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Inclusion and exclusion in nutrigenetics clinical research: ethical & scientific challenges

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Abstract

Background/Aims: There are compelling reasons to ensure participation of ethnic minorities and populations of all ages worldwide in nutrigenetics clinical research. If findings in such research are valid for some individuals, groups, or communities, and not for others, then ethical questions of justice – and not only issues of methodology and external validity – arise. This paper aims to examine inclusion in nutrigenetics clinical research and its scientific and ethical challenges. ***Methods:*** 173 publications were identified through a systematic review of clinical studies in nutrigenetics published between 1998 and 2007. Data such as participants' demographics as well as eligibility criteria were extracted. ***Results:*** There is no consistency in the way participants' origins (ancestry, ethnicity or race) and ages are described in publications. A vast majority of the studies identified was conducted in North America and Europe and focused on "white" participants. Our results show that pregnant women (and fetuses), minors and the elderly (≥75 years old) remain underrepresented. ***Conclusion:*** Representativeness in nutrigenetics research is a challenging ethical and scientific issue. Yet, if nutrigenetics is to benefit whole populations and be used in public and global health agendas, fair representation, as well as clear descriptions of participants in publications are crucial.

Introduction

The selection of participants in clinical studies is a crucial task. It may seem a truism to state that researchers must select a population sample that is appropriate to answer their research questions or hypotheses. And yet, this is a challenging task, in several respects.

First, the selection of participants may be affected by competing interests: researchers may be torn between the desire to exclude individuals who could potentially bias the study results or decrease its statistical power, on one hand, and, on the other hand, the fear of compromising the validity and usefulness of their findings for a broader and general population (external validity). In all clinical studies, the choice of participants may be "heavily influenced by the wish to maximize the chance of observing specific clinical effects of interest" [1, p. 4]. In the same vein, overly strict eligibility criteria may affect the generalizability of findings, which mainly depends on the representativeness of study samples. As stated by Boushey et al., "the difficulty with selecting a sample is ensuring that the sample is representative of the entire target population" [2, p. 680]. This, in turn, calls for an appropriate definition of a "target" population.

Such methodological issues have been widely debated in the literature, in most fields of biomedical research, including clinical nutrition studies [2-7]. Nonetheless, controversy is particularly heated in genomics/genetics research. According to Janssens et al., there is no single golden standard by which population and study design should be selected in such research. They stress that "the choice of the target population is not arbitrary, but rather is a trade-off of the effectiveness, costs and harmful side effects of available interventions, among other factors" [8]. In genetic studies, including genome-wide association studies, algorithmic approaches have been developed to "stratify" populations in order to take into account variables or confounders that could affect the identification and the scope of genetic associations [9], as well as to preserve the external validity of the findings, despite population genetic diversity and admixture. The emergence of personalized health interventions – most often referred to as personalized medicine – as well as the development of genomic sciences in medical care – have dramatically revived the debate

pertaining to the use of the concepts of “race”, “ancestry” and “ethnicity” (as proxies for genetic variations or predispositions, for instance) in clinical research and medical practices [9-22]. Yet, an attempt to synthesize or fully grasp the many controversies and issues that these concepts have generated would go beyond the scope of this paper.

Beyond methodology and external validity issues, the definition of what constitutes appropriate representation in clinical research is further complicated by major ethical requirements and guidelines, and, in particular, by issues of justice and equity. For a long time, however, the principles of justice and equity in research ethics have centered on the prevention of exploitation and abuse of vulnerable individuals and populations (such as children, minorities, pregnant women, etc.). As such, ethical requirements linked to the justice principle focused on the risks of biomedical research rather than on fair access to clinical studies and appropriate representativeness [23]. As a consequence, policies aiming to prevent the exploitation of individuals and populations in biomedical research had a pernicious effect: the protection afforded to vulnerable people has significantly prevented the latter from gaining a fair access to clinical studies. Yet, if results in biomedical research are valid for some individuals, groups, or communities, and not for others, then questions of fairness and justice – and not only issues of methodology and external validity – arise [24]. An equitable selection of subjects in clinical research is thus crucial.

Strategies, guidelines and policies designed to promote a greater justice in biomedical research and improve the representation of women, ethnic minorities, and children in clinical trials have been implemented in several Western countries [25-32]. Yet, recent studies indicate that such a representation is still limited despite regulations and recommendations [29,33]. Moreover, it has been noted that discussion of diversity, inclusion, and representation in clinical research is often missing from published studies [29,34].

In Canada, several articles of the Tri-Council Policy Statement on Ethical Conduct for Research involving Humans (TCPS) [35] are inspired by distributive justice principles in biomedical research involving human beings. According to the Interagency Advisory Panel

on Research Ethics, these provisions require that "[…] [t]he inclusion in research of participants representative of the general population should normally be respected, unless there is a valid reason for not doing so. […] those claiming a valid reason for excluding particular groups from research would bear the onus of persuading the REB [Research Ethics Board] of its validity. […] Overall, then, distributive justice norms in the TCPS should help the research community to design reasonable and scientifically grounded inclusion and exclusion criteria that strike a just balance for those participating in human research" [36].

Although the issue of an equitable selection of subjects in clinical research has been much debated, the present paper aims to examine representativeness and some inclusion and exclusion criteria in nutrigenetics clinical studies, as well as the ethical challenges that they raise. With the introduction of genetic technologies and their application to nutritional sciences, the field of nutrigenomics and nutrigenetics developed rapidly. Considering that the terms "nutrigenomics" and "nutrigenetics" are frequently used interchangeably in the literature, in this paper, nutrigenomics is defined as the study of the variability of food-genome interactions using information from the entire genome of an individual, while nutrigenetics refers to investigations on food interactions with specific candidate genes [37]. However, definitions of nutrigenomics as opposed to nutrigenetics may remain controversial [37].

Nutrigenetics information is expected to be relevant for treatment and also for prevention of chronic diseases, as well as for health promotion in the general population, including patients, at-risk as well as healthy individuals. In terms of global health, both industrialized and emerging countries are now facing a growing epidemic of the same chronic diseases and have to cope with marked inequalities in healthcare access [38]. In this context, nutrigenomics and nutrigenetics call for the right of whole populations to benefit from their results [38]. How then to promote nutrigenetics research that would benefit all communities and populations? Like in biomedical research ethics in general, equity in research participation, just as fair and sound inclusion of subjects, should be pre-requisites.

Methodology

Sample and analysis

We performed a systematic review of clinical studies in nutrigenetics and nutrigenomics published between 1998 and 2007 inclusively. Studies for potential inclusion were identified through a PubMed search. As nutrigenomics is a recent word that was indexed and introduced as a MeSH category encompassing nutrigenetics in PubMed only as of 2008, we completed our search with different combinations of the following keywords: "food", "nutrient", "diet", "gene", "interaction" and "association". The search was limited to titles and abstracts of original articles and reviews, commentaries and letters were excluded. Based on the NIH definition [39], all intervention and/or observational studies that involved human beings as participants were considered as *clinical* studies, while studies limited to the analysis of human cells or tissues only with no other active human participation than tissue or cell donation were excluded. Moreover, to be included in our sample, studies had to meet the following criteria: 1) to have a specific gene component (e.g., candidate gene or polymorphism), 2) a dietary component: nutrient (from the diet or as a supplement), food, dietary pattern (e.g., Mediterranean diet), etc. and 3) describe an interaction between 1) and 2) that may impact health, disease onset, or nutritional biological pathways. A total of 173 studies met these criteria. These publications constituted the sample upon which we performed a detailed content analysis. The data extracted from these publications for use in the present paper were: a) authors' geographical location; b) participants' geographical location; c) participants' particulars, such as race, ethnicity, origin, nationality, ancestry, age, sex, comorbidities, and any other available data linked to participants' description, as well as any exclusion and inclusion criteria reported by the authors. The description of participants was completed in many cases with the tables provided by the authors to present their results. The following elements were also extracted from the publications of our sample: d) all authors' statements or comments about the potential or actual impact of genetic variations linked to ethnicity; e) all limitations of study results explicitly acknowledged and reported by the authors. It has to be noted that in 120/173 publications of our sample (hereafter: "*referring publications*"), authors referred to previous publications and/or previous or ongoing studies (hereafter: "*referred publications*") for the description of the methodology of their

study, and/or of their participants or of their selection. Consequently, we consulted all *referred publications* (≅190 publications) to gather as much information as possible about participants' location, age, and ethnic origin.

Limitations

Given the recent use of the terms "nutrigenomics" and "nutrigenetics", the results of our search for clinical studies in this field is likely limited by the keywords (and combinations) that we chose. Nutrigenetics and nutrigenomics cover disparate fields and complex mechanisms that can be described in many different ways. Thus, our sample might not include all clinical studies that could have been identified with other keywords and that could have met the three selection criteria mentioned above.

Studies that only measured gene expression, without pointing out and referring to a particular polymorphism or specific DNA sequence(s) or variation were also excluded.

Finally, we could only identify participants' exclusion or inclusion criteria that were explicitly reported by the authors in their publications or that could be inferred from population sample descriptions such as provided in the publications. Yet, only a full review of research protocols could give a real picture of the explicit exclusion or inclusion criteria used in nutrigenetics research. As mentioned above, 120 publications referred those readers interested in getting more information about the participants or the methodology of the study to one or several previously published papers. Yet, 30 of these 120 publications provided us with one or more references which we could not access (e.g., papers or books not accessible on the Internet or not accessible without fees from the electronic journals and library databases of our university). Moreover, 14 publications referred to an ongoing or previous study from which participants were recruited or in which participants took part but for which they did not provide any explicit reference in their bibliography. In 4 of these 120 publications, the references given for the description of the methodology, of the participants and/or of their selection were inaccurate (e.g., reference to the abstract of a poster at a symposium, an incomplete reference, a reference to a theoretical paper that contributed no useful information about the participants of the referring study, etc). Finally,

instead of providing the expected full description of the methodology of the study and/or of the participants, several *referred papers* turned to other previous publications for the same purpose (and in turn, some of the latter publications referred the readers to even earlier papers for the same descriptions). We did not extend our analysis of references beyond the references provided by *referring publications*.

A. RESULTS

1. Geographical location of participants and authors

Of the 173 publications in our sample, participants' location was explicitly reported or could be inferred with certainty as being in Europe for 73 studies (42%), and North America for 68 studies (39%) (fig. 1). The other studies were conducted with participants in Asia (17%) and Central America (5%). Our search parameters did not identify any publication explicitly reporting participants' location in Africa, South America or Oceania. The participants' location was *not explicitly* reported or could not be inferred with certainty in 5 cases (3%).

A majority of studies was conducted by one – or more – researchers affiliated with institutions located in North America (excluding Mexico) (62%) and Europe (54%). Our data indicate that there are more studies with authors located in North America and Europe than studies with participants located in the same areas, which suggests a certain level of decentralization of nutrigenetics research (fig. 1).

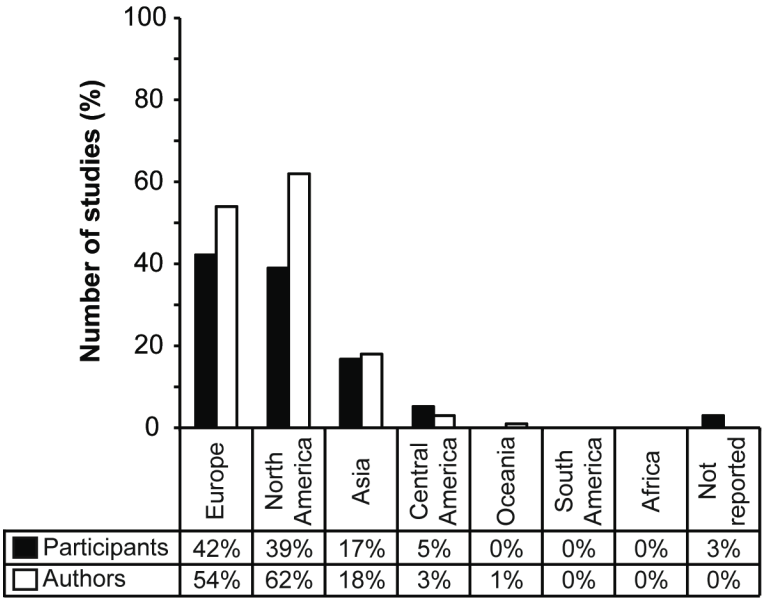


Figure 1
Hurlimann et al, 2011

Fig. 1. Geographical location of participants and authors. Values were obtained from the whole sample of studies (n=173). Total of percentages is superior to 100, as some studies were conducted on more than one continent and some publications had authors in more than one continent. A complete list of the countries of participants and authors is available in online supplementary table 1.

2. Participants' "origin"

Our sample of studies provides scant and often ambiguous information about participants' race, origin, ancestry or ethnicity. It appears that there is little coherence between publications in the way the terms race/ethnicity/ancestry/origin/ and even nationality are used to describe sample populations (see table 1 and supplementary table 2). In such circumstances, it is a challenging task to present our results in a coherent way and to understand what scope or meaning researchers attribute to the terms they use to describe their sample populations. Similarly, the way ethnicity, race, origin or ancestry was inferred or measured by researchers is rarely explicitly reported. For the purposes of this paper, given the lack of a consensual definition for such concepts as "race", "ethnicity" or "ancestry" and the inconsistency in the use of such categories across studies, the term

"origin" will be used to describe any mention relating to participants' ethnicity, race, origin, ancestry or nationality.

Table 1. Participants' "origin" as reported in publications of studies in which the whole population sample is described as being of the same origin (i.e. *non-mixed studies*) (n=88)

Race/ethnicity[1]	Nationality[2]	Nationality & race/ethnicity[3]	Ancestry[4]	Geography[5]
White (14); **Caucasians (11)**; **White Caucasians(1)**; **French-Canadians (4)**; **French-Canadian descent (2)**; **Caucasians from French-Canadian descent (1)**; **Non-Hispanic White (2)**; **European-Americans (1)**; **European Caucasians (1)**; Han Chinese (6); Japanese (5); Chinese (4); Mestizo (2); American-Indians (1)	*Portuguese (1); Danish (2); Spanish (2); British (1); Finnish (2); Dutch (1); Scottish (1); Greek (2);* Chinese (3); Japanese (4); Costa-Ricans (1)	**German-Caucasians (1); Dutch-Caucasians (1); French-Caucasians (1); Spanish Caucasians (1); Polish Caucasians (1)**; **Italian White (1); White Americans (1);** Mexican-Americans (1); Hispanic Americans (2)	**European ancestry(1);** *"Mixed ancestry common to the upper Midwestern region of the US and belonged to no particular ethnic group" (1)*	**Western European origin (1)**
All descriptions in **bold font** may be considered as referring to white/Caucasian participants (n=46). All samples that likely contained a majority of "white/Caucasian" participants appear in *italic* (n=13). This classification into 5 categories is adapted from Fullerton et al. [40].				
[1]The category "Race/Ethnicity" gathers descriptions of origins that explicitly used the terms "race" or "ethnicity" or that could be interpretatively linked to such concepts. While this classification is relatively straightforward for descriptions such as "Han Chinese", "Caucasian", "White" or "Hispanic Americans", for instance, we are fully aware that descriptions such as "Japanese", "Chinese", "European American" or "French-Canadian" could arguably be classified into other categories. However, a choice was made in each case considering other details provided in the publication: for instance, in one publication of our sample, participants were described as "patients who are at least 75% Japanese […]". [2]In at least 20 publications of non-mixed studies (23%), participants' origin was described in terms of nationality only, with no explicit reference to "race", "ethnicity", "ancestry" or "origin". [3]The column "Nationality & Race/Ethnicity" gathers the non-mixed studies that combined both descriptions usually used to describe a race or an ethnicity and words denoting a nationality. [4]The category "Ancestry" lists descriptions that explicitly used the word "ancestry". [5]Descriptions of origins that seemed to be mainly linked to a broad geographical location were grouped in the category "Geography".				

Only in 11 publications of our sample (6%) did authors *explicitly* mention that ethnicity was self-reported by participants. However, such an ethnicity inferring method was likely used in a majority of studies, through demographic questionnaires that were not always described in the publications. 6 studies of the whole sample (3%) *explicitly* mention the use of genomics tools such as HapMap data, but it is not clear in these cases to what extent such data were actually used in order to measure or validate participants' origin.

Information about participants' origin could be found in 124 publications (72%), thus participants' origin could not be determined for 49 studies of our sample (28%). Included in the latter category are all publications that did not report any other information about participants' origin than the geographical location of the clinical research.

Of these 124 publications, 88 studies (71%) involved participants who were all described as sharing the same origin (hereafter "*non-mixed studies*"). Included in this group were all studies in which participants with a same origin were explicitly described as constituting "*more* than 98%" of the sample, or in which participants were explicitly described as "all", "nearly all", "mainly" or "overwhelmingly" from the same origin. In these *non-mixed studies* (n=88), we classify participants' origin descriptions according to 5 categories (adapted from Fullerton et al. [40]; see table 1). In the remaining 36 studies (i.e., 29%), population samples were explicitly described as being composed of groups of different origins (hereafter "*mixed studies*"). As shown by Figure 2A, 89% of these studies (i.e., 32 studies) included at least one "white" or "Caucasian" participant. "White" or "Caucasian" participants were *not* recruited *at all* in 4 studies (11%)(fig. 2A).

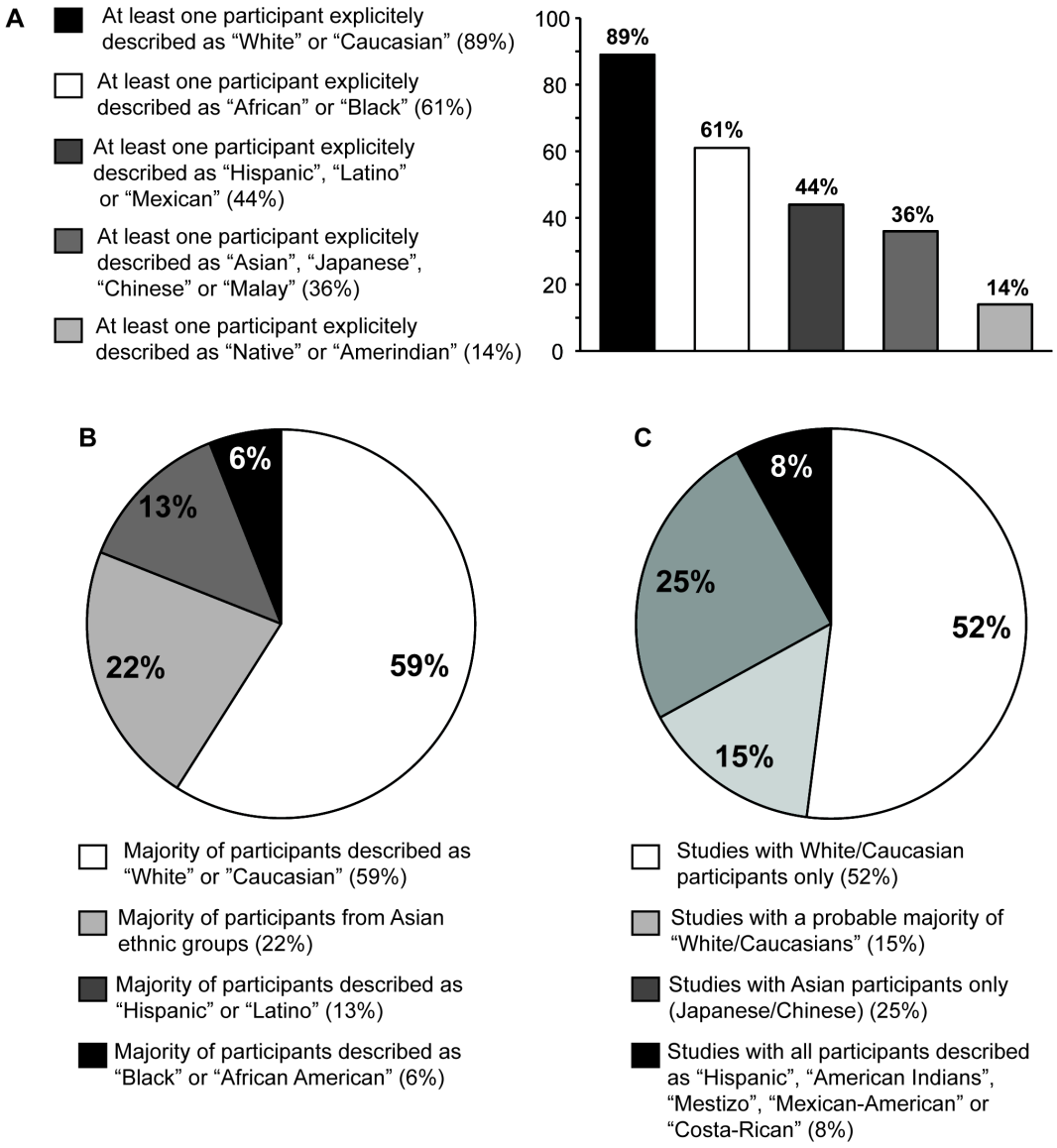


Figure 2
Hurlimann et al, 2011

Fig. 2A. Ethnic representation in studies in which population sample is described as being composed of groups of different origins (*mixed studies*). Values are in percentages and were obtained from 36 non-mixed studies. Note: While white/Caucasians were always explicitly named when represented in these 36 studies, there are 13 publications where the origin of the minority group was not described explicitly (e.g., "other" or "unknown"). Thus, the percentages indicated in this figure only take "explicit" descriptions of origins into consideration. Complete data are available in online supplementary table 2. **Fig. 2B.** Ethnic majorities in studies in which population sample is described as being composed of groups of different origins (i.e. *mixed studies*). Values are in percentages and were obtained from the 32 mixed studies where the proportion of each ethnic group was provided. Complete data are available in online supplementary table 2. **Fig. 2C.** Participants' origin in studies in which the whole population sample is described as being of the same origin (*non-mixed studies*). Values are in percentages and were obtained from 88 non-mixed studies. The category "Studies with white/Caucasians participants only" gathers the studies in which participants' origin was described with the words that appear in bold in table 1. The category "Studies with a probable majority of "White/Caucasians" gathers the studies in which participants' origin was described with the words that appear in italic in table 1. There is no study in which all participants were described as "Black", "African-American" or "African".

Figure 2B and online supplementary table 2 provide a more complete picture of the different ethnic groups represented in all mixed studies. In 32 publications of 36 *mixed* studies (89%), authors reported the proportion (in percentages) of the participants belonging to the same ethnic group. Such information was not provided in 4 *mixed* studies (11%). In 59% of the publications where the proportion of each ethnic group was provided (n=32), participants described as "white" or "Caucasians" constituted the majority (although this majority was low in 3 cases, where African-Americans/blacks almost reached the same percentage) (fig. 2B and online supplementary table 2).

Finally, our results indicate that of 88 *non-mixed studies*, at least 46 (52%) involved white/Caucasian people *only*. This proportion is certainly higher, as participants described as "Danish", "British" or "Scottish", for instance, are likely in majority "white/Caucasians". However, it cannot be inferred from such descriptions that it was the case for all participants. Figure 2C summarizes these results: it shows that white/Caucasian populations are the most targeted ones in *non-mixed studies*, while in our whole sample, not a single study involved *exclusively* black/African/Afro-American participants.

In summary, whatever the many ways used to designate "white" people (with potentially different descent or place of residency), our results show that they remain the most studied population.

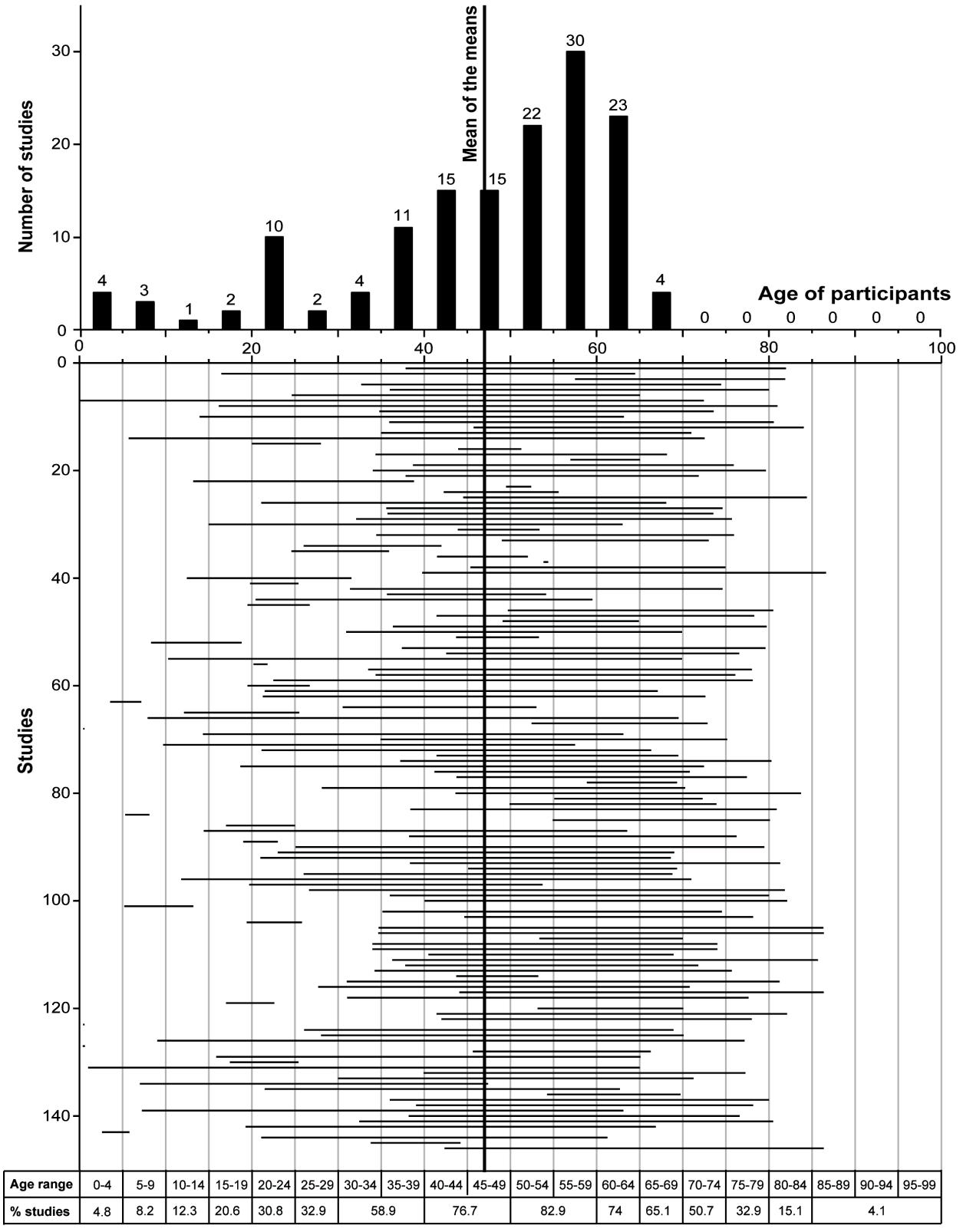
3. Age of participants

Eligibility criteria relating to the age of the participants could be identified for 106 studies (61% of our whole sample). Thus, such criteria were not reported in 67 publications of our sample (39%). According to these criteria, people ≥75 years old were not eligible in 70% (n=74) of these 106 studies, and people <20 years of age (minors, adolescents, children, infants) were *not* eligible in 72% (n=76) of them. In comparison, people aged between 40 and 49 were eligible in 86% of these studies while people aged between 50 and 59 in 89% of them. Percentages decrease progressively after this age to reach 15% for people aged ≥85 years (data not shown). While eligibility criteria are crucial in order to address the

ethics of fair inclusion in clinical research (see section “Discussion” below), they do not give a true picture of participants who were *actually* recruited into the studies.

The mean age ±standard deviation (SD) of the participants who were *actually* recruited into the studies of our sample was reported or could be determined in 146 cases (84% of our whole sample; details can be found in the legend of figure 3). A majority of the studies have included participants from the age categories of 30-39, 40-49, 50-59, 60-64, 65-69 and 70-74 years old (see percentages in the table of fig. 3). A histogram in fig. 3 shows that in 85% (124/146) of the studies in which mean age ±SD could be determined, the mean age of the sample for the population studied was between 30 and 74. Thus, the majority of studies target individuals between 30 and 74 years of age. Conversely, a minority of studies focus on younger and older populations. Only 15% of the studies have a mean age smaller than 30 years old and 0% of studies have a mean age of 70 years old or more.

Finally, it must be stressed that by reporting age distribution within 2 SD, we covered the inclusion of approximately 95% of the participants in each study. Yet, according to a normal distribution, participants who are represented in an age category that lies within the second standard deviation from the mean only account for 13.6% of the entire population. We did not take this into account. Moreover, as there are many cases where mean age ± 2SD in a study did not encompass the whole age category interval located at its upper and lower limits, percentages of studies including participants of a given age category in the table of fig. 3 may be inflated and this limit is probably more important for the first and the last age categories included in the mean age ±2SD for each study.



Age range	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
% studies	4.8	8.2	12.3	20.6	30.8	32.9	58.9		76.7		82.9		74	65.1	50.7	32.9	15.1	4.1		

Figure 3. Age of recruited participants**.** Each horizontal line represents the mean age ± 2SD of the studied populations in one study, and therefore approximately the range of age of the participants [135]. Values were obtained from the 146 studies in which mean age ±SD was reported or could be determined (84% of the

whole sample). Mean age ± SD was not provided in 28 cases but could computed in 8 of these cases on aggregated data and extrapolated in the 20 remaining cases. In the latter cases, mean age ±SD was extrapolated on a presupposed normal distribution from the values provided in the publications such as age ranges for all participants or median age and IQR (e.g., SD=IQR/1.34896 and mean age=median age). The table on the bottom indicates the percentages of studies for which at least a part of the age range is in the corresponding age category. The histogram reports the number of studies in which participants' mean age is included in a given interval. The bold vertical line indicates the mean of all mean ages, i.e., 47 years ("mean of the means").

4. Source of study populations

In 103 publications of our sample (59%), authors *explicitly* indicated that the participants of their study were already part of, or were recruited from, either a previous or an ongoing study (e.g., EPIC, Framingham Offspring Study, Quebec Family Study, but also smaller studies). However, this number is actually higher, as some research groups who have several publications in our sample used the same cohorts without reporting it explicitly.

B. DISCUSSION

1. Participants' geographical location

Beyond issues of ethnic representativeness in clinical research, the concentration of nutrigenetics studies in Europe and North America such as demonstrated by our results raises concerns in terms of equity and justice in biomedical research and global health.

The inclusion of emerging countries in genomics and genetics research, as well as the global health applications expected to stem from this research, have been much debated [38,41-43]. While it is challenging to determine to what extent nutrigenetics could actually benefit emerging countries, in particular in its current – and still early – stage of development [38], it remains that chronic diseases, on which most current nutrigenetics studies focus (e.g., cancer, diabetes and cardiovascular diseases), are still neglected in the global health agenda [44]. Chronic diseases cannot be seen anymore as being prevalent only in rich countries: they will account for the most common causes of death by 2015 in both the developed and

the developing world [45]. Moreover, while underfeeding is still an important issue in many places, emerging economies are also grappling with malnutrition that has accompanied their nutrition transition and the global food crisis [46]. Now, an increasing number of genomic and/or nutrition studies demonstrate the deep impact of early nutrition (be it underfeeding or malnutrition) on children's development and on their health as adults, as well as on future generations [47-56]. In this respect, nutrigenetics research, along with epigenetics research, could be a powerful tool notably: a) to understand the long-term and intergenerational consequences of malnutrition and hunger worldwide; b) to develop potential preventative measures that could benefit both developed and developing countries; and c) to set up a shared agenda on research priorities.

However, in order to achieve such goals and promote optimal health on a *global* scale, nutrigenetics research should also be conducted in developing countries, with local participants and local foodstuffs. Indeed, the usefulness and validity of research results obtained solely in industrialized countries may be limited to these countries. First, the micronutriment content and bioaccessibility of studied foodstuffs may vary considerably, depending notably on the place where such foods are grown (e.g., [57-60]). Second, the methods of diagnosis and management of diseases that are studied in nutrigenetics research may vary from one country to another and such differences in clinical practices may impact the external validity of clinical studies [61]. Third, significant cultural and ethnic differences in eating habits, as well as in food production and preparation exist among nations [58,62]. The processing and storage of foods may impact nutritional values and nutrient content of the food [63]. Such differences may threaten the efficacy of any potential research result application or public health recommendations that would be based on clinical studies conducted solely in developed countries.

Conducting nutrigenetics research in developing countries is certainly a challenging task. Financial limitations and resource-limited settings constitute serious obstacles to such research. But it also raises important ethical issues. While many of the latter are common to any type of research in genetics (such as informed consent and privacy issues), others may arise specifically in nutrigenetics research [38] or with more acuteness in underserved

countries or populations [64-66]. For instance, the evaluation of the impact of dietary programs, specific foodstuffs or lack of given micronutrients on genome expression, stability or integrity may be "stymied by the ethics of randomizing recipients" [67, p. 1139] to a control group consisting of individuals, who like many others in the same region or country, are lacking access to basic nutrition (see [67] for an example of such an issue in a non-genetic nutrition study). In any case, despite such challenges and obstacles, sound nutrigenetics research could eventually benefit emerging countries and global health, only, and only if, it is conducted also within their borders.

2. Participants' "origin"

Generalisability and external validity of clinical research results depend on an appropriate inclusion of all groups worldwide. In genomics and genetics research in particular, any limitation in the representativeness of population diversity may have a considerable impact on results. In this respect, it is worth stressing that the frequency of genetic variants may not only differ substantially between populations or ethnic groups (e.g., [68]), but also within such populations or groups (e.g., [69,70]). "Therefore, before appropriate genotyping panels can be established, the extent of functional genetic variation in candidate genes needs to be determined, especially in understudied populations" [71, p. 340]. Thus, the assumption that the discovery of common genetic variants and patterns in some populations will benefit all populations or all people in a given population is far from shared by everyone. The impact of admixture in populations and genomic variability on research results – as well as the efficacy of the methodological tools used to overcome such issues – remain controversial. The debate is particularly fierce in pharmacogenomics, genetic association studies and genome-wide association studies, especially when it comes to using race, ancestry or ethnicity as proxies for genotype [8-10,17,20,72-75]. But it has become clear that caution is needed when generalizing genetic research findings across ethnic populations (e.g., [76]).

In nutrigenetics, researchers face identical issues. As stated by Lewis and Burton-Freeman, and demonstrated by our results, studied populations are often restricted to one ancestral

or ethnic group and, as a consequence, the data "cannot be reliably applied to all individuals or other populations" [77, p. 428S]. In this respect, it is crucial to understand how prevalent a specific polymorphism involved in gene-nutrient interactions has to be to warrant genotype-specific recommendations for subgroups in the population (e.g., [78, p. 46]). In our sample, only 48% of the publications mention or comment on the prevalence or frequency of studied polymorphisms.

The challenges faced by researchers in nutrigenetics may be even greater than the aforementioned ones, as heterogeneity in study samples is not only introduced by genetics, but also by cultural factors. Indeed, there are major ethnic differences in dietary intake and food exposure that further complicate analysis [79,80]. In other words, apart from controversies linked to the use of racial categories as proxies for genotypes, ethnicity matters in nutrigenomics, just as it does in any clinical nutrition research. It is therefore of the utmost importance to consider the influence of acculturation on diet and health, in particular when considering study result applications, whether it be to individuals or to whole populations [3]. Moreover, ethnic differences may impact the validity of a food frequency questionnaire (hereafter: "FFQ") results [81]. Adaptation of such questionnaires to diverse cultural settings is certainly a challenge [82], all the more since cultural differences in dietary habits should not be reduced to ethnic categories either, given the many variations in dietary patterns that may also occur within ethnic groups. Yet, a lack of such adaptation may raise ethical issues in terms of justice and equity in access to research, in particular when participants who are unable to fill out questionnaires – an inability that may be caused by poorly adapted questionnaires – are excluded from an ongoing research project. Such an exclusion criterion was explicitly reported in 11 (6%) publications of our sample. It is worth noting that the use of a FFQ was reported in 97 publications (56%) of our whole sample, and 25 of them (26%) *explicitly* reported an adaptation of food questionnaires according to the ethnicity of the participants or to food customs in given areas. However, there is scarce information about the extent and the nature of such adaptations in the publications.

Currently, nutrigenetics research is often limited to the study of the interactions of one single-nucleotide polymorphism with one dietary component on one disease outcome [83], in a specific population. Our results consistently show that such research mainly focuses on "Caucasians" or "white" populations. Such limitations must be addressed and this will require, notably, analyses of gene-food interactions in populations of varying ethnicities [58,79]. There is another compelling reason to support a greater inclusion of ethnic minorities in nutrigenetics research. Ethnic minorities (as well as populations in developing countries and socio-economically disadvantaged people) carry a disproportionate burden of chronic diseases [29,84], the same diseases on which many nutrigenetics studies focus (e.g., cancer, diabetes and cardiovascular diseases). In such a context, a lack of representation of ethnic minorities may lead to an exclusion of people most likely to be in need of treatment or prevention measures resulting from the interventions or hypotheses being tested in such research. This may not only affect external validity, it also constitutes a serious concern about justice and equity in clinical research, and potential discrimination by unduly restricted access to medical research to those who would benefit the most from it. Thus, Ngo and colleagues suggest that studies in nutrition should not only *include* ethnic minorities and vulnerable populations, but even *target* them [6].

We may note that our results indicate that ethnicity was explicitly reported as being a criterion for exclusion from the study or analyses in a few cases (6/173), and that in only one of these did the authors endeavor to explain the rationale behind the exclusion. In the latter case, the authors stated that "races other than white or African-American were excluded from the analyses to reduce the potential variation in results by other races and because their numbers were too small to study separately". Beyond rare *explicit* exclusions of certain ethnicities, our results indicate that in 88 studies of the 124 publications in which information about participants' origin was provided (51%), participants were described as belonging to one same origin (table 1), and in 59 of these cases (67%), participants were certainly (52%) or likely (15%) white/Caucasians (fig. 2C and table 1). Our results also indicate that in *mixed studies*, white/Caucasian was the origin of the majority of the participants (fig. 2B, and online supplementary table 2).

It remains crucial that all clinical research reports provide a clear description of their population samples. Our results indicate that in 49 publications of our whole sample (28%), we could not find any information about participants' origin including in referred publications (see Methodology). Moreover, in cases where such information was provided, precision was lacking in how terms like race, ancestry, or ethnicity were actually used and understood. Overall, it appears that there is a persistent inconsistency in the use of such categories across studies. Such findings are very similar to those reported by Fullerton and colleagues, who state that despite calls for greater clarity and precision in the description of the populations studied in genetic research, there is a documented, persistent ambiguity in the use of the terms race/ethnicity/ancestry [40]. Descriptions in terms of nationality (which occur in 20 publications out of the 124 publications in which information about participants' origin was provided, i.e., 16%; see table 1) are particularly uninformative about participants' origins and sometimes even troubling, such as was the case in two publications in which "women with non-German nationality" were explicitly excluded from the study, or where all participants were described as being "born in Denmark". Another example of striking ambiguity, found in 2 publications, is the breakdown of the participants into a "Jewish" group and a "Caucasian/white" one, as if such groups were necessarily distinct.

This situation generates much concern both at a scientific and ethical level. Scientifically, an appropriate description of the participants in a study is needed to consider whether research findings may be generalized to the whole population or specific subgroups only. Appropriate representation of ethnic minorities in clinical research is an ethical requirement. Thus, exclusion from clinical research *without appropriate reasons* is, in itself, ethically problematic.

Certainly, the inclusion of ethnic minorities in nutrigenetics research raises many challenges (see BOX 1). But the exclusion of ethnic minorities motivated solely on the basis of such challenges are indefensible from an ethical standpoint [25, p. 100].

Box 1

Challenges raised by the inclusion of ethnic minorities in nutrigenetics research

- The inclusion of ethnic minorities in nutrigenetics clinical studies may impact study results due to population stratification and other confounding factors, while the exclusion of ethnic minorities may affect the external validity of the study. Striking a balance between the two is difficult [86]. Any exclusion, be it implicit or explicit, needs to be stated and justified scientifically and ethically.
- Defining an appropriate study population in terms of origin, race, ethnicity or ancestry is challenging in itself. Even in the United States, where it is a legal requirement for NIH-funded studies [105], there is still much uncertainty about what constitutes an "appropriate" minority inclusion [106-108]. Moreover, there is still much confusion and ambiguity in the ways ethnicity, race or ancestry are to be understood, inferred, measured, assessed and reported [20,40,109]. Yet inadequate reporting of ethnic representation may constitute a significant barrier to the assessment of the external validity of nutrigenetics research.
- The use of race, ethnicity or ancestry as a proxy for genotype remains highly controversial. Yet many commentators and scientists agree that the use of such categories may be deemed necessary in clinical research. As stated by the National Human Genome Research Institute, in all cases researchers should avoid overgeneralization by using population labels that are as specific as possible [110].
- Given the level of admixture – as well as differences in dietary patterns – in population groups themselves, we should not assume that variations in allelic frequencies or food habits actually reflect or could be reflected by racial or ethnic categories only (modified from Duster, [111]).
- Researchers should be ready to get involved in the debate surrounding the socio-ethical issues linked to the potential resurgence of race as a biological concept, and the risks of discrimination and stigmatization that their study findings could raise [9-22].
- There are documented barriers to the recruitment and retention of minorities in clinical research, including cultural gaps between researchers and participants, language issues, and costs. Yet, strategies exist to overcome such obstacles [29,112-121].
- There are significant challenges to the assessment and measurement of dietary intake in ethnic minorities [6,81,122] and the adaptation of any FFQ to diverse cultural dietary habits [82].

3. Age of participants

The underrepresentation of elderly people and children (as well as infants and pregnant women) in biomedical research has received much attention in recent years. Evidence of

the extent of this phenomenon and its potential impact has been reported and commented on by many authors, in various fields of clinical research [25,29,33,61,85-90].

Age does matter in *nutrition* research (e.g., [91]). The proportion of elderly people is increasing in a significant manner in developed countries and this growth has serious implications for health care needs, public policy and research priorities [92]. Yet, much remains to be learnt on elderly-specific nutritional needs and the influence of diet on the aging process [93]. Inadequate nutrition is a major problem affecting elderly people's health and it needs to be further studied [94,95]. Similarly, several knowledge gaps were identified that pertained to infants', children's and adolescents' nutritional needs [78, p. 170].

Age also matters in *genetics*, including nutrigenetics. There are variations in gene expression across a lifespan [90]. In addition, Qi and Liang stress that "the strength of both the genetic and dietary effects may change across life, and therefore, the gene-diet interactions may be more likely to be identified at certain stages of life than others" [96, p. 35]. Thus, age should be considered as a significant factor in nutrigenetics interactions [83,97]. Beyond the study of interactions between nutrients and genes themselves, research is now increasingly focusing on epigenetics/epigenomics mechanisms that may be affected by nutrition and that may have significant impacts at any life stage. A growing number of articles and reviews now debate and comment on the mechanisms that could explain how early-life (including prenatal) nutrition can affect epigenetic mechanisms and, in turn, health, later in life [47,52-56]. In the same way, during aging, some genes may be aberrantly expressed due to altered epigenetic marks [98]. At this stage, knowledge in this area is confined to proof-of-principle studies in animal models and very few and limited human studies [53,99]. As a consequence, new knowledge gaps have been identified, with new research priorities such as the study of the variation of individual nutritional requirements brought on by epigenetics, lifestyle, environment, and geography [78, p. 170] *during the course of a lifetime*; the development of biomarkers of disease risk and interventions aiming to prevent or reverse the adverse effects of a poor early life environment [47,53]; and the

identification of genes and pathways which are likely to be regulated epigenetically during aging and where effects of aging may be modulated by nutrition [98].

The results of our analysis of published studies in nutrigenetics offer a valuable opportunity to consider the importance of age as a crucial variable in nutrigenetics studies, on one hand, and to address the need for a broader inclusion of participants of all ages, on the other. In the first place, our analysis shows that demographic characteristics, such as the age distribution of participants, were often poorly documented and it could not be ascertained in 16% of the published articles in our sample. This lack of information about such demographic characteristics of the participants in publications is problematic, both in terms of science and ethics. Without such information, how can readers assess the scope and the utility of study results, as well as the representativeness of a sample population? In this context, it is crucial to acknowledge that any explicit or implicit exclusion of the elderly, pregnant women, infants, children and adolescents from clinical studies in nutrition may raise important ethical and scientific concerns – in particular if the rationale of such an exclusion is not carefully reported and clearly justified in research protocols.

Our findings also clearly demonstrate that at this stage, nutrigenetics studies tend to focus on middle-aged populations. Our results indicate that even without an explicit exclusion of elderly people, very few nutrigenetics studies focused on them (at least if elderly is >74 years of age; see fig. 3) This suggests that age-based exclusions may not be planned in the formal study design but could be a result of other inclusion/exclusion criteria. First, the age of onset of most chronic diseases targeted by nutrigenetics research necessarily impacts the age distribution of participants. Second, exclusion criteria such as pre-existing health problems, higher risk of comorbidities, intake of medications that could affect study results, potential cognitive impairments, and the exclusion of so-called “unhealthy” participants from control groups inevitably restrict the elderly from participating in clinical research. Finally, it has also been argued that a limited representation of vulnerable populations in clinical research could also result from the characteristics of the recruitment procedures or even of a reluctance to recruit such populations [87].

While the principle of justice requires a fair access to clinical research for all groups in the population, researchers and research ethics committees must also wonder whether exposing vulnerable populations to research procedures is ethically justified. Such a question cannot be answered without a sound review of the scientific validity of research protocols, as well as an appropriate assessment of the risks and the benefits of the research for the participants and the group they represent.

In this respect, it is worth stressing again that "the ultimate goal of nutrigenomics is to determine the optimal nutrition for everyone, at any life stage" [78, p. 163]. This statement, as well as the aforementioned knowledge gaps, offer a solid rationale for a broader inclusion of pregnant women and fetuses, neonates, infants, children and adolescents, as well as the elderly, in nutrigenetics research projects, as is the case for many other fields of research. Yet, that does not imply that the recruitment of these populations in nutrigenetics studies would be relevant or feasible in all cases, given the current state of development of this new field of research and the various hypotheses or interventions that may be tested in these studies. But in any case, it cannot be assumed that genome-nutrition interactions are negligible or of no interest for the elderly or the very young. If nutrigenetics research aims to develop and implement personalized nutrition interventions, it is legitimate to doubt that such a goal would cease to be relevant after a certain age.

Certainly, research with the elderly, pregnant women and children may raise difficult practical, methodological and ethical challenges (BOX 2). A full review of these difficulties would go beyond the scope of this paper. In any case, researchers should not avoid research that would, of necessity, include these populations, as a means of properly addressing research goals, simply to avoid such difficulties or the potentially more demanding ethical requirements. Research protocols should not include arbitrary age cutoffs [100, p. 2], nor should age be used as a proxy for such conditions as cognitive impairment [25, p. 8], incapacity to consent, or many current or potential comorbidities, nor as a proxy for difficulties in follow-up or compliance. Therefore, research ethics committees should clearly challenge age-based restrictions that are not scientifically grounded. As stated by Bartlett and colleagues, many commentators argue that the exclusion of elderly people from much

medical research is not "good science" but discrimination against the old, which plays a significant part in sustaining differential opportunities to benefit from research [25, p. 8]. The same concerns may well be expressed regarding pregnant women and fetuses, infants, children and adolescents.

Box 2

Challenges raised by the inclusion of the elderly, pregnant women, infants, children and adolescents in nutrigenetics research

- The obtention and quality of informed consent (and/or assent) from vulnerable populations is a well-known issue [123-127].
- Both the genetic testing of children and their participation in genetic research raise ethical concerns in terms of beneficence and protection of (future) autonomy [127,128]. This is particularly true in nutrigenetics studies that would aim to investigate, in children, the precursors of adult complex late onset diseases or the potential heredity of epigenetics mechanisms. Data collection and storage procedures, protection of confidentiality, risks of discrimination and stigmatization must be considered and handled with care [126].
- The notion of minimal risk or acceptable burden in research involving vulnerable populations is still controversial [129,130]. It is worth noting here that a rigorous evaluation of food-health interactions and nutrition programs in children or the elderly may raise ethical conundrums, in particular when such an evaluation would require to randomize participants in a control group (e.g., [67]).
- The validity and reliability of tools used to assess nutritional intake or behaviors in older participants [95,131], infants and children [78,132], or adolescents (e.g., [132,133], as well as their recruitment [134] and compliance may also raise difficult practical and methodological challenges.

4. Source of study populations

The frequent use of pre-existing cohorts as a sample population may be problematic. Haga concisely described the issues at stake by stressing that "although convenient and likely to include detailed phenotypic data collected over a long period", existing cohorts are most often representative of a single population only, "limiting the generalization of the study findings" [101, p. 82]. Haga also notes that "[m]any of the existing cohorts may have been established before federal [U.S.] efforts to bolster participation of women and minorities in

biomedical research" [101, p. 82]. Such issues must also be seriously considered in nutrigenetics clinical research.

In a significant number of studies in our sample (n=103, i.e., 59%), authors reported that their participants were either part of, or were recruited from, previous or ongoing (usually larger) studies. As we found that such information was not always explicitly reported in the publications of our sample, the number of studies in which pre-existing cohorts were used is actually higher. It must be noted that several studies in our sample were conducted on the same populations or on participants that were recruited from or part of the same pre-existing cohorts. Yet in all cases where studied populations were the same or similar, all resulting publications in our sample reported results on distinct food-polymorphism(s) interactions.

In this paper, we comment on the utmost importance of diversity and broad inclusion in nutrigenetics research. In a public and global health perspective, appropriate inclusion and representativeness of all groups and populations may not be reached if participants in a majority of nutrigenetics studies are systematically recruited from pre-existing or identical cohorts whose characteristics and demographics remain the same. Indeed, our results show that in our sample, nutrigenetics interactions are mostly described for whites/Caucasians, located in North America and Europe (be it in the same cohorts or not, by the same researchers or not). Thus, each time researchers recruit their participants from these pre-existing cohorts in order to test new hypotheses in nutrigenetics, they may reinforce this trend and limit the application of research findings to populations whose demographics do not diverge substantially from that of these pre-existing research samples.

CONCLUSION

While nutrigenetics is still at the first stages of its development, it may impact every one of us, healthy or not, at any age. In such a context, the location where the studies are conducted, as well as the age and origin of participants, do matter and underrepresentation

of certain groups of the population in nutrigenetics clinical research raises scientific and ethical concerns. Yet, as stressed by Bartlett and colleagues, "[i]n an ideal world, trial populations would reflect all those in need of the intervention being tested, but such an ideal is unlikely to be attainable in most instances" [25, p. 103]. This may be particularly true in nutrigenetics, given the many challenges raised by its methodological complexity. Such a complexity creates an inevitable tension between the aim to maximize the chances of observing significant nutrigenetics effects by excluding, from clinical studies, those individuals that could adversely affect results, on the one hand, and the ideal of justice in the research agenda as well as in the access to clinical research, on the other. Yet, in the long term, the underrepresentation of individuals from many countries, of ethnic minorities and of specific age categories in nutrigenetics research might threaten the efficiency of its expected applications in global and public health, creating "nutrigenetics" orphans and exacerbating health disparities.

Certainly, individual researchers as well as research ethics boards do not have the power to ensure an appropriate representation of ethnic minorities and populations of all ages worldwide in the global nutrigenetics research agenda. However, both may participate in its promotion by designing, or reviewing with care, exclusion and inclusion criteria in research protocols. Any reasons for specific exclusions or inclusions should be explicitly stated and justified, ethically and scientifically.

Despite their importance, eligibility criteria are often not reported adequately in publications [102,103]. In addition, as eligibility criteria may not give a true picture of the participants who were actually recruited into clinical studies, one of the major concerns illustrated by our results is the confusion and/or lack of coherent information about the participants' demographics and the use of certain concepts such as race and ethnicity in clinical research reports. Clearly, complete and coherent reporting of such information remains crucial in order to assess the external validity of study findings, as well as the actual representation of diversity in nutrigenetics research. In this respect, editorial guidelines and other recommendations, such as the CONSORT statement [102] or ICH guidelines [104], if fully acknowledged and followed by authors as well as peer reviewers,

may promote adequate reporting and thus increase awareness of the scientific and ethical issues at stake.

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Supplementary table 1. Participants' and authors' geographical location by countries

Continents	Countries	Number of studies[1] in which participants are located in the specific continent/country mentioned on the left	Number of studies[1] in which authors are affiliated with an institution based in the specific continent/country mentioned on the left
Asia	China (including Taiwan)	14	15
	Japan	10	11
	Singapore	4	5
	India	1	1
Central America	Costa Rica	7	5
	Bahamas	2	0
Europe	United Kingdom (including Scotland)	19	22
	Spain	13	21
	The Netherlands	12	13
	Germany	4	5
	Denmark	4	4
	France	4	5
	Italy	4	5
	Finland	3	4
	Greece	2	2
	Poland	2	2
	Czech Republic	2	2
	Portugal	1	1
	Romania	1	1
	Russia	1	1
	Sweden	1	2
	Austria	0	1
	Switzerland	0	1
	Norway	0	1
North America	USA	53	87
	Canada	15	21
Oceania	Australia	0	1

[1]Total number of studies=173. Same studies may involve participants as well as authors in different countries.

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Supplementary table 2. Proportion of ethnic groups as explicitly reported in 36 mixed studies.

Ethnicity[1]	%[2]	Ethnicity	%	Ethnicity	%
White Hispanic African-American	91 4.5 4.5	Caucasian African-American Asian Others	63 26 5 5	Other white Jewish French-Canadian Others	60 32 5 3
Black White	53 47	Caucasian African-American	77 23	White Others	95 5
Chinese Malays Asian-Indian	64 21 15	Hispanic (Puerto Rican descent) African-American White	66 32 2	Japanese-American White Latino African-American Native Hawaiian Other	25 22 21 19 7 6
White African-American	51 49	Non-Hispanic White Non-Hispanic Black Others	94 3 3	Spanish settlers Indigenous Amerindians West Africans	65 28 7
Japanese Caucasian Native Hawaiian	60 26 14	Chinese Malays Asian-Indian	61 22 17	Japanese Japanese American	58 42
White (non Hispanic) Hispanic Black (non Hispanic)	91.4 4.4 4.2	Caucasian African-American Hispanic Asian	90 6 3 1	Non-Hispanic White Non-Hispanic Black Mexican-American	39 31 30
Caucasian African-American Asian Native American Other heritages	65 25 5 3 2	Japanese-American White Latino African-American Native Hawaiian Other ethnic/racial origin	26 23 22 16 7 6	Non-Hispanic White Hispanic White Others	60 28 12
Caucasian African-American Hispanic	92 4 4	Hispanic White Non-Hispanic White	62 38	Latina White African-American	37 34 29
White African-American (Black)	55 45	White Others	86 14	African-American White	61 39
White Others	98 2	Chinese Malays Indian	61 21 18	Caucasian Hispanic African-American	91 4 4
Caucasian Jewish East Asian Others	84 5 4 7	White African-American Hispanic Asian Others/unknown	n/a	African-American Non-Hispanic White	n/a
Mexican American Asian Caucasian African American Arabian	47 25 16 9 3	White Hispanic White non-Hispanic Others	n/a	Hispanic Non-Hispanic White	n/a

[1] The "Ethnicity" column lists the different ethnic groups represented in each mixed study.
[2] The "%" column indicates the proportion of each ethnic group in the sample of the study.

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