OA may therefore choose not to file a claim with the Workers' Compensation Board and instead remain exposed to the causing allergen in the workplace (397). Even in Quebec, where an effective compensation system is in place, a study by Provencher et al. showed that there were approximately three times more individuals identified by OA specialists as having a high probability of OA per year than individuals whose claims were actually compensated each year by the Workers' Compensation Board (453). There are sparse data on characteristics and disease outcomes for individuals with OA who choose not to file a claim with the Workers' Compensation Board. It seems that the most frequent causal agents are no different in individuals with suspected OA than in those whose OA is accepted by the Workers' Compensation Board. In the study by Provencher and co-workers, about 15% of reported cases of OA

were not covered by the Workers' Compensation Board and were therefore not eligible for compensation. This was especially the case for workers with agricultural activities and those with suspected OA where farm animals were suspected of causing asthma (453).

There are several reasons for which claims for OA may not be reported to the compensation agencies. Many compensation agencies in Canada have shifted to so-called "experience-rating" of the premiums that need to be paid by employers, meaning that premiums in subsequent years will be higher for employers who file more claims (337). The advantage of such an approach is that employers are interested in improving workplace safety, as it may lead to a lower number of claims and therefore lower costs. However, employers may "encourage" their workers not to report injuries or occupational diseases. Some employers may even pay premiums for those workers who do not call in sick and do not report workplace injuries. Further, it is possible that employers outsource unsafe work to smaller companies where workplace health and safety issues may be taken less seriously. Such workplaces may not accept trade unions, or they may hire contract employees such as seasonal workers on a temporary work permit who may not know that they are covered by the Workers' Compensation Board or may be reluctant to file a claim for fear of losing their work permit. Self-employed workers, who are frequently not covered by the Workers' Compensation Board, will therefore not file a claim if an occupational disease or injury occurs (337).

One of the original aims of this study was to investigate whether participants born outside Canada would take longer before filing a claim with the Workers' Compensation Board compared to individuals who were born in Canada, resulting in worse socio-economic and OA outcomes. However, the sample included only 9 (15%) individuals with migrant backgrounds. Probably due to the heterogeneous nature of major socio-economic factors in this migrant population, as well as the small sample size, the disease and socio-economic outcomes determined in this study did not differ according to immigration status.

As discussed in the Introduction of this thesis, higher income is in general associated with better health outcomes; this association was confirmed by Wilkins and co-workers for the Canadian setting (485). Absolute poverty usually refers to having less than an absolute minimum income level based on the costs of basic needs (486). In Canada, the definition of low income set by Statistics Canada is frequently used. However, the cut-off is set differently every year, so it is difficult to objectively select a minimum set of necessities for basic life (486). Quebec is the province with the highest proportion of individuals living on a low income (19%) compared to other provinces in Canada (the Canadian average is 16%) (486). We defined low income as having an income at the time of diagnosis that was less than 110% of the cut-off value for low income as defined by Statistics Canada. Even using that stricter definition, the Quebec average was below the national average. One explanation for this finding is that workers who are eligible for

compensation are more often skilled workers with somewhat higher salaries than unskilled workers who may work in part-time jobs or smaller companies and may work on temporary employment contracts.

Twenty-eight study participants, or 48% of the study population, were members of a labour union. Also, about two-thirds of the participants were employed by a company with more than 20 employees. In larger companies, workplace health and safety issues are usually taken more seriously, with safety training offered and formal operating procedures and rules laid down. The proportion of larger companies that host trade unions is higher (486). Further, there is a higher likelihood of inspections by government agencies or Workers' Compensation Board representatives in response to worker or union complaints about health and safety conditions (337). Also, it is far more difficult to relocate a worker with OA to stop ongoing exposure to the causal agent in a small company, where job opportunities are limited and the workers may all work in the same room. Small company size has been shown to be a risk factor for job change or unemployment in individuals with OA (399).

In the article published in the European Respiratory Journal, we showed that workers who are older, earn a higher salary and have asthma related to HMW allergens are exposed for a longer time with symptoms prior to removal from exposure. Our study was the first to investigate associations between socio-economic factors and this important prognostic factor.

Older workers generally earn higher salaries, are more likely to have dependent children and may encounter more problems in finding a new job. These factors may make subjects more reluctant to report to a medicolegal agency. Also, individuals with dependent children remain exposed for a longer time with symptoms prior to removal from exposure, as they may hesitate to claim compensation because they fear losing not only their job and income, but also their self-esteem and status as a provider for the family. Most of these arguments would also hold for married men.

We also found that subjects with an educational profile higher than the secondary level tended to be exposed for a longer time with symptoms prior to removal from exposure, which is different from findings published by other researchers. Low educational level has been identified as a risk factor for work-related asthma in the young population (406), for a delay until a diagnosis of OA is made (441) and as a predictor for unemployment after a diagnosis of OA (160, 399). However, when we controlled the analysis for other important covariates (sex, immigration and marital status, income, age, having dependent children to support), education, probably because of its association with income, was no longer significantly associated with the number of years of exposure with symptoms before removal from exposure.

In our study, higher income was associated with a longer exposure in the workplace with symptoms prior to removal from exposure. This is contrary to the findings of a study by Poonai and co-workers in Ontario/Canada, in which the time taken to obtain a diagnosis of OA was longer in subjects with a

low household income (441). This difference might be explained by the fact that the outcome of our study was slightly different. We measured the median exposure time with symptoms before removal from exposure, while in the study by Poonai, the mean duration of symptoms was determined before the final clinical diagnosis was made. However, in a later study by the same researchers, lower household income was no more related with time to diagnosis of OA (454). The time it takes to make a final diagnosis depends on many factors, such as awareness and the availability of information about OA to workers, employers and physicians, as well as access to specialized centres. Other important factors may include the severity of symptoms, the nature and extent of work exposure and the compensation that is offered. We explain the difference in our findings by the fact that the comprehensive system of management and compensation of OA in Quebec does not prevent workers with lower income from claiming compensation, but rather allows them to seek help and investigation without significant loss of income and with an opportunity to retrain into a new job at a similar or even higher salary. By contrast, workers with higher income and higher education are probably more hesitant to claim as they have more to lose in terms of income and retraining opportunities. Part-time workers may fear job loss or refusal of employment insurance eligibility, while workers in well-paid jobs face a possible loss of income or social status (42). OA is a condition that, according to the results of our study, may have more detrimental effects on workers with

higher socio-economic status, a situation that is the reverse of what is found for most health conditions.

Prolonged exposure of symptomatic workers in their workplace was associated with: 1) increased asthma severity at diagnosis and persistent bronchial hyperresponsiveness with the need for increased anti-asthma medication at re-evaluation, more than two-and-a-half years after cessation of exposure; and 2) higher direct costs for the medico-legal compensation agency.

Most follow-up studies of OA have consistently shown that the duration of exposure with symptoms was the principal determinant for the persistence of asthma after cessation of exposure (53, 173, 174). However, even after adjusting for asthma severity in our model, socio-economic factors (income and dependent children), as well as age and the nature of the agent, remained significantly associated with the length of time with symptoms prior to removal from exposure, which demonstrates that these factors play a significant role on their own. These findings are unique. They also show that socioeconomic factors, which have been largely neglected in previous studies to date, play a critical role in OA. Past studies failed to demonstrate that subjects with more severe asthma are more likely to be unemployed after diagnosis (160, 180, 399). However, none of these studies investigated direct costs to the medico-legal agency for compensation for lost income and functional impairment. In this respect, our study must also be considered as original because we could analyze precise information on costs for

compensation, which information was kindly provided to us by the Quebec Workers' Compensation Board.

In the multivariate analysis, higher age and remaining exposed in the workplace with symptoms for more than 12 months were associated with higher direct costs for compensation even after controlling for employment status. In a working population, indirect costs due to absenteeism and presenteeism related to asthma may even be higher than direct costs (362). Individuals with asthma have been shown to have lower levels of self-related work-effectiveness due to their condition (354, 357, 358), and it has been shown that in chronic conditions such as asthma, more work performance is lost from presenteeism than from absenteeism (487).

Manuscript no. 2

In the second article, published in the Journal of Occupational and Environmental Medicine, we were able to show that a high proportion of patients with OA have moderate impairment in disease-specific quality of life, elevated levels of psychological distress and a high prevalence of psychiatric (mood and anxiety) disorders two years after their initial diagnosis.

Despite the fact that most of the study participants were no longer working at the workplace that caused OA at the time of re-evaluation, participants had moderately impaired quality of life as measured with the

AQLQ(S). This is in line with past studies showing that more than 70% of subjects continue to have symptoms and use asthma medication despite having been removed from the workplace for more than two years (488). In workers with different allergic manifestations due to natural latex, Al-Otaibi and co-workers reported a decrease in disease-specific quality of life impairment with increasing time since the diagnosis was made and duration of symptoms (409).

There is limited evidence for the association of psychological stress and asthma morbidity in individuals with OA [29]. When considering the available evidence about the impact of this stress on individuals with non-OA, we can imagine that an additional psychological burden is associated with OA. This is in line with past findings showing that subjects with OA had slightly but significantly higher impairment in asthma-specific quality of life than those with non-OA, even after controlling for asthma severity (407). In a study of asthmatics affiliated with a health maintenance organization in the United States, patients with WEA had lower quality of life, as measured by the mood disturbance, social disruption and health concern subscales of the Sydney Asthma Quality of Life questionnaire, compared to those with no WEA (166).

In our study, between 35% and 47% of participants had clinically significant levels of psychological distress and 35% met criteria for one or more current mood or anxiety disorders according to the PRIME-MD. Without considering asthma severity, in non-OA patients seen in our hospital asthma

clinic, the prevalence of anxiety or mood disorder was comparable at 31% (379). In our study, all the subjects were compensated for OA; it would be reasonable to expect that the prevalence of mood and anxiety disorders is greater in this population than in most other populations of asthmatics. However, there are currently no data available that would lead us to conclude that the prevalence of psychiatric disorders is lower in individuals with uncompensated OA or in those with WEA. We are not aware of any other study that has determined the prevalence of psychiatric disease in a population of patients with OA, with the exception of the study by Yacoub et al. in our clinic population that reported 35% of OA patients having possible or probable anxiety disorder and 23% possible or probable dysthymia (410).

Our study shows that the principal factor associated with impact on quality of life and psychological outcomes is the severity of asthma. There are conflicting findings concerning the correlation between objective parameters of asthma severity and anxiety levels. Some studies show significant correlations between peak expiratory flow variability and self-reported anxiety in the Beck Anxiety Symptom Inventory (489), whereas other studies did not report any correlation between psychological distress and lung function (384, 490). Depression does not appear to be associated with objective measures of asthma severity. In a pilot study, asthmatics with a history of mood disorders seemed to have less severe airway obstruction and less severe asthma (491). Elevated depression scores were associated with perceived asthma severity and risk, but not with intubation history, number of

hospitalizations or asthma medication history (492). Interestingly, we found a correlation between the proportion of sputum eosinophils and mood disorders. It has been shown that eosinophilic airway inflammation is more pronounced following antigen challenge during final examinations among college students and is associated with higher self-reported psychological stress (377).

While the PSI questionnaire provides a continuous measure of the number and severity of psychological symptoms, PRIME-MD diagnoses are categorical: individuals are classified by the presence or absence of a particular disorder based on the presence or absence of a defined number of diagnostic criteria according to the DSM-IV. Therefore, the severity of psychiatric disorders as measured by the PRIME-MD cannot be quantified (493). Clinically, anxiety and depressive symptoms (and disorders) overlap significantly, so it can sometimes be difficult to determine whether these disorders are separate entities or different manifestations of the same disorder (489).

In this study, for the first time, we identified risk factors that were present at the time of OA diagnosis and were associated with decreased disease-specific quality of life, increased psychological distress, and a diagnosis of psychiatric disease later in time when the individuals were re-evaluated to set the DAP.

In the multivariate linear regression a priori model, the asthma severity compound score was the only factor significantly associated with the

AQLQ(S) total score. Other covariates, such as sex, age, current employment status and the time since diagnosis of OA and consequent removal from the causal allergen, all factors found significant at a $p<0.2$ level in the univariate analysis, were not significantly associated with disease-specific quality of life.

Being married at the time of diagnosis was associated with more severe quality of life impairment, measured as the total AQLQ(S) and in the SGRQ symptom score. In general, married individuals often have better health status than their unmarried counterparts (494). However, the contrary is also true: very close relationships such as an unhappy marriage may have a negative effect on mental health (265) whereas singles seem to have better health outcomes when compared to those in low-quality marriages, as shown in hypertension research studies (268). Job loss due to OA and resulting income and social status losses may influence quality of life; this could be even more important in individuals who have a dependent spouse.

Participants who were members of labour unions at the time of diagnosis had lower psychological distress levels at re-evaluation. The mission of a labour union is to defend the economic, professional and social interests of workers, especially in the workplace. Workers may thereby benefit from labour union assistance in terms of complying with the requirements of filing a claim for compensation. Moreover, they may receive support during the rehabilitation phase (e.g. in finding a new workplace, exploring possibilities for re-training programs, receiving legal support, etc.), which

would explain lower levels of psychological distress at the time of re-evaluation.

Although employment status at the time of re-evaluation was significantly related to quality of life and psychological outcomes in the univariate analysis, this was not the case in the multivariate analysis, in contrast to asthma severity, which was significantly correlated to quality of life and psychological outcomes in both the univariate and multivariate analyses. In workers with asthma due to diisocyanates, quality of life and perception of asthma symptoms were related to employment status and asthma control even after controlling for various confounders such as age, smoking, sex and atopy status (403).

Another important finding that has previously never been investigated in the field of OA was the association between direct costs and psychological outcomes. We found small to medium significant correlations between quality of life measures and the anger subscale of the PSI questionnaire and compensation costs. The correlation was strongest with the CFI compensation component, which reflects disease severity. As many factors influence CLI costs (age and income at the time of diagnosis being the most important factors), it is not surprising that we could not find any association between quality of life, psychological distress and costs for CLI.

Manuscript no. 3

In the third article, published in Health and Quality of Life Outcomes, we found high correlations between impaired asthma-specific quality of life and standard measures of psychological distress, and moderate correlations between impaired asthma-specific quality of life and psychiatric morbidity (i.e. mood and anxiety disorders). We also found that a cut-off value of <5.1 on the AQLQ(S)'s emotion subscale could reliably identify individuals with clinically significant levels of depressive and/or anxiety symptoms who require further evaluation by a validated psychiatric interview. To our knowledge, the use of a disease-specific quality of life measure like the AQLQ(S) to identify individuals with a high probability of psychiatric disease has not been previously published and, thus, is unique. In addition, information on internal consistency and construct validity of the AQLQ(S) in a study population of individuals with OA have not been previously reported. Therefore, our study contributes to the on-going validation of this instrument.

Various and probably many unknown factors contribute to impairment of quality of life in individuals with asthma. Malo and co-workers have reported a weak but significant correlation between the original AQLQ with FEV1, bronchial responsiveness and asthma severity in a more extensive sample of individuals with occupational and non-OA (407). The AQLQ(S) used in our study and the original AQLQ questionnaires differ on one point: in the AQLQ(S), five generic activities (strenuous exercise, moderate exercise, work-related activities, social activities and sleep) replaced specific activities

that could be chosen by the patient in the original questionnaire (465). We were able to reproduce these findings and find a larger correlation of the AQLQ(S) subscales and total score with the objective asthma severity score. We also found a high correlation between the symptom domain of a widely used quality of life questionnaire in chronic obstructive lung disease – the St. George's Respiratory Questionnaire, which provides support for quality of life being related to factors other than objective markers of disease severity.

We found medium-to-high correlations between the individual AQLQ(S) and the PSI. In point-biserial correlations between AQLQ(S) and PRIME-MD outcomes such as having a psychiatric disorder, the correlations were in the range of small to medium. In a population sample in Australia, major depression according to the PRIME-MD was associated with dyspnoea, waking at night and morning symptoms in asthmatics, and these symptoms were shown to have the greatest impact on decrease in quality of life scores in the SF-36 (383). When using the Hospital Anxiety and Depression (HAD) scale, Rimington and co-workers found a moderate correlation of the HAD depression subscale and a somewhat lower correlation of the HAD anxiety subscale on the one hand with the AQLQ symptoms subscore on the other hand in a sample of asthmatic patients attending primary care offices in the UK (490). In that study, hardly any correlation between HAD anxiety and depression subscales on the one hand and lung function expressed as forced expiratory volume in one second (FEV1) or peak flow on the other hand could be demonstrated (490). By contrast, Hommel and co-workers reported that

anxiety and depression influenced asthma-specific quality of life measured with the Living with Asthma Questionnaire (LWAQ). When performing regression analysis, these authors demonstrated that anxiety had an independent main effect on LWAQ when the model was controlled for depression (489).

Given the frequent co-occurrence of psychological distress or psychiatric morbidity in individuals with OA, it would be of great help to have tools available that are easy to administer and can be used to identify individuals at risk for these conditions. The AQLQ(S) has been used in a large variety of clinical therapeutic trials and many cross-sectional studies carried out in patients with OA. Measuring quality of life with the AQLQ(S) allows us to determine the impact of asthma on respiratory symptoms, emotional function, activity limitation as well as environmental stimuli. These factors are also important to acknowledge in clinical practice when assessing a patient with asthma. In our sample of individuals with OA who have been removed from exposure to the sensitizing agent, using a cut-off point of 5.1 in the emotional function subscale most reliably distinguishes individuals with significant psychological distress, whereas a cut-off of 4.7 can be used to identify individuals who are at risk of relevant psychiatric disorders according to the PRIME-MD evaluation. We do not suggest that the evaluation of patients with the AQLQ(S) emotional subscale can replace a structured diagnostic interview by a psychiatrist – which is considered to be the gold standard – for the diagnosis of psychiatric diseases. Questionnaires such as

the HAD have been shown to have a sensitivity of 66-78% and specificity of 83-97% for the diagnosis of either depression or anxiety disorders in a general practice setting (476). Therefore, even the administration of tools specifically designed to screen for psychiatric disorders would not make it possible to arrive at an accurate diagnosis and start treatment without performing a structured psychiatric interview. The advantage of using the AQLQ(S) questionnaire is that it is widely available and regularly used in clinical practice and trials. It could therefore be used as a screening test: Considering the results of the emotional subscale would not only enable us to measure the impact of asthma on quality of life, but also help to identify some individuals for whom a more extensive investigation, such as a structured psychiatric interview, is warranted. The diagnostic performance of the test using a cut-off of <5.1 in the emotional subscale score of the AQLQ(S) is a modest means of identifying clinically important psychological distress according to the PSI. However, performance is lower for the diagnosis of current psychiatric disorders according to the PRIME-MD, which relies on, diagnostic criteria for depressive and anxiety disorders as based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DSM-IV. In fact, the positive predictive value for the diagnosis of current psychiatric disease using a cut-off of 4.7 is close to the predictive value of flipping a coin, and would even be lower when this test is performed in a population with a lower prevalence of psychiatric disorders.

Importantly, we must mention that it is not known whether interventions specifically targeted to decrease psychological distress or psychiatric disorders change the natural course of both conditions, that is OA and concurrent mental disorders. It is also currently not known whether treatment of psychological distress or psychiatric morbidity (using either psychotherapy or pharmacotherapy) might affect asthma and psychosocial outcomes in individuals with OA. Disease management programs for major depressive disorders have been shown to be beneficial in reducing the severity of depression, maintaining employment, increasing short-term adherence to medication and improving the individual's quality of life while being cost-effective (495). There is limited evidence from a randomized controlled trial in individuals with mild and moderate asthma suggesting that cognitive behavioral therapy is associated with improvements in mood, lung function, medication adherence, and asthma-related quality of life (496).

In a recent systematic review, Lerner and Henke have shown that individuals with depression have higher unemployment rates, more absenteeism and lower at-work performance than individuals without depression (497). When on medical leave, individuals with poor mental health are at risk for prolonged work absence (498). Co-morbid psychiatric disorders are one of the reasons for adverse socio-economic outcomes in terms of unemployment and income loss. Since these disorders can influence the individual's adherence to medication, lifestyle behaviours such as smoking and managing environmental asthma triggers, this could at least partially

explain the persistent symptomatology and bronchial hyperresponsiveness in many individuals with OA seen even years after the end of exposure to a sensitizing agent (152, 499).

3.2.1. Originality of results

Only a few previous studies have investigated the associations between socio-economic factors and asthma-specific outcomes and only one pilot study has investigated psychiatric distress and the prevalence of mental disorders in individuals with OA.

- This is the first descriptive study that sought to characterize individuals with OA diagnosed by SIC by studying various important socio-economic factors and their associations with disease and cost outcomes.

- Despite the limited sample size, the high participation rate and the good characterizations of the study participants by the extensive investigations, including SIC, minimize the risks of significant bias and misclassifications.

- We have found intriguing results that were contrary to the study hypothesis. Indeed, the finding that having a higher revenue is associated with more

severe disease is highly original and contrary to what is almost consistently found for all types of diseases. These unexpected results should encourage other researchers who work in developed and lesser-developed countries to initiate similar studies.

- We were able to show for the first time that those individuals with symptoms who remain in the workplace for a shorter time not only have less severe asthma, but this shorter time interval is also associated with lower costs for compensation for the Workers' Compensation Board when compared with those individuals for whom this interval is longer.

- We showed that some socio-economic factors at the time of OA diagnosis were associated with worse quality of life and increased the psychiatric distress levels about two and a half years later when the individuals were re-evaluated by the Workers' Compensation Board. These associations have not been previously investigated in a prospective manner for OA.

- We have provided additional validation of the AQLQ(S) questionnaire developed by Juniper et al. in a study population of individuals with OA and have shown that the emotional function sub-domain of this questionnaire can identify individuals with clinically significant levels of psychiatric distress.

3.2.2. Generalization of results

The medico-legal and socioeconomic aspects of OA in Quebec as a "model" reflective of the situation in developed countries

In the study, the effects of various socioeconomic factors were targeted, examined and quantified in Quebec/Canada, where a broad compensation system is in place. Although it is highly likely that socio-economic factors also play a role in other parts of the world, their nature and impact would need to be examined in relation to specific compensation systems in place. In countries where workers' compensation includes costs for re-education, loss of salary, and impairment (DAP), our findings can probably be extrapolated to these countries with an expectation of similar associations.

The compensation system in Quebec should be considered as a reference standard worldwide because of its excellence in diagnosis, the quality of readaptation programs offered by the Quebec CSST, and the leading role played by the CSST in allocating permanent impairment/disability compensation. Compared to the situations in many industrialized countries, OA is less common than pneumoconiosis in developing countries. As reported by Jeebhay and Quirce in a recent review, the spectrum of OA-causing agents is more diverse and less consistent due to uneven industrial development in developing countries (500).

In these countries, the relatively under-developed or even non-existent surveillance systems probably result in significant underreporting of this condition (500). In developing countries, the management of individuals with OA is often poor and diagnosis is often based on clinical impressions, history findings, and simple diagnostic tools rather than on the results of SIC or other elaborated tests, such as analysis of inflammation by BPT, ENO, and sputum cell counts (500, 501). In developing countries there is often inadequate or no compensation available for OA (500). The ways in which these differences between developed and less-developed countries might be associated with different socioeconomic outcomes warrant further investigation.

In countries such as the United States, where disputes about compensation are usually settled through litigation in an adversarial setting, the impact on quality of life and psychological distress might be even more pronounced and other socio-economic factors might be associated with OA outcomes. In other countries like France, compensation for OA relies on lists of accepted causative agents and a compatible history. If a worker has proven occupational disease but the causative substance is not listed, he/she has to make a claim through a judicial procedure (397). Switzerland and Germany have lists of accepted causative agents. If a substance is not on the list, the worker can still be compensated if evidence from epidemiologic studies prove a strong association in a given exposure group with the development of OA. Uncertainty as to whether a claim will be accepted or not

will most likely have a negative impact on quality of life and increase psychological distress in these individuals.

In countries where possibilities of retraining for a new job are poor and are limited to younger individuals, older individuals may remain exposed in the workplace or leave the workplace. Depending on the compensation system, they will suffer a pronounced loss of income and may have severe limitations in quality of life and increased psychological distress compared to others who live in countries where re-training and compensation for loss of income are offered, even for individuals of older age.

Compensation claims and costs for occupational injuries have been shown to be influenced by economic cycles. Compensation claims tend to decline in recessions and rise in times of economic recovery (502). How these factors influence quality of life and psychological distress in individuals with OA is unknown. Therefore, the outcomes of our study might have been different if repeated a few years later when economic growth differed from what it was in 2004-2006.

3.3. Conclusions

Advanced age, having a higher salary and having OA to HMW allergens all seem to predict a longer interval during which a subject is symptomatic in the workplace; this consequently increases the severity of asthma at diagnosis. Therefore, surveillance programs are needed that are designed to identify such workers in their workplace and allow for the removal of the causal occupational allergen or the reassignment of the worker to a new workplace.

Our study suggests that it is important to consider quality of life, concomitant psychological distress and psychiatric morbidity in individuals with OA, even once their exposure to the causing allergen has ended. A large proportion of patients with OA have significant impairment in disease-specific quality of life, with elevated levels of psychological distress and psychiatric (mood and anxiety) disorders. Quality of life, as well as some psychological distress parameters at re-evaluation, correlates well with objective measures of disease activity, which seems to play the principal role.

Socio-economic factors, such as employment status, marital status, income and the number of years of employment at the time of diagnosis also influence disease-specific quality of life and psychological outcomes, though to a lesser degree.

Disease-specific quality of life correlates with direct costs for compensation by the Workers' Compensation Board. One can assume that impaired quality of life correlates to a similar degree with indirect costs for absenteeism and presenteeism. These findings underline the importance of psychological distress and comorbid psychiatric disorders in patients with OA. Easy-to-administer tools for the detection of individuals with such conditions are available and should be used.

By performing disease-specific quality of life assessment with the AQLQ(S), we could identify individuals with significant psychological distress or psychiatric disorders and offer more elaborate and conclusive investigations, such as a standardized psychiatric interview and treatment if necessary.

3.4. Implications and suggestions for further research

3.4.1. Implications of the study results on the management of workers with possible OA

When we identify socio-economic factors that are associated with prolonged symptomatic exposure in the workplace that leads to worse disease-specific and higher costs for compensation, targeted screening and surveillance programs can be initiated, with the goal of identifying individuals whose respiratory symptoms have recently developed in the workplace.

This would mean that surveillance programs could be initiated in industries where workers are exposed to HMW allergens, are older, and are known to have higher incomes. As a theoretical example, we could imagine a program involving well-skilled laboratory workers exposed to enzymes used for protein biochemistry. Screening could be done using a screening questionnaire that is sensitive for the diagnosis of WRA, such as the one used recently by Labrecque et al. (193). Individuals identified with such a questionnaire could then rapidly undergo a standardized evaluation to either confirm or rule out OA. The results of our study that showed that a prolonged time with symptoms is associated with worse asthma outcomes and higher costs for compensation could lead to physicians and decision makers of the Workers' Compensation Board becoming aware that a swift, broad

investigation is necessary to decrease the risk of a severe course of OA. This could lead to a shorter time interval that an individual has to wait before he gets appropriate clinical investigations in a tertiary center for SIC and workplace assessment by an occupational hygienist.

Those individuals with asthma could be evaluated with questionnaires like the AQLQ(S) to determine their impairments in quality of life. Married individuals, those that are not unionized, have low incomes, and have been with the same employer for longer times or those with severe impairments in the emotional sub-domain of the AQLQ(S) should be preferentially referred to a psychiatrist for mental disorder evaluations. Due to the associations of these socio-economic factors with higher compensation costs, the additional costs required to diagnose and treat psychiatric disorders might be lower in the long term than the costs that accumulate if these disorders are not taken into account. This would be true if identification and treatment of these disorders are associated with better asthma treatment compliance resulting in lower asthma severity.

Asthma severity is taken into account when individuals are investigated by the Workers' Compensation Board to set compensation for DAP. However, the major part of the compensation expenses is incurred for income replacement and rehabilitation. Untreated, clinically significant psychiatric disease will most likely impede successful reintegration in the workforce and, thus, will significantly increase these costs.

We have shown that, at about two and a half years after a diagnosis of OA, there is a very high prevalence of mood and anxiety disorders when individuals are re-evaluated by the Workers' Compensation Board to grant permanent disability indemnity. Currently, airway caliber, hyperresponsiveness, and medication use are the only criteria used to determine levels of impairment by the Quebec Workers' Compensation Board. Thus, disability, which represents the impact of impairment, is not assessed. Results of the AQLQ(S) or psychological questionnaires such as the PSI or the PRIME-MD evaluation should be advocated to provide additional information that can be used for assessing disability. The findings of our study might influence decision makers to incorporate evaluations using instruments like the PRIME-MD or a psychiatric assessment to diagnose mental disorders in this population.

3.4.2. Implications for future research projects

1. Immigration status

It will be important to determine the effect of immigration status on asthma-specific outcomes in a larger sample of individuals with OA because there were too few subjects born out of Canada in our sample. However,

when planning such a study, researchers must consider the heterogeneity of such a population and limit their investigation to a subgroup of workers with a specific background, e.g. immigrants who come from South America, and work in a blue-collar profession. These individuals have been shown to be more vulnerable to developing allergies when moving to more industrialized host countries (245).

2. Studies in workers with work-exacerbated asthma and asthma not related to the workplace

One must compare the correlation of psychiatric disorders and psychological distress with asthma-specific quality of life measures, such as the AQLQ(S), not only in workers with OA but also those with WEA and asthma that is unrelated to the workplace. Compensation for WEA differs in various countries. In Quebec, compensation for WEA is difficult to obtain because a positive result for SIC is requested before compensation is granted. In other countries like the UK, benefits for workers diagnosed with OA and WEA are small. Given the often similar outcomes regarding asthma severity, medication needs, loss of employment and income are considered in practice as one entity; so-called work related asthma (165).

3. Studies in subjects with other types of workplace related diseases

It would be interesting to investigate if the associations found in our study also hold true for respiratory alveolitis or pneumoconiosis. It might be expected that in countries where compensation is granted for OA and respiratory alveolitis, similar socio-economic factors would be associated with disease outcomes.

Unlike that for OA, the natural disease course of pneumoconiosis is usually different; progression of the disease is more closely related to the intensity and the cumulative dose of exposure to inorganic dusts in the workplace (503). Some workers with mild disease may even remain in the workplace when exposure is controlled by technical measures and by using personal protective devices. Nevertheless, even when the worker is completely removed from the causative workplace, there is only limited, if any improvement in lung function, unlike OA where complete recovery can occur. Therefore, it can be hypothesized that different associations between disease outcomes and socio-economic factors exist, at least after a diagnosis of the condition and subsequent removal from the workplace.

Validation of the tools used in our study could be done with individuals referred to the hospital by the Workers' Compensation Board for investigating pneumoconiosis. However, it would be relevant to replace the AQLQ(S) with a validated version of the SGRQ, which was developed to assess disease-specific quality of life impairments in patients with interstitial lung disease

(504). To assess disease severity, total lung function needs to be determined with a body plethysmograph to assess possible lung restriction, measure the transfer factor, perform spiroergometry, and analyze blood gases at rest and during peak exercise. Tools like the PSI and the PRIME-MD could be used in the same manner. It would also be possible to collect information regarding costs for compensation by the Workers' Compensation Board and use the same questionnaire on socio-economic factors as the one we used.

Another condition outside the field of respiratory disease is occupational allergic contact dermatitis. This condition can develop only in individuals who have been previously exposed to a workplace substance and have acquired sensitization to that substance. As with OA, prolonged exposure results in more severe disease expression and can lead to regional or even hematogenous dissemination of the disease. As with OA, eczema can persist even after exposure has ended and individuals can still have severe impairments in their quality of life (505, 506). Dalgard et al. showed that individuals with lower education levels and mid-level incomes had a higher prevalence of allergic contact dermatitis compared to those with higher education and income levels (507). It can be hypothesized that the same associations between socio-economic factors and disease outcomes would be found in individuals with this disease entity, as we have shown for individuals with OA. For such a study, however, one needs to replace the AQLQ(S) with an alternative measure like the Dermatology Life Quality Index, which has been validated with individuals with chronic hand eczema (508).

4. Need for a long-term prospective study

One must prospectively investigate patients in terms of the evolution of their quality of life, psychological distress levels and psychiatric morbidity from the time individuals enter the workforce, at the time the first respiratory symptoms occur at work, when OA is diagnosed and patients are removed from the workplace and undergo rehabilitation. This would help to determine if asthma and psychiatric conditions occur simultaneously or if one precedes the other. Workers could be prospectively investigated over the next few years to determine how the adverse socio-economic outcomes we have found in individuals about two years after a diagnosis of OA affects long-term outcomes such as asthma control and compensation costs. In this regard, one could evaluate the effect of asthma severity or control status as well as the effects of high psychological distress and psychiatric disorders on outcomes, such as employment status and the amount of time between removal from work until successful reintegration into the workforce. We then need to study the effects of asthma and socio-economic factors on absenteeism, productivity at the workplace and subsequently indirect costs.

5. Test for usefulness of interventions

Before we can implement routine screening for psychiatric disorders in clinical investigations for OA, we need to investigate what impact a diagnosis of mental disorders has on the clinical management of these workers. We have to demonstrate that it is feasible to refer these individuals for further investigations and that treatment can be effectively administered. Then, we need to investigate whether intervention programs can reduce psychological distress and/or prevent the development of psychiatric morbidity in patients with OA, and whether the same factors influence quality of life and psychological distress in countries with different medical and compensation systems.

6. Developing and testing other tools

When the benefits of routine screening can be proven, questionnaires and instruments should be developed that are specifically designed and validated to diagnose mental disorders in individuals with respiratory diseases like asthma. Instruments like the PRIME-MD have been criticized on the grounds that the results obtained for those with medical illness might be confounded by the medical illness itself (509). Questionnaires like the HADS have been proposed and adopted by some because they do not include

potentially confounding items. However, this questionnaire has been criticized because only sparse data on psychometric properties and validity are available (509). Therefore, other measures like the HADS should be investigated in study populations with OA.

The results of our study suggest that the AQLQ(S) emotional functioning subscale can be used to identify patients with potentially clinically significant levels of psychological distress. However, this concept, the utility of the questionnaire and the feasibility to include this measure in the evaluation of patients need to be investigated prospectively in a clinical population referred for the investigation of OA.

The extra time needed for additional tests in a clinical setting should be limited as much as possible and should not interfere with the measures and exams that are necessary to diagnose OA. In our study, self-administration of the questionnaires, evaluations with the PRIME-MD, and performing sputum induction took one to two hours in addition to the basic examinations that were requested to set the DAP. These investigations were guided and supervised by a technician. Therefore, shorter forms of already established questionnaires should be developed and validated, which could then be included in routine investigations and might even be administered to individuals with limited literacy.

Questionnaires could be administered electronically by e-mail or on touch-screen computers. Questionnaires in an e-mail format allow respondents to respond immediately and can be sent to patients the day

before they arrive at the clinic for specialist investigations. The results of these questionnaires might even be used to plan additional investigations (e.g., evaluation by a psychiatrist). The data are easy to compile and enter directly into a database, such as electronic patient files. Electronic questionnaires have the advantage that errors during administration can be pointed out to the respondent and the responses can be accepted only after the errors are corrected or missed questions are answered.

To better evaluate the current status of asthma, tests should be used that have been shown to be closely correlated with other objective markers of disease severity, such as symptoms, airway hyperresponsiveness to external stimuli, and inflammation in the airways. AHR can be assessed by performing BPTs with direct (e.g., methacholine, as currently used in Quebec) or indirect stimuli (e.g., exercise, hypertonic saline, and mannitol).

In a pilot study conducted in our hospital, we showed that BPT with mannitol was a useful test for assessing impairment/disability and asthma activity in workers with OA. This was because mannitol can better discriminate subjects according to the severity of their disease when expressed as airflow limitation, and airway inflammation reflective of eosinophilic inflammation and ENO levels (143). Furthermore, performing BPT with mannitol allows for collecting sputum at the same time, which results in less time needed for an examination. However, these promising results need to be verified in larger prospective studies.

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