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Published in:
Clinical Nutrition

DOI:
10.1016/j.clnu.2023.04.026

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Ni, X., Su, H., Lv, Y., Li, R., Liu, L., Zhu, Y., Yang, Z., & Hu, C. (2023). Modifiable pathways for longevity: A Mendelian randomization analysis. *Clinical Nutrition*, *42*(6), 1041-1047. https://doi.org/10.1016/j.clnu.2023.04.026

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Download date: 01-11-2023

Clinical Nutrition 42 (2023) 1041–1047

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Modifiable pathways for longevity: A Mendelian randomization analysis

Xiaolin Ni [a, *], Huabin Su [b], Yuan Lv [b], Rongqiao Li [b], Lei Liu [c], Yan Zhu [d], Ze Yang [a], Caiyou Hu [b]

[a] The Key Laboratory of Geriatrics, Beijing Institute of Geriatrics, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital/National Center of Gerontology of National Health Commission, 100730, PR China
[b] Jiangbin Hospital, Guangxi Zhuang Autonomous Region, 530021, PR China
[c] Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[d] Center for Health Statistics and Information, National Health Commission of Peoples Republic of China, Beijing 100044, PR China

ARTICLE INFO

Article history:
Received 28 March 2022
Accepted 28 April 2023

Keywords:
Longevity
Risk factors
Mendelian randomization
BMI
Metabolism

SUMMARY

Background: A variety of factors, including diet and lifestyle, obesity, physiology, metabolism, hormone levels, psychology, and inflammation, have been associated with longevity. The specific influences of these factors, however, are poorly understood. Here, possible causal relationships between putative modifiable risk factors and longevity are investigated.

Methods: A random effects model was used to investigate the association between 25 putative risk factors and longevity. The study population comprised 11,262 long-lived subjects (≥90 years old, including 3484 individuals ≥99 years old) and 25,483 controls (≤60 years old), all of European ancestry. The data were obtained from the UK Biobank database. Genetic variations were used as instruments in two-sample Mendelian randomization to reduce bias. The odds ratios for genetically predicted SD unit increases were calculated for each putative risk factor. Egger regression was used to determine possible violations of the Mendelian randomization model.

Results: Thirteen potential risk factors showed significant associations with longevity (≥90th) after correction for multiple testing. These included smoking initiation (OR:1.606; CI: 1.112–2.319) and educational attainment (OR:2.538, CI: 1.685–3.823) in the diet and lifestyle category, systolic and diastolic blood pressure (OR per SD increase: 0.518; CI: 0.438–0.614 for SBP and 0.620; CI 0.514–0.748 for DBP) and venous thromboembolism (OR:0.002; CI: 0.000–0.047) in the physiology category, obesity (OR: 0.874; CI: 0.796–0.960), BMI (OR per 1-SD increase: 0.691; CI: 0.628–0.760), and body size at age 10 (OR per 1-SD increase:0.728; CI: 0.595–0.890) in the obesity category, type 2 diabetes (T2D) (OR:0.854; CI: 0.816–0.894), LDL cholesterol (OR per 1-SD increase: 0.743; CI: 0.668–0.826), HDL cholesterol (OR per 1-SD increase: 1.243; CI: 1.112–1.390), total cholesterol (TC) (OR per 1-SD increase: 0.786; CI: 0.702–0.881), and triglycerides (TG) (OR per 1-SD increase: 0.865; CI: 0.749–0.998) in the metabolism category. Both longevity (≥90th) and super-longevity (≥99th), smoking initiation, body size at age 10, BMI, obesity, DBP, SBP, T2D, HDL, LDL, and TC were consistently associated with outcomes. The examination of underlying pathways found that BMI indirectly affected longevity through three pathways, namely, SBP, plasma lipids (HDL/TC/LDL), and T2D ($p < 0.05$).

Conclusion: BMI was found to significantly affect longevity through SBP, plasma lipid (HDL/TC/LDL), and T2D. Future strategies should focus on modifying BMI to improve health and longevity.

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Abbreviations: BMI, body mass index; CI, confidence intervals; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IVW, inverse variance-weighted; GWAS, genome-wide association studies; LDL, low-density lipoprotein; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratio; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides.

* Corresponding author.
E-mail address: xiaolin_ni7@126.com (X. Ni).

https://doi.org/10.1016/j.clnu.2023.04.026
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1. Introduction

The world's population is aging. Life expectancy since the start of the twenty-first century has increased by 5.5 years [1] and it is estimated that the number of people over the age of 80 will triple by 2050 and increase over sevenfold by 2100 [2]. This extended lifespan is a recent development and is not the product of evolution. Because of this lack of evolutionary adaptation, people of advanced age are vulnerable to a variety of chronic and degenerative diseases, such as cardiovascular disease, cancer, and neurodegeneration. As a result, older persons face a reduced quality of life and a significant financial burden [3].

The maintenance of healthy longevity is an important strategy to cope with aging and the avoidance of age-associated diseases [4]. Both physical and mental factors, including diet, regular exercise, avoidance of excess alcohol and smoking, and having an optimistic outlook, influence longevity. Observational studies have linked alcohol consumption and physical activity with life expectancy [5] and interventions to promote healthy lifestyles have proved effective [3]. The China Hainan Centenarian Cohort Study found that centenarian longevity had inverse relationships with nutritional status and obesity and a positive relationship with sex hormones, while nutritional status and obesity were inversely related to sex hormones. Optimizing nutritional status and avoiding obesity may increase the levels of sex hormones and promote centenarian longevity and successful aging [6]. In addition, the finding of a U-shaped association between late-life systolic blood pressure (SBP) and all-cause mortality suggests that blood pressure is also a potential risk factor for longevity [7]. In the past few decades, studies in both model organisms and humans have identified a series of genetic pathways associated with lipid metabolism and glycemic indices that regulate lifespan. Lipid-related interventions and keeping blood glucose fluctuations in the normal range are conducive to longevity [8–10]. However, although previous observational studies have provided much of the data on causal links between possibly modifiable factors and longevity; unfortunately, this type of study is prone to confounding bias and reverse causation [11]. In addition, randomized trials are often inconclusive due to limited data. Therefore, none of these researches have provided a specific formula for living a long and healthy life.

Mendelian randomization is an effective analytic approach that uses genetic variants as instrumental variables in the analysis of potential risk factors. As these variants are randomly sorted during meiosis and are not subject to subsequent environmental change, their use reduces the risk of reverse causation and confounding [12]. These analyses are frequently used for the evaluation of interventions on outcomes as they are able to avoid many of the drawbacks of observational studies.

Based on the findings of many previous studies on possibly modifiable risk factors associated with longevity, we hypothesized that such possibly modifiable risk factors are causally related to longevity. In this study, longevity was defined as survival to ages above 90 or 100 years or belonging to the top 10% or 1% of survivors in a population. The genetic variants were first identified from large-sample genome-wide association studies (GWAS) and we then investigated the relationships between these and longevity using two-sample Mendelian randomization to explore effective and unbiased interventions to promote healthy longevity.

2. Methods

2.1. Selection of possible modifiable risk factors

PubMed was searched for meta-analyses on the epidemiology of longevity using the search terms "((longevity) AND risk factor) AND meta-analysis". The search was undertaken on December 3, 2021, and was restricted to meta-analyses published in the previous five years. Potential risk factors were selected from PubMed searches with the terms: "(((longevity) AND risk factor) AND cohort)" (search conducted on December 3, 2021). Mendelian randomization (MR) analyses were searched for with the terms: "((longevity) AND ((Mendelian randomization) OR Mendelian randomization)" (search conducted on December 3, 2021). This identified 800 publications. After the exclusion of review articles and articles not describing longevity, 22 articles remained and were included in the study. The 46 potentially modifiable risk factors associated with longevity were classified into seven categories: Diet and Lifestyle, Obesity, Physiology, Metabolism, Hormones, Psychology, and Inflammatory Factors (Supplementary Table 1). After the exclusion of a number of potential risk factors that lacked GWAS data, 25 factors were finally included in the Mendelian randomization analysis. A flowchart detailing the inclusion and exclusion procedures is shown in Fig. 1.

2.2. Two-sample MR design

A two-sample MR design was applied following ten simple rules [13]. This used genetic variants as instrumental variables using single-nucleotide polymorphisms (SNPs) identified from GWAS investigations. Three MR assumptions were used for the unbiased estimation of possible causal relationships, namely, (i) that the SNPs were associated with exposure, (ii) that the SNPs were independent of confounding of the exposure-outcome association, and (iii) that the SNPs were only able to affect the outcome by exposure [14]. The need for institutional approval of the study was waived as the data were from published material with no inclusion of patient data.

2.3. Longevity data source

Genetic associations with longevity were obtained from a recently published GWAS meta-analysis [15] analyzing subjects of European ancestry from approximately 20 family- or population-based cohorts in the USA and Europe, specifically, France, Denmark, Iceland, Finland, Italy, The Netherlands, and the UK. The GWAS summary database included cohorts that participated in one or more of the previously published GWA studies on longevity [16,17]. The analysis included subjects over the ages of 90 or 99 (90th and 99th survival percentiles, respectively) (N = 11,262/3484) using census data from the appropriate country, sex, and birth cohorts. The controls (N = 25,483) had either died before reaching the 60th percentile or whose last follow-up was before this time.

2.4. Data sources and selection of variants

The genetic variants for the modifiable risk factors were selected from the largest GWAS conducted primarily amongst individuals of European ancestry. Information on the exposure data sources is given in Table 1; these included educational attainment [18] (age when regular smoking was begun, cigarettes per day, drinks per week, age when smoking was discontinued) [19], sleep duration [20], physical activity [21], iron and selenium levels, body size at age 10, hormone levels (osteocalcin, luteinizing hormone, and total testosterone) [22] and estradiol [23], BMI [24], body fat [25], obesity [26], blood pressure (SBP and DBP) [18]), venous thromboembolism, fasting glucose [27], T2D [28], plasma lipids (LDL cholesterol, HDL cholesterol, TC, and TG [29]), and subjective wellbeing [30].

The Neallab data which was performed using the program BOLT_LMM have been transformed before MR analyses

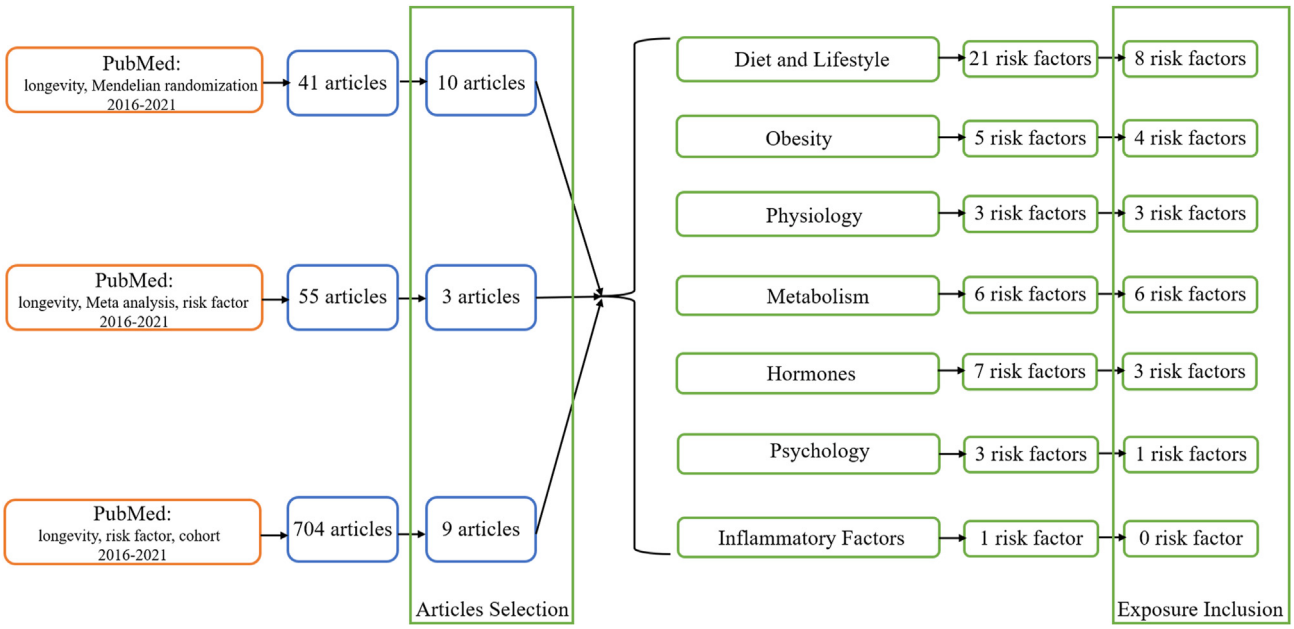

Fig. 1. The screening process for potential risk factors used in the study.

(Supplementary Table 2). The clump procedure in Plink software was used to determine the instrumental variables for modifiable risk factors. SNPs that were linked with the risk factors at the genome-wide significance threshold ($p < 5E\text{-}08$) were chosen while those that were strongly associated with longevity were omitted. In the case of SNPs in linkage disequilibrium ($r^2 > 0.1$) within traits, the variant with the highest association with exposure (the smallest p-value) was selected. Lastly, SNPs that were not included in the longevity GWAS were omitted. Altogether, between 1 and 1062 SNPs were used as instrumental variables for the various factors. The phenotypic variance accounted for by these variants was between 0.004% for estradiol and 7.649% for BMI. The estimates

Table 1
Overview of the data sources of the instrumental variables used in the Mendelian randomization study.

Exposure class	Exposure	Sample size	Ancestry	Unit[a]	SNPs[b]	Data source
Diet and lifestyle	Educational attainment	459,327	European	1-SD increase in years of educational attainment	300	PMID: 29892013
	Age Of Initiation of Regular Smoking	341,427	European	years old	7	PMID: 30643251
	Cigarettes Per Day	337,334	European	1-SD increase in number of cigarettes smoked per day	30	PMID: 30643251
	Drinks Per Week	941,280	European	1-SD increase in log-transformed alcoholic drinks/week	46	PMID: 30643251
	Smoking Cessation	547,219	European	Binary phenotype with current smokers coded as "2" and former smokers coded as "1"	9	PMID: 30643251
	Smoking Initiation	1,232,091	European	ever smoked regularly compared to never smoked	109	PMID: 30643251
	Sleep Duration	128,266	European	hour per day	3	PMID: 27494321
	Physical activity	91,105	European	average vector magnitude for each 30-s epoch	17	PMID: 30531941
	Metal Iron	64,979	European	mg	3	MRC-IEU
	Metal selenium	461,384	European	mg	1	MRC-IEU
	Osteocalcin	3301	European	relative fluorescent units	3	PMID: 29875488
Obesity	body size at age 10	454,718	European	\	362	MRC-IEU
	BMI	694,649	European	1-SD increase in body mass index	1062	PMID: 30239722
	Body fat	100,716	European	percentage	8	PMID: 26833246
	Obesity	263,407	European	\	16	PMID: 23563607
Physiology	Diastolic Blood Pressure	757,601	European	1-SD increase 11.3 mmHg	240	PMID: 30224653
	Systolic Blood Pressure	757,601	European	1-SD increase 20.7 mmHg	220	PMID: 30224653
	Venou thromboembolism	361,194	European	\	13	Neale lab
Hormone	Luteinizing	3301	European	mmol/L	1	PMID: 29875488
	Total testosterone	3301	European	mmol/L	1	PMID: 29875488
	Estradiol	456,348	European	mmol/L	1	PMID: 34737426
Metabolism	Fasting Glucose	76,558	European	mmol/L	15	PMID: 20081858
	T2D	452,244	European	odds of type 2 diabetes	268	PMID: 29632382
	HDL	188,577	European	1-SD increase in HDL cholesterol	134	PMID: 24097068
	LDL	188,577	European	1-SD increase in LDL cholesterol	101	PMID: 24097068
	TC	188,577	European	1-SD increase in total cholesterol	125	PMID: 24097068
	TG	188,577	European	1-SD increase in triglycerides	75	PMID: 24097068
Psychology	Subjective well being	298,420	European	\	1	PMID: 27089181

Note: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, total triglyceride; T2D, type 2 diabetes; SNP, single-nucleotide polymorphism; SD, standard deviation.
[a] Units as used in the MR analysis.
[b] Number of SNPs included in MR/number of SNPs identified in GWAS.

of the effects of the SNPs were flipped with unrelated effects and alleles to synchronize the data between exposure and the longevity GWAS.

2.5. Statistical analyses

An accurate estimation of causal effect sizes requires that the associations are linear and not influenced by statistical interactions. Inverse variance-weighted (IVW) was used for the main analysis. To calculate a single IVW for each exposure, the odds ratios of the SNPs were assembled using a multiplicative random effects meta-analysis [14]. While this allows precise estimation of possible causal relationships, it is possible that pleiotropy or invalid instrument bias may occur if the MR assumptions do not hold. We, therefore, used several types of sensitivity analysis to counteract these issues, specifically, the weighted median method, MR-Egger regression, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO). The weighted median method checks for invalid instrument bias and gives a causal assessment if more than half of the weight is represented by valid SNPs [31]. MR-Egger regression can assess and regulate directional pleiotropy, although it has low precision [32]. The MR-PRESSO method assesses the potential influence of outlier SNPs on the results and is thus an estimate of potential pleiotropy [32].

We assessed the indirect effects of indicators between lifestyle and outcomes within the framework of the multivariate MR and constructed a network for MR analysis [33]. Notably, we only used instrumental variables for exposure and extracted corresponding information on exposure, outcome, and mediator variables. Finally, 95% confidence intervals for indirect effects were calculated using the 1000-run bootstrap method.

The statistical analyses were conducted in R 3.6.3 using the packages “MendelianRandomization” [34] and “MRPRESSO” [32].

The results were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). To adjust for multiple testing, we used a Bonferroni-corrected, two-sided significance level of 0.002 (0.05 divided by 25 risk factors). P-values above the Bonferroni-corrected significance level, but below 0.05 were considered to represent a potential association.

3. Results

3.1. Modifiable risk factors and longevity: principal findings

Of the 46 potentially modifiable risk factors for longevity that were investigated, 21 were related to diet and lifestyle, five to obesity, three to physiology, six to metabolism, seven to hormones, three to psychology, and one to inflammatory factors (Supplementary Table 1). A number of factors were excluded due to a lack of GWAS data, resulting in a final inclusion of 25 factors in the Mendelian randomization analysis (Fig. 1 and Table 1).

Using a random-effects inverse-variance weighted (IVW) model to examine the effects of diet- and lifestyle-related factors, we observed a possible association between genetic liability to educational attainment and higher longevity odds (≥90th) (OR:2.538, CI: 1.685–3.823). The IVW method was used because of significant heterogeneity in the SNPs used as instrumental variables. The estimates for the causal effect of educational attainment were consistent with sensitivity analysis using weighted median and mode-based methods and MR-Egger regression intercepts did not find evidence of directional pleiotropy (Supplementary Table 4). Smoking initiation was associated with both longevity (≥90th) (OR:1.606; CI: 1.112–2.319) and super-longevity (≥99th) (OR:1.902; CI: 1.067–3.388) (Fig. 2 and Supplementary Table 3), with no pleiotropic outliers identified (Supplementary Tables 4 and 5). Genetically predicted age at the start of regular smoking, cigarettes per day, drinks per week, termination of smoking, sleep duration, physical activity, metal iron, metal selenium, and osteocalcin were not associated with either longevity (≥90th) or super-longevity (≥99th) (Fig. 2 and Supplementary Table 3).

In our analysis of factors in the obesity category, factors linked to lower longevity odds (≥90th) included (Fig. 2 and Supplementary Table 3) genetic liability to obesity (OR: 0.874; CI: 0.796–0.960), genetic predisposition to higher BMI (OR per 1-SD increase: 0.691; CI: 0.628–0.760), and genetically predicted larger body size at age 10 (OR per 1-SD increase:0.728; CI: 0.595–0.890). The following genetically predicted risk factors were associated with super-longevity (≥99th) (Fig. 2 and Supplementary Table 3): obesity (OR per 1-SD increase: 0.801; CI 0.694–0.925), body size at age 10 (OR per 1-SD increase: 0.695; CI: 0.505–0.956), BMI (OR per 1-SD increase: 0.649; CI: 0.556–0.757) and body fat (OR:0.466; CI: 0.241–0.901). The MR-Egger regression intercept did not suggest horizontal pleiotropy for BMI, body fat percentage, or other obesity-related traits (Supplementary Tables 4 and 5).

There was a suggestive association between predicted higher SBP and DBP and lower odds for both longevity (≥90th) and super-longevity (≥99th). The per one SD (~20.7) increase of SBP on longevity is estimated to be 0.518 (95%CI: 0.438–0.614, $p = 3.093E-14$) and on super-longevity is estimated to be 0.536 (95%CI: 0.406–0.706, $p = 9.575E-06$). The per one SD (~11.3) increase of DBP on longevity is estimated to be 0.620 (95%CI: 0.514–0.748, $p = 6.052E-07$) and on super-longevity is estimated to be 0.581 (95%CI: 0.441–0.765, $p = 1.120E-04$). A genetic predisposition to venous thromboembolism was also suggested to be linked with lower odds for longevity (≥90th) (OR:0.002; CI: 0.000–0.047) (Fig. 2 and Supplementary Table 3). The causal estimates for physiology-related factors were essentially in agreement with the weighted median and mode-based sensitivity analyses. The MR-Egger analysis of DBP suggested potential pleiotropy due to a significant deviation of the intercepts from zero; however, the MR-PRESSO analysis showed no outlying SNPs and the p-value of the global test was below 0.01 (Supplementary Table 5).

For causal analysis of metabolism-related factors and longevity, genetic susceptibility to type 2 diabetes (OR:0.854; CI: 0.816–0.894), elevated LDL cholesterol (OR per 1-SD increase: 0.743; CI: 0.668–0.826), elevated total cholesterol (OR per 1-SD increase: 0.786; CI: 0.702–0.881), and elevated triglyceride levels (OR per 1-SD increase: 0.865; CI: 0.749–0.998) were associated with lower odds for longevity (≥90th) (Fig. 2 and Supplementary Table 3). Higher odds (≥90th) were seen only with predicted HDL cholesterol (OR per 1-SD increase: 1.243; CI: 1.112–1.390). Predicted risk factors associated with super-longevity (≥99th) (Fig. 2 and Supplementary Table 3) included T2D (OR:0.855; CI: 0.795–0.919), HDL cholesterol (OR per 1-SD increase: 1.293; CI 1.090–1.535), LDL cholesterol (OR:0.664; CI: 0.564–0.782), and total cholesterol (OR:0.714; CI 0.601–0.848 for TC). Predicted fasting glucose was not significantly linked to longevity. These results were sustained in the sensitivity analyses in both longevity (≥90th) and super-longevity (≥99th) (Supplementary Figs. 1 and 2).

Although hormonal and psychological factors appeared to be significantly associated with longevity, no causal relationship was found between hormone levels (luteinizing hormone, total testosterone, estradiol) or subjective well-being and longevity (Supplementary Table 3). However, the analysis used only a single variant accounting for a small proportion of the variance of these hormonal and psychological factors and thus had reduced power for the detection of an effect (Supplementary Table 3). It is thus possible that these factors may have a small effect on the longevity

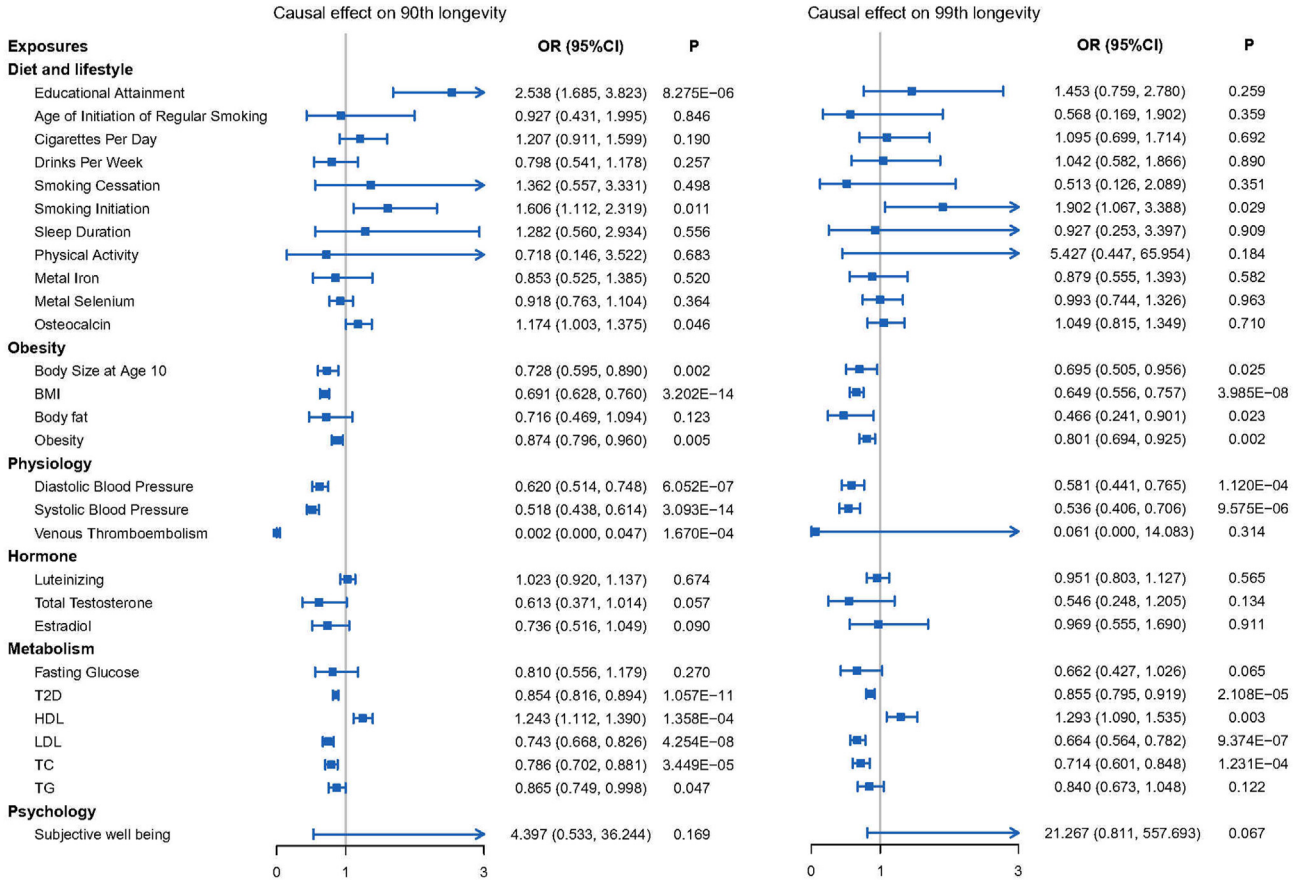

Fig. 2. OR_{SD} for associations between genetically predicted risk factors and longevity. An inverse-variance weighted (IVW) method was used to summarize the odds ratio estimates for individual SNPs. OR_{SD} = odds ratio for SD unit increases in risk factors. SNP = single-nucleotide polymorphism. †OR_{SD} was calculated based on longevity data for the 90th and 99th survival percentiles, respectively.

odds. In general, smoking initiation in diet and lifestyle factors, body size at age 10, BMI, and obesity in obesity, DBP and SBP in physiology, and T2D, HDL, LDL, and TC in metabolism were consistently associated with both longevity (≥90th) and super-longevity (≥99th).

3.2. Mediation by modifiable risk factors

Based on the results of the possible causal relationships between exposure and outcome, we found that the factors that influenced longevity were mainly associated with obesity, physiology, and metabolism. A summary of the possible associations between the nine modifiable risk factors (body size at age 10, BMI, obesity, DBP, SBP, T2D, HDL, LDL, and TC) and longevity is shown in Fig. 3. BMI indirectly affected longevity through three pathways: SBP (p = 0.07, β = −0.045), plasma lipids (HDL (p = 1.307E-04, β = −0.122)-TC (p = 0.013, β = −0.070)-LDL (p = 1.311E-04, β = −0.437)), and T2D (p = 1.824E-04, β = −0.163). DBP indirectly affected longevity through SBP (p = 3.266E-05, β = −0.516) (Supplementary Table 6).

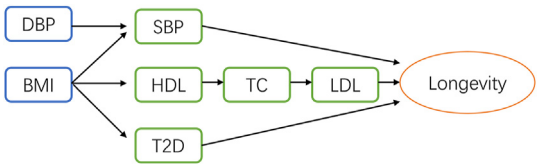

Fig. 3. Summarized overview of the putative associations of risk factors with longevity. BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; T2D: type 2 diabetes; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol.

4. Discussion

In this MR study using genetic variants as substitutes for risk factors, we found that nine of the original 46 selected factors were significantly related to both longevity (≥90th) and super-longevity (≥99th). Higher predicted levels of HDL cholesterol were linked to greater odds of longevity, whereas lower odds were found for body size at age 10, BMI, obesity, DBP, SBP, T2D, LDL cholesterol, and total cholesterol. There was a suggestive link between the later of starting smoking and higher longevity odds, while higher educational attainment, low genetic liability to venous thromboembolism, and genetically predicted lower TG were associated with higher odds for longevity (≥90th) but not for super-longevity (≥99th). However, it seems extreme effect sizes of venous thromboembolism on longevity. Venous thromboembolism itself will cause cardiovascular and cerebrovascular diseases and seriously affect life expectancy [35]. In this study, venous thromboembolism was a dichotomous variable. Therefore, our results show that the probability of longevity is extremely low, which is logical. In addition, due to the influence of the data itself, there were fewer instrumental variables and limited sample size for the causal relationship between venous thromboembolism and longevity, which would also decrease the credibility of the results and the effect values.

The exclusion of pleiotropy and alternative causes is often a challenge in Mendelian randomization studies. The observation of high I^2 values for a number of factors suggests the presence of pleiotropy in this study. Because of this, we conducted sensitivity analyses using MR Egger regression, weighted medians, and MR-PRESSO, which allow unbiased estimation of causal effects if the instrumental variables are invalid [36,37]. Many of the factors had either significant or suggestive relationships with longevity, and it is also possible that this is also the case for DBP; however, DBP showed pleiotropy and was found to be non-significant by MR-PRESSO. The mediation analysis showed that DBP was indirectly related to longevity through SBP, which may explain the pleiotropy problem. Our previous investigations into the epidemiology of a healthy and long-lived population in the Shanglin area of Guangxi also found that SBP was more associated with longevity than DBP [38].

Modifiable risk factors form part of pathways associated with longevity; this was also confirmed by the mediation analysis. The modifiable risk factor BMI is likely to function as an upstream cause with more direct effects mediated by SBP, plasma lipids (HDL/TC/LDL), and T2D. Obesity is a heterogeneous phenotype that can be measured by the crude index, BMI [39]. Excess body weight and adiposity lead to insulin resistance and inflammation, as well as hormonal and metabolic changes that result in atherosclerosis, tumorigenesis, degenerative disease, and aging. Both human and animal studies have shown the benefits of low body weight on health and longevity [40] and further work is needed to fully elucidate the underlying physiological pathways. However, regardless of the precise mechanisms, our analysis highlighted low BMI as a critical target for the promotion of health and longevity. BMI ultimately affects health and longevity through blood pressure, blood lipids, and the development of type 2 diabetes.

4.1. Strengths and limitations

Our study attempted to explore effective and impartial interventions to promote healthy longevity by analyzing the causal relationships between 46 potentially modifiable risk factors in seven categories and longevity. The major strength is our investigation of multiple factors associated with longevity using the data of a large GWAS. Many of these factors have not been previously investigated using the Mendelian randomization approach, including factors for which suggestive associations were found, including selenium, osteocalcin, obesity, body size at age 10, estradiol, luteinizing hormone, and subjective wellbeing [41,42]. For factors that have been assessed in previous studies, the large numbers of cases and controls used in the present analysis resulted in greater analytical power for the detection of causal links as well as a more accurate estimation of the magnitudes of the effects. Comparison of the findings of this study with those of previous investigations on factors promoting longevity allowed us to detect the likelihood of false positives in previous reports e.g., alcohol consumption, physical activity, and fasting glucose.

The validity of the causal associations identified in this analysis depends essentially on the robustness of the instrumental variable assumptions. The different sensitivity analyses demonstrated the robustness of the findings in terms of the assessment of pleiotropy and invalid instrument bias. In addition, we used multiple, independent, and genome-wide variants as instrumental variables, thus ensuring the fulfillment of the first MR assumption. The factors representing exposures and the longevity phenotypes representing outcomes were obtained from GWAS summary statistical data on European subjects, thus there are no racial complications.

However, the main limitation of this study is that the data sources are from different databases with inconsistent sample sizes. If there is a non-linear relationship, it may interfere with normal associations. Secondly, the lower variations in exposure shown by the genetic instruments for age at start of smoking, time of stopping smoking, sleep duration, iron, selenium, osteocalcin, body fat, luteinizing, total testosterone, estradiol, and subjective well-being resulted in low precision. Consequently, the absence of associations for these factors cannot be assumed to represent a lack of causal effect. Another limitation is that the exposure factors that contribute to longevity are not comprehensive due to the absence of suitable data in the literature. Further research is required to explore exposure factors that are directly associated with healthy longevity and the biological pathways underpinning the associations.

5. Conclusions

Body size at age 10, BMI, obesity, DBP, SBP, T2D, HDL, LDL, and TC were identified as modifiable factors influencing longevity. Of these, BMI was found to be a critical target affecting longevity through SBP, plasma lipids (HDL/TC/LDL), and T2D. Therefore, future strategies should focus on modifying BMI to improve health and longevity.

Funding sources

This work is supported by grants from by the Natural Science Foundation of China (82260289, 91849118); Guangxi Natural Science Foundation (2014GXNSFDA118028, 2018GXNSFAA138156, guike0991198); Self-funded Scientific Research Project of the health and family planning commission of Guangxi Zhuang Autonomous Region (Z20170162).

Statement of authorship

XN and HS conceived and designed the study, literature search and wrote the original draft. LL and YZ did the data collection, formal analysis and methodology, XN, YL and RL did the visualization, and methodology. CH and XN did project administration and coordination and reviewed and edited the manuscript. XN, HS and CH accessed and verified the data. All authors had final responsibility for the decision to submit for publication.

Conflicts of interest

The authors declare no competing financial interests relevant to this article. All financial and material support for this research has no potential conflicts. All authors read and approved the final manuscript.

Acknowledgments

We thank all study participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.04.026.

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