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ORIGINAL ARTICLE

The impact of sociodemographic status on the association of classical cardiovascular risk factors with coronary artery disease: a stratified Mendelian randomization study

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Abstract

Objectives: Low socioeconomic status (SES) is associated with cardiovascular risk factors and increased coronary artery disease (CAD) risk. We tested whether SES is an effect modifier of the association between classical cardiovascular risk factors and CAD using SES-stratified Mendelian Randomization in European-ancestry participants from UK Biobank.

Study Design and Setting: We calculated weighted genetic risk scores (GRS) for the risk factors body mass index (BMI), systolic blood pressure, low-density lipoprotein cholesterol, and triglycerides. Participants were stratified by Townsend deprivation index score. Logistic regression models were used to investigate associations between GRSs and CAD occurrence. Additionally, stratification based on GRS-adjusted Townsend deprivation index residuals was conducted to correct for possible collider-stratification bias.

Results: In a total sample size of N = 446,485, with 52,946 cases, the risk for CAD per standard deviation increase in genetically influenced BMI was highest in the group with the lowest 25% SES (odds ratio: 1.126, 95% confidence interval: 1.106−1.145; odds ratio: 1.081, 95% confidence interval: 1.059−1.103 in high SES), remaining similar after controlling for possible collider-stratification bias. The effects of genetically influenced systolic blood pressure, low-density lipoprotein cholesterol, and triglyceride on CAD were similar between SES groups.

Conclusion: CAD risk attributable to increased BMI is not homogenous and could be modified by SES. This emphasizes the need of tailor-made approaches for BMI-associated CAD risk reduction.

Keywords: Coronary artery disease; Socioeconomic status; Body mass index; Cardiovascular diseases; Mendelian randomization; Effect modification

1. Introduction

Individuals with low socioeconomic status (SES) are at an increased risk of developing cardiovascular disease (CVD) [1−4]. Although it is known that a low SES is associated with adverse lifestyle factors such as smoking, alcohol consumption, unhealthy diet, and physical inactivity [5−8], the exact mechanisms underlying the link between SES and risk for CVD are still relatively unclear. Additionally, classic cardiovascular risk factors such as high body mass index (BMI), elevated blood lipid levels, and systolic blood pressure (SBP) play prominent roles in the pathogenesis of (atherosclerotic) CVD [9]. Simultaneously, studies indicate that these classic risk factors are also generally more prevalent in individuals with lower SES [10−13], emphasizing the complex interplay between SES, CVD risk factors, and the development of disease.

In a previous study conducted in the UK biobank, it was shown that as much as 40% of the association between low education, as a reflection of low SES, and increased CVD risk was mediated by BMI, blood pressure, and smoking behavior [14]. Additionally, evidence is emerging that the risk for CVD associated with the classical CVD risk factors

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What is new?

Key findings

- Classical cardiovascular risk factor are associated with coronary artery disease in Mendelian randomization in all groups based on socioeconomic status.
- In people with the lowest socioeconomic status, the association between genetically-influenced body mass index and coronary artery disease was strongest.

What this adds to what was known?

- Maximum effect of intervention studies might be dependent on the socioeconomic status.
- While Mendelian randomization studies usually study population averages, relevant subgroup effects might exist.

What is the implication and what should change now?

- Intervention studies in all relevant subgroups should be investigated more to ensure largest effects on population health.

is not universal throughout subgroups of the general population and differs, for example, already for different age groups and for the different sexes in observational studies [15,16]. The heterogeneous risk factor–CVD associations in different groups of the general population emphasize the need of a ''tailor-made'' approach for clinical decision-making. These observations are in line with the general hypothesis that atherogenic cardiovascular diseases are not a single disease entity but as a dynamic disease construct with changing pathogenesis depending on specific patient characteristics throughout life. For example, and in line with this concept, we previously showed, using Mendelian Randomization (MR) approaches, that the impact of genetically influenced increased BMI on the risk of developing type 2 diabetes was dependent on the age of diagnosis with older people with higher BMI were less susceptible for developing type 2 diabetes [17]. In addition, the impact of classical genetically influenced CVD risk factors on coronary artery disease (CAD) attenuated for increasing age of diagnosis [18].

We hypothesized that SES is an important factor that can modify the impact of classical CVD risk factors on CVD, in addition to age and sex. If confirmed, this would mean that interventions tailored to specific SES groups may achieve a larger reduction in CVD risk not only due to low SES groups having a higher average BMI but also due to SES acting as a catalyst for BMI-attributable CAD risk. To omit potential reverse causation and/or most confounding in our analyses, we used a MR approach. Here, genetic variants are used as instrumental variables for given exposures to approximate the effect of life-long exposure to risk factors on the development of disease outcomes [19–21]. In the present study [22], we assessed the associations between classical genetically influenced CVD risk factors and CAD, stratified for SES, in a large cohort of European-ancestry participants from the UK Biobank.

2. Methods

2.1. Study setting and population

The UK Biobank is a prospective general population cohort with 502,628 participants between the age of 40 and 70 years at the moment of enrollment [23]. Recruitment took place between 2006 and 2010 (more information can be found online; https://www.ukbiobank.ac.uk). Invitation letters were sent to eligible adults registered to the National Health Services and living within a 25-mile distance from one of the assessment centers. Participants provided information on their lifestyle and medical history through touch-screen questionnaires and physical measurements. Blood samples were collected for biochemistry analyses and genotyping.

The UK biobank study was approved by the North-West Multicenter Research Ethics Committee. Access for information to invite participants was approved by the Patient Information Advisory Group for England and Wales. All participants in the UK Biobank provided a written informed consent. The present study was accepted under project number 56340.

We restricted all our analyses to participants of European origin (N = 446,485), as to limit confounding by ethnic genetic variation. Townsend Deprivation Index (TDI) scores, a measure of SES, were collected at baseline for nearly all of the participants in the study (N = 445,965).

2.1.1. Genotyping, genetic imputations, and genetic risk scores

For our study, we conducted stratified MR analyses, where weighted genetic risk scores (GRS) were used to represent the genetically determined higher BMI, low-density lipoprotein (LDL) cholesterol levels, triglyceride (TG) levels, and SBP. These weighted GRS were calculated using independent lead genetic variants (P value $< 5 \times 10^{-8}$) that have been previously identified in genome-wide association meta-analyses in which the UK Biobank population did not contribute. The GRS score for BMI was based on data from 339,224 individuals; 76 single nucleotide polymorphisms (SNPs) [24], LDL cholesterol level on 188,577 individuals; 15 SNPs [25], TGs on 188,577 individuals; 20 SNPs [25], and SBP 200,000 individuals; 42 SNPs [26].

The published beta estimates for the independent lead variants in these genetic meta-analyses were subsequently used to calculate the weighted GRS for each CVD risk factor for each participant in the UK biobank study. Overlapping independent lead variants [25] between LDL cholesterol and TG levels in the genetic risk scores were not taken into account in the calculation of the GRS with the intention to limit bias by (directional) pleiotropy.

The genotyping of the UK Biobank population was performed for roughly 50,000 participants by Affymetrix, using a BiLEVE Axiom array. For the other UK Biobank participants, the genotyping was performed using the Affymetrix UK Biobank Axiom array. More information on the genotyping processes can be found online (https://www.ukbiobank.ac.uk). Based on the genotyped data from these arrays, the UK Biobank resources performed imputation on the autosomal SNPs using the UK10K haplotype [27], 1000 Genomes Phase 3 [28], and Haplotype Reference Consortium [29] as reference panels.

2.1.2. Socioeconomic status

To stratify the UK biobank population into different SES groups, we used the TDI [30]. This calculated index score, defined at the moment of enrollment, is a composition of four different variables, all related to SES: unemployment, nonownership of a home, nonownership of a car, and household overcrowding [30]. Importantly, the TDI is not linked to a specific individual but instead linked to the postal codes from the UK Biobank participants and is therefore a reflection of overall SES of the neighborhood in which the participants are living.

The TDI scores recorded within the UK Biobank ranged between −6.26 and 11.00, and lower scores are reflective of a higher SES in the neighborhood. Using quartiles of these scores, the population was divided into four groups. Because some individuals had very high TDI values, we performed sensitivity analyses by dividing the highest TDI group into two subgroups based on the 87.5 percentile of TDI and repeated the main analysis accordingly.

2.1.3. Coronary artery disease

CAD occurrence (either before or after enrollment in UK Biobank) was the primary outcome for the analyses. Diagnoses were coded according to the International Classification of Diseases [23]. Here, the study outcome was CAD which we defined as angina pectoris (I20), myocardial infarction (I21 and I22), and acute and chronic ischemic heart disease (I24 and I25). Cases were ascertained through a UK Biobank algorithm combining data from linked hospital admissions, death registries, reports from the general practitioner, and self-report.

2.2. Statistical analysis

All the analyses were done using R (v4.1.0) statistical software (The R Foundation for Statistical Computing, Vienna, Austria) [31]. In our MR analyses, the associations between genetically determined CVD risk factors and CAD were calculated using multivariable-adjusted logistic regression analyses, with CAD as dependent and the weighted GRS score as exposure and corrected for age, sex, and the first 10 principal components. In addition, the analyses were stratified by the TDI score categories to study the possible effect modification of the association between the genetically influenced CVD risk factor and CAD by SES. The results derived from these models (with accompanied 95% confidence intervals [CIs]) can be interpreted as the change in odds on CAD for every increase in standard deviation (SD) in genetically determined exposure. All analyses were adjusted for age, sex, and the first 10 genetic principal components to correct for possible population admixture. Additional analyses were performed where we stratified the study population for men and women. We tested for evidence for an interaction on a multiplicative scale by adding an interaction term between the GRS and TDI (both as continuous variables) in the multivariable-adjusted logistic regression models on CAD. The different genetic risk scores were examined separately. For these analyses, we reported the P values for interaction, corrected for multiple testing using the Bonferroni adjustment method. Therefore, we required a P value <0.0125.

However, stratification by TDI can introduce collider bias when there is a conditional relationship between the genetic risk score and TDI (e.g., the mean GRS score is higher in either the low or high TDI group). As explained in detail previously in Coscia et al. [32], when a variable (TDI) in a causal diagram is directly affected by two other variables, such as the risk factor (BMI, blood pressure, LDL cholesterol, and TG levels) corresponding GRS, conditioning on TDI might introduce a collider (Fig. 1). In line with this paper, in a sensitivity analysis, we controlled for the possible presence of such bias in the main analyses, by defining strata defined by quantiles of the residual TDI

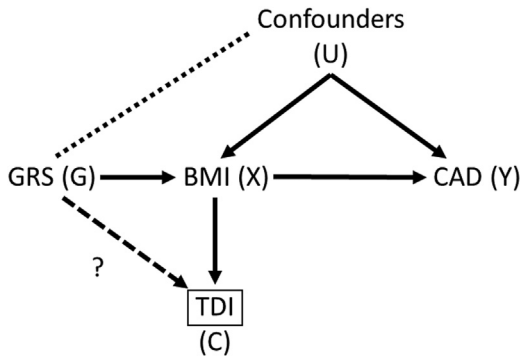

Fig. 1. Directed acyclic graph (DAG) illustrating the relationship between the studied variables. When variable G (GRS) and variable C (TDI) are directly linked, TDI can be considered a collider variable, becoming a dependent variable when conditioned on. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1. Baseline characteristics of the study population

Variable name	Quartile 1 (*N* = 111,563)	Quartile 2 (*N* = 111,427)	Quartile 3 (*N* = 111,488)	Quartile 4 (*N* = 111,487)	Total (*N* = 446,495)
Sex, Female (%)	60,302 (54%)	60,929 (55%)	61,493 (55%)	59,736 (54%)	242,742 (54%)
Age	57.3 (7.8)	57.2 (7.9)	56.6 (8.1)	55.9 (8.2)	56.8 (8.0)
Townsend Deprivation Index Score	−4.4 (−6.3, −3.7)	−3.0 (−3.7, −2.3)	−1.3 (−2.3, 0.2)	2.4 (0.2, 11.0)	−2.3 (6.3, 11.0)
BMI	27.0 (4.3)	27.2 (4.5)	27.4 (4.7)	28.0 (5.3)	27.4 (4.7)
Systolic blood pressure	141 (19.6)	141 (19.6)	140 (19.6)	139 (19.7)	140 (19.7)
Diastolic blood pressure	82.3 (10.5)	82.3 (10.6)	82.2 (10.7)	82.0 (10.9)	82.2 (10.7)
LDL Cholesterol	5.76 (1.1)	5.7 (1.1)	5.7 (1.1)	5.6 (1.2)	5.7 (1.1)
Triglycerides	1.5 (0.2, 11.3)	1.5 (0.2, 11.3)	1.5 (0.2, 11.2)	1.5 (0.2, 11.3)	1.5 (0.2, 11.3)

Abbreviations: TDI, townsend deprivation index; BMI, body mass index.

Data are mean (SD) for normally distributed continuous variables or median (IQR) otherwise. Percentages are shown for dichotomous variables.

collider. We calculated the residual TDI, a variable that is free from any influences of the instrument variable (the GRS) [32], by calculating residuals using linear regression analyses with TDI as outcome and the genetic risk score as an independent variable. Using the residuals, new subgroups were defined based on quartiles, and the main analyses were repeated accordingly.

3. Results

3.1. Baseline characteristics of the UK biobank study population

When stratified in quartiles for TDI score, the study sample (Table 1) consisted of 446,495 individuals of which 52,946 (12%) had CAD. Participants in quartile 4 (the group with the highest TDI scores) had a higher mean measured BMI (28.0 vs. 27.0 kg/m^2) and a lower mean age (55.9 vs. 57.3 years) compared with quartile 1 (reflective of the lowest TDI).

3.2. Mendelian randomization analyses

In quartile 1, around 10% of the participants (N = 11,526) developed CAD before or during follow-up. With a higher TDI (quartiles 2 till 4), the percentage of participants with CAD increased to around 14% (N = 16,158) in quartile 4.

The logistic regression models in our MR analyses without stratification by TDI showed that a one SD increase in genetically determined BMI (odds ratio [OR]: 1.107 [95% CI: 1.096, 1.117]), SBP (OR: 1.068 [95% CI: 1.058, 1.078]), LDL cholesterol (OR: 1.086 [95% CI: 1.077, 1.097]), and TGs (OR: 1.053 [95% CI: 1.044, 1.063]) were all associated with a higher risk of CAD.

In the stratified analyses, we observed that the effect estimate of CAD by genetically determined BMI increased as TDI increased (Fig. 2A). The OR for CAD per SD increase in genetically influenced BMI was 1.08 (95% CI: 1.06, 1.10) in quartile 1 vs. 1.13 (95% CI: 1.11, 1.15) in quartile 4. Using a logistic model that included a multiplicative interaction term between the TDI score and the genetic risk score, and after correcting for multiple testing, the OR of CAD per SD increase in BMI differed significantly dependent on the TDI groups (P value for interaction = 0.0049). For SBP, LDL cholesterol, and TG levels, the OR for CAD per SD increase was similar in the different TDI groups (Fig. 2B–D), although a trend was observed for TGs having a weaker effect estimate in the group with the highest TDI (quartile 4; Fig. 2D; P value for interaction = 0.073). P values for interactions were 0.27 for SBP and 0.44 for LDL cholesterol level.

In subsequent analyses where we further stratified the highest TDI group (quartile 4) because of the large range in TDI values in this group (ranging from 0.2 to 11.0), the OR for CAD per SD increase in genetically influenced BMI in the 75–87.5 percentile TDI group was 1.11 (95% CI: 1.08, 1.14), whereas in the group with TDI values above the 87.5 percentile the OR was 1.14 (95% CI: 1.11, 1.17).

3.3. Sensitivity analyses

In logistic regression analyses, only genetically influenced BMI was associated with TDI (estimate: 0.0016, 95% CI: 0.0013, 0.0019). Therefore, the analysis that studied the association between genetically influenced BMI and CAD, stratified for TDI, was repeated using new BMI GRS_free subgroups of TDI (“IV free”). These results did not substantially differ from the main analysis (Supplementary Table 1).

4. Discussion

We performed MR analyses using calculated genetic risk scores for CVD risk factors to investigate their association

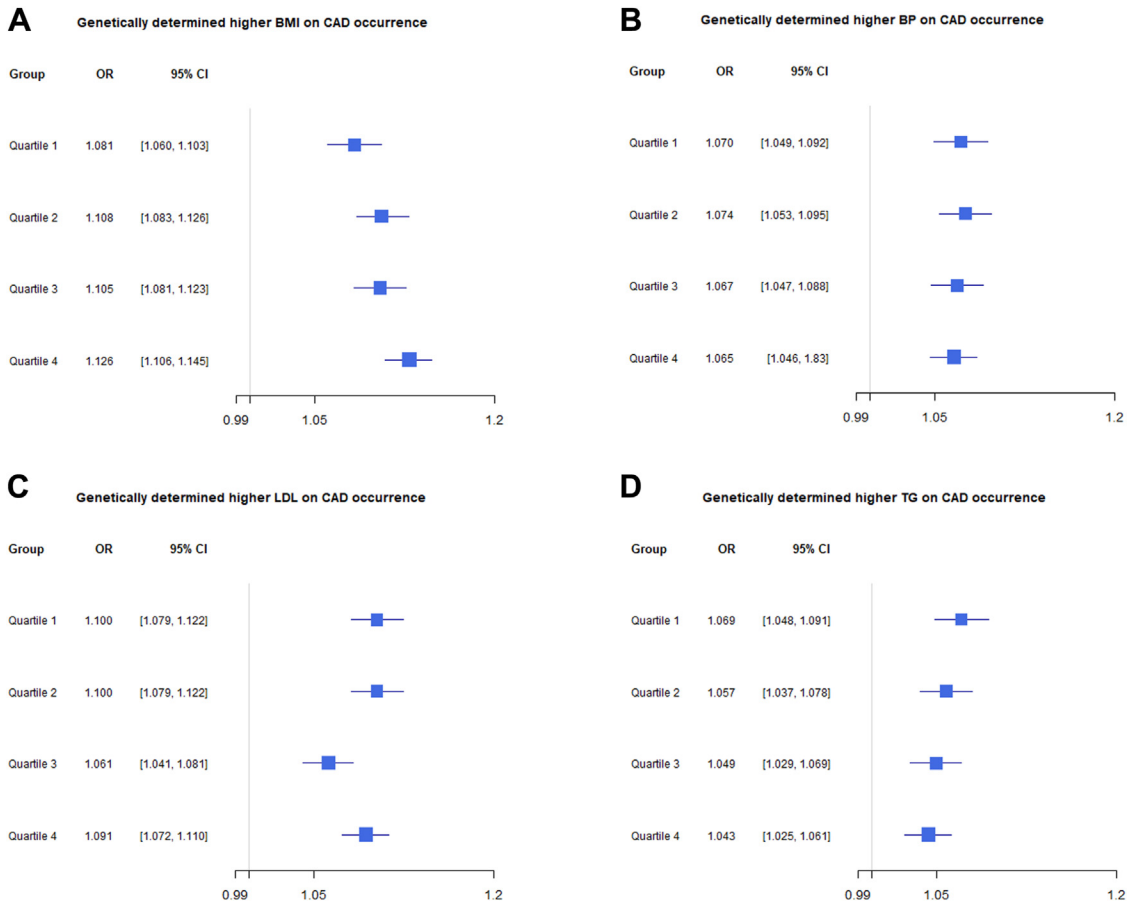

Fig. 2. Association between genetically determined risk factors body mass index (A), systolic blood pressure (B), LDL cholesterol (C), triglyceride (D), and coronary artery disease stratified for socioeconomic status estimated ORs represent the effect per SD increase in risk factor GRS on CAD. Results obtained using a logistic regression with genetic risk score as exposure, corrected for age, sex, and the first 10 principal components and were stratified for SES. BMI, Body Mass Index; SBP, systolic blood pressure; TG, triglyceride; SES, socioeconomic status. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

with CAD in different SES groups, using data from 446,495 European-ancestry participants from the UK Biobank. Results indicated that in every SES group, each investigated genetically influenced risk factor (BMI, SBP, LDL, and TGs) was associated with an increased risk of CAD, confirming the previously observed effects of these risk factors on CAD. However, for genetically influenced BMI, the observed effect on CAD differed between SES groups. Specifically, in the lower SES group, the increased risk on CAD per SD increase BMI was larger compared with the highest SES group. Suggestive evidence was observed that the association between TGs and CAD was weakest in people having the highest TDI. These results could be an indication that an increased BMI is not only more prevalent in low SES groups but that the risk associated with a one-unit increased BMI is also higher.

To the best of our knowledge, the present study is the first to investigate the impact of classic CVD risk factors on CAD occurrence in different subgroups of SES in an MR analysis. Of interest, earlier MR studies have shown age-specific effects attributable to CVD risk factors [17,18]. These findings, together with the findings from the present study, further illustrate that the effect of CVD risk factors is not homogeneous but subgroup-specific instead.

To illustrate, a hypothetical intervention in our study population leading to an equal reduction (e.g., one SD) in BMI across all groups would lead to a relatively larger case reduction of CAD in the lower SES group. A one-SD reduction of BMI would lead to 1.081 lower odds of developing CAD attributable to BMI in the highest SES group. Conversely, the same one-SD reduction would lead to 1.126 lower odds in the lowest SES group. With both a larger incidence and a bigger effect size, a one-SD reduction of BMI leads to a larger absolute case reduction in the low SES group. By not recognizing the different effect attributable to BMI in different SES groups and using the overall increased risk (OR: 1.107), a hypothetical intervention would assume an underestimation and overestimation of case-reduction in high and low SES groups, respectively.

Our findings on the subgroup-specific impact of BMI on CAD risk could be caused by different body compositions in different socioeconomic groups. BMI is generally thought to have a linear relationship with CVD incidence

[33]. However, it is a measure of overall adiposity that takes into account body weight and length, but not body composition variables such as fat mass and muscle mass. It is possible that the increased CAD risk in groups of lower SES could be because groups of lower SES have a higher body fat percentage. However, there is currently not much literature on body composition in different socioeconomic groups. The distribution of fat is another aspect to consider. Literature has shown that compared with subcutaneous fat, visceral fat is associated with a higher risk for CAD [34]. It could be hypothesized that the body fat of individuals of lower SES consists of a larger proportion of visceral fat than the body fat of individuals of higher SES. As there are, to our knowledge, currently no sufficient reliable genetic instruments for visceral fat, we were unable to test this hypothesis. Thus, subsequent studies should aim to explore the potential differences in body composition between SES groups.

It has been shown that low SES is one of the strongest predictors toward engaging in lifestyle risk behavior associated with cardiovascular death [35]. These include smoking, alcohol consumption, and an unhealthy diet. All of these lifestyle factors are in turn associated with increased liver fat and/or visceral fat, which are known to increase CAD risk [36,37]. It is therefore possible that lifestyle risk behavior could lead to different body compositions between SES groups, which in turn could explain our results.

Although SBP, TG, and LDL cholesterol are assumed to be causal risk factors for CAD incidence, there does not seem to be a difference in effect between SES groups according to our results. Thus, it is likely that interventions targeting SBP, TG, or LDL cholesterol would have a comparable effect on CAD incidence, independent of SES.

The main strength of this study is the large sample size as well as considerable number of CAD cases. This ensured statistical power for our analyses on the association between CVD risk factors and CAD occurrence. The MR method also aims to prevent possible reverse causation or confounding. Finally, our findings on the associations between known CVD risk factors and CAD are directionally consistent compared with earlier literature, which increases the credibility of our main findings. Some limitations should also be considered. First, we used the TDI as an indication of SES. As TDI is only measured at baseline, potential changes in SES during follow-up cannot be taken into account. To add, TDI is calculated based on geographical data and therefore is not a measure of individual SES, but a measure of environmental poverty. Furthermore, using a measure of neighborhood SES could provide suitable target locations for potential tailor-made intervention policies. Second, our study population from the UK Biobank consists of Caucasian participants. Therefore, the generalizability of our results to other ancestry groups is limited. This is especially relevant as prevalence of CVD risk factors differs between ethnic groups [38]. However, limiting the study population to Caucasians greatly reduces the heterogeneity between participants.

In conclusion, our findings indicate that CAD risk attributable to BMI is not homogenous and is modified by SES. Although genetically influenced BMI was associated with CAD in all SES subgroups, tailor-made approaches for risk reduction dependent on SES should be considered to optimize the reduction in disease risk.

CRediT authorship contribution statement

Leon G. Martens: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing − original draft, Writing − review & editing. **Daan van Hamersveld:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing − original draft. **Saskia le Cessie:** Conceptualization, Validation, Writing − review & editing. **Ko Willems van Dijk:** Validation, Writing − review & editing, Supervision. **Diana van Heemst:** Validation, Writing − review & editing, Supervision. **Raymond Noordam:** Conceptualization, Methodology, Software, Validation, Formal analysis, Writing − review & editing, Supervision.

Declaration of competing interest

None declared.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2023.07.009.

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