Modifiable lifestyle factors and heart failure: A Mendelian randomization study

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Background Lifestyle factors may be important targets in the prevention of heart failure. The current knowledge on the relationship between lifestyle factors and heart failure originates mostly from observational studies. The objective of this study was to investigate causal associations of multiple lifestyle factors with heart failure risk by using Mendelian randomization.

Methods We obtained summary statistics data for single nucleotide polymorphisms associated with the following 5 lifestyle factors at genome-wide significance in genome-wide association studies of European-descent individuals: smoking, alcohol consumption, coffee consumption, physical activity, and sleep duration. The corresponding data for heart failure were acquired from a genome-wide association study comprising 47,309 cases and 930,014 controls of European ancestry. For the primary analyses, we used the inverse-variance weighted method.

Results Genetic predisposition to smoking initiation (ever smoked regularly) was robustly associated with a higher odds of heart failure (odds ratio: 1.28; 99% CI: 1.21-1.35). Genetically predicted longer sleep duration was associated with a lower odds of heart failure (odds ratio per hour/day: 0.73; 99% CI: 0.60-0.89). We found no associations of alcohol consumption, coffee consumption, and physical activity with heart failure.

Conclusions This Mendelian randomization study showed that smoking initiation increases heart failure risk, whereas longer sleep duration decreases the risk of heart failure. Sleep duration should be regarded as novel risk factor in heart failure prevention guidelines. The potential causal role of alcohol and coffee consumption and physical activity for heart failure warrants further investigation in future larger Mendelian randomization analyses. (Am Heart J 2020;227:64-73.)

Heart failure is a growing public health problem worldwide, with high morbidity and mortality rates.[1] The prevalence and incidence rates of heart failure are expected to increase in the upcoming years, mainly because of aging but also because of improved treatment. This makes prevention of heart failure an important public health goal.

Lifestyle-related risk factors are amenable to modification and may therefore be relevant targets in the prevention of heart failure. The current knowledge on the relationship between lifestyle factors and heart failure has originated mostly from observational studies. Prospective studies have consistently reported a detrimental association between smoking and incident heart failure,[2-4] and a lower risk of heart failure with increased levels of physical activity.[4-10] The literature has been inconclusive on the direction and strength of the associations between alcohol[4,11,12] and coffee consumption[13,14] and sleep duration[4,15-17] with risk of heart failure. An important limitation of these observational studies is that the causality of the associations cannot be deduced, as the results might be biased by unmeasured confounding and reverse causation.

A Mendelian randomization (MR) approach is an instrumental variable analysis that uses genetic variants that are associated with different levels of a modifiable risk factor to assess the causal effect of a risk factor on disease.[18] Genetic variants are randomly allocated at conception, and therefore, the level of a specific exposure will usually be unrelated to the level of other exposures, such as potential confounders. Additionally, MR studies avoid reverse causation bias because genetic variants cannot be affected by disease status.

MR studies have been performed on some lifestyle factors and heart failure, including insomnia,[19] body mass

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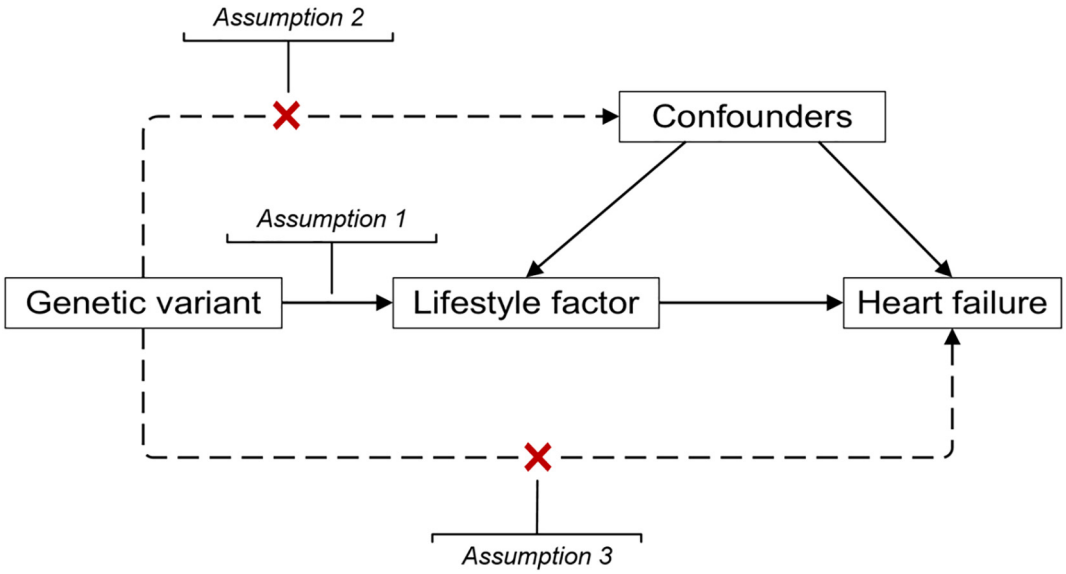
Figure 1



Overview of the instrumental variable assumptions of the MR design.Assumption 1: The genetic variants (SNPs) are robustly related to the lifestyle factor. Assumption 2: The genetic variants (SNPs) are independent of confounders. Assumption 3: The genetic variants (SNPs) affect heart failure only through the lifestyle factor.[18]

index (BMI),[20] sleep duration,[21] and physical activity.[21] Yet, previous MR analyses on sleep duration and physical activity had low power. Recently, larger genome-wide association studies (GWASs) for sleep duration,[22] physical activity,[23] and heart failure[24] have become available. Furthermore, to the best of our knowledge, no previous MR study has investigated the causal associations of smoking, alcohol consumption, and coffee consumptions with risk of heart failure, whereas GWASs are available for these lifestyle factors. Therefore, the aim of this study was to investigate the causal associations of the 5 lifestyle factors, including smoking, alcohol consumption, coffee consumption, physical activity, and sleep duration, with heart failure risk by using an MR approach and the most recent and largest GWASs on lifestyle factors and heart failure.

Methods

Study design

For this study, we used a 2-sample MR design and single nucleotide polymorphisms (SNPs) as instrumental variables for the lifestyle factors. Key assumptions of this method include the following: (1) the SNPs are related to the lifestyle factor (the exposure), (2) the SNPs are independent of confounders, and (3) the SNPs affect heart failure (the outcome) only through the lifestyle factor (the exposure) (Figure 1).[18]

Data sources and data preparation

A detailed overview of all data sources can be found in Supplementary Table I. Briefly, for each lifestyle factor, we identified the largest published GWAS among individuals of European ancestry. For smoking and alcohol consumption, we used summary statistics data from the GWAS and Sequencing Consortium of Alcohol and Nicotine Use consortium.[25] We used the SNPs of the smoking initiation trait (ever smoked regularly) in our main analysis. The smoking cessation and smoking heaviness traits were used as complementary analyses. For alcohol consumption, we used the SNPs for heaviness of self-reported alcohol consumption. From a pooled GWAS of 4 population-based cohorts, we extracted summary statistics data for coffee consumption.[26] Furthermore, we obtained the direction of the associations between the different coffee-associated SNPs and caffeine metabolites.[27] The GWAS on device-measured physical activity in the UK Biobank was used for the identification of SNPs associated with moderate to vigorous physical activity levels.[23] For the complementary analysis, we used SNPs for sedentary behavior from another GWAS in UK Biobank.[21] For sleep duration, we extracted summary statistics data from a recently published GWAS on self-reported sleep duration in UK Biobank.[22] For the complementary analyses, we used the SNPs for long (≥9 h/d) and short (<7 h/d) sleep duration.[22] Only SNPs associated with each lifestyle factor at the genome-wide

significance level ($P < 5 \times 10^{-8}$) were used as instrumental variables in the present MR study to ensure that the first MR assumption is likely to hold. The phenotypic variance explained by the genetic instruments varied from 0.073% for physical activity to 2.3% for smoking initiation (Supplementary Table I).

We extracted the associations between the identified SNPs and heart failure from the currently largest available GWAS meta-analysis on heart failure among individuals of European ancestry performed by the Heart Failure Molecular Epidemiology for Therapeutic Targets Consortium (Supplementary Table I).[24] This GWAS meta-analysis included 26 studies with 47,309 heart failure cases and 930,014 controls. The GWAS was adjusted for age, sex, and principal components. Heart failure assessment was performed by at least 1 of the following methods in all cohort studies: discharge registries, cause of death registries, or physician adjudication/diagnosis. The GWAS was not stratified by etiological subtype because of insufficient power. All studies included in the meta-analysis obtained ethical approval, and all participants provided written informed consent.

We used LDlink (Version 3.8) to assess whether the SNPs of 1 trait situated on the same chromosome were in linkage disequilibrium with each other ($r^2 > 0.1$). If this was the case, the SNPs with the largest *P* values were excluded. We harmonized the data by checking whether both data sets share the same allele pairs and by aligning the β coefficients to the same allele (the exposure-increasing allele). We verified whether the allele frequencies for the exposure-increasing alleles were similar in the exposure and heart failure data sets (Supplementary Tables I-V). We did not remove palindromic SNPs because the SNPs were oriented to the forward strand in all data sets. The total number of SNPs included in the analysis was 359 for smoking initiation, 91 for alcohol consumption, 14 for coffee consumption, 7 for physical activity, 77 for sleep duration, 22 for smoking cessation, 47 for smoking heaviness, 4 for sedentary behavior, 7 for long sleep duration, and 26 for short sleep duration (Supplementary Table I).

Statistical analyses

The statistical analyses were conducted in RStudio (Version 1.1.463) with R Packages MendelianRandomization[28] and MRPRESSO.[29] We corrected for multiple testing by using a Bonferroni-corrected 2-sided *P*-value of .01 ($P = .05/5$ exposures) and calculated 99% CIs.

We plotted the β coefficients and corresponding standard errors of the SNP-exposure association against the β coefficients and standard errors of the SNP-outcome association to get a first impression about the presence of unbalanced pleiotropy and the direction of the causal effects.

For our main analyses, we used the inverse-variance weighted (IVW) method to obtain the causal estimates for the association between the lifestyle factors (smoking initiation, alcohol consumption, coffee consumption, physical activity level, and sleep duration) and heart failure.[18] For each genetic variant, a Wald ratio estimate was obtained by dividing the SNP-outcome association by the SNP-exposure association. To obtain 1 causal estimate for each lifestyle factor, the Wald ratio estimates were combined using IVW meta-analyses with multiplicative random effects. The Cochran *Q* statistic was used to evaluate heterogeneity across the estimates derived from individual SNPs.

We performed several sensitivity analyses. First, we used the weighted-median method. The median of the weighted Wald ratio estimates is a consistent estimate of the causal effect if a minimum of 50% of the weight has been derived from valid instrumental variables.[30] Second, we performed the MR-Egger regression to test for directional pleiotropy. An intercept largely deviating from zero is an indication of directional pleiotropy, as well as a large difference in causal estimates compared to the IVW method. The MR-Egger estimate is a consistent estimate of the causal effect if the pleiotropic effects of genetic variants are independent of the instrument strength (the so-called Instrument Strength Independent of Direct Effect assumption).[30] Third, we evaluated the presence of outlier SNPs by using the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method. We tested whether the causal estimates significantly differed before and after removal of the potential outliers, the so-called distortion test.[29] The MR-PRESSO method requires that at least 50% of the SNPs is valid and relies on the Instrument Strength Independent of Direct Effect assumption. Fourth, we checked for pleiotropic associations between the genetic variants and potential confounders for the exposures with less than 20 independent SNPs by using the Phenoscanner Database (Version 2). The SNPs with pleiotropic associations with potential confounders (including BMI, weight, diabetes, coronary artery disease, blood pressure, cholesterol, and other lifestyle traits) were excluded in a sensitivity analysis. Fifth, we performed multivariable MR analyses to obtain causal estimates for smoking initiation adjusted for the genetic correlation with alcohol consumption and vice versa.[18] Smoking and alcohol traits have a high correlation in the population, as these are both addictive behaviors. Therefore, pleiotropy might not be ruled out completely by the other sensitivity analyses.

In our complementary analyses, we used similar statistical methods as described above to assess the causal effects of smoking cessation, smoking heaviness, sedentary behavior, and short and long sleep duration with heart failure. The odds ratios (ORs) for smoking cessation were eventually inversed to change the

reference category from former smokers to current smokers.

We conducted post hoc power calculations for our main IVW analyses using an online power calculation tool (https://sb452.shinyapps.io/power/) with the significance level set at .01 (Supplementary Table III).[31]

Results

Smoking

Genetic predisposition to smoking initiation (ever smoked regularly compared to never smoked) was associated with a higher odds of heart failure (OR: 1.28; 99% CI: 1.18-1.38) (Figure 2 and Supplementary Figure I). The *Q* statistic indicated heterogeneity across SNPs (Supplementary Table II). The OR estimates were similar across all sensitivity analyses, and the intercept of the MR-Egger regression was close to zero (−0.002; 95% CI: −0.006 to 0.003), which means that there was no indication of directional pleiotropy. Adjustment for alcohol consumption in the multivariable MR analysis did not change the results (OR for ever versus never smoking: 1.30; 99% CI: 1.18-1.40).

The complementary analyses showed that genetic predisposition to smoking cessation (former smoker compared to current smoker) was robustly associated with lower odds of heart failure (Figure 3). Furthermore, a 1-SD increment in number of cigarettes smoked daily was associated with 1.29 times (99% CI: 1.06-1.57) higher odds of heart failure.

Alcohol consumption

Genetically predicted higher alcohol consumption was associated with a nonsignificant higher odds of heart failure in the analyses based on the IVW (OR per 1-SD increase in log-transformed alcoholic drinks per week: 1.11; 99% CI: 0.85-1.46), weighted median, and MR-Egger methods (Figure 2 and Supplementary Figure 2). The *Q* statistic indicated heterogeneity across SNPs (Supplementary Table II). MR-PRESSO identified 2 outlying SNPs, rs13107325 and rs28601761, with potential pleiotropic associations with, among others, BMI and coronary artery disease, respectively. Exclusion of these SNPs did not alter the results (distortion test *P* value: .606). The estimate fully attenuated after adjustment for smoking initiation in the multivariable MR analysis (OR per 1-SD increase in log-transformed alcoholic drinks per week: 1.01; 99% CI: 0.74-1.38).

Coffee consumption

There was no association between genetically predicted coffee consumption and heart failure (OR per 50% change in coffee consumption: 1.06; 99% CI: 0.86-1.31) (Figure 2 and Supplementary Figure III). Consistent estimates were obtained by the weighted median and MR-Egger methods. MR-PRESSO identified 2 outlying SNPs, rs10865548 and rs66723169, which have been significantly correlated with BMI. Excluding these 2 SNPs led to an attenuation of the causal estimate (OR per 50% change in coffee consumption: 1.00; 99% CI: 0.89-1.11, distortion test *P* value: .017). Exclusion of 2 additional pleiotropic SNPs (rs574367 with BMI and rs1260326 with weight and diabetes) did not alter the results. A similar association was observed for individual SNPs related to higher or lower caffeine metabolites with heart failure (Supplementary Figure VI).

Physical activity

Genetically predicted moderate-to-vigorous physical activity was not associated with heart failure (OR per 1-SD increment in metabolic equivalent of task [MET] min/wk: 0.89; 99% CI: 0.50-1.61) (Figure 2 and Supplementary Figure IV). Exclusion of rs429358—located nearby the APOE gene region and correlated with several other traits (eg, coronary artery disease, cholesterol, and diabetes)—did not alter the results. There was no clear association between sedentary behavior and heart failure risk (OR per 1-SD increase in sedentary behavior: 1.26; 99% CI: 0.80-1.99) (Figure 4).

Sleep duration

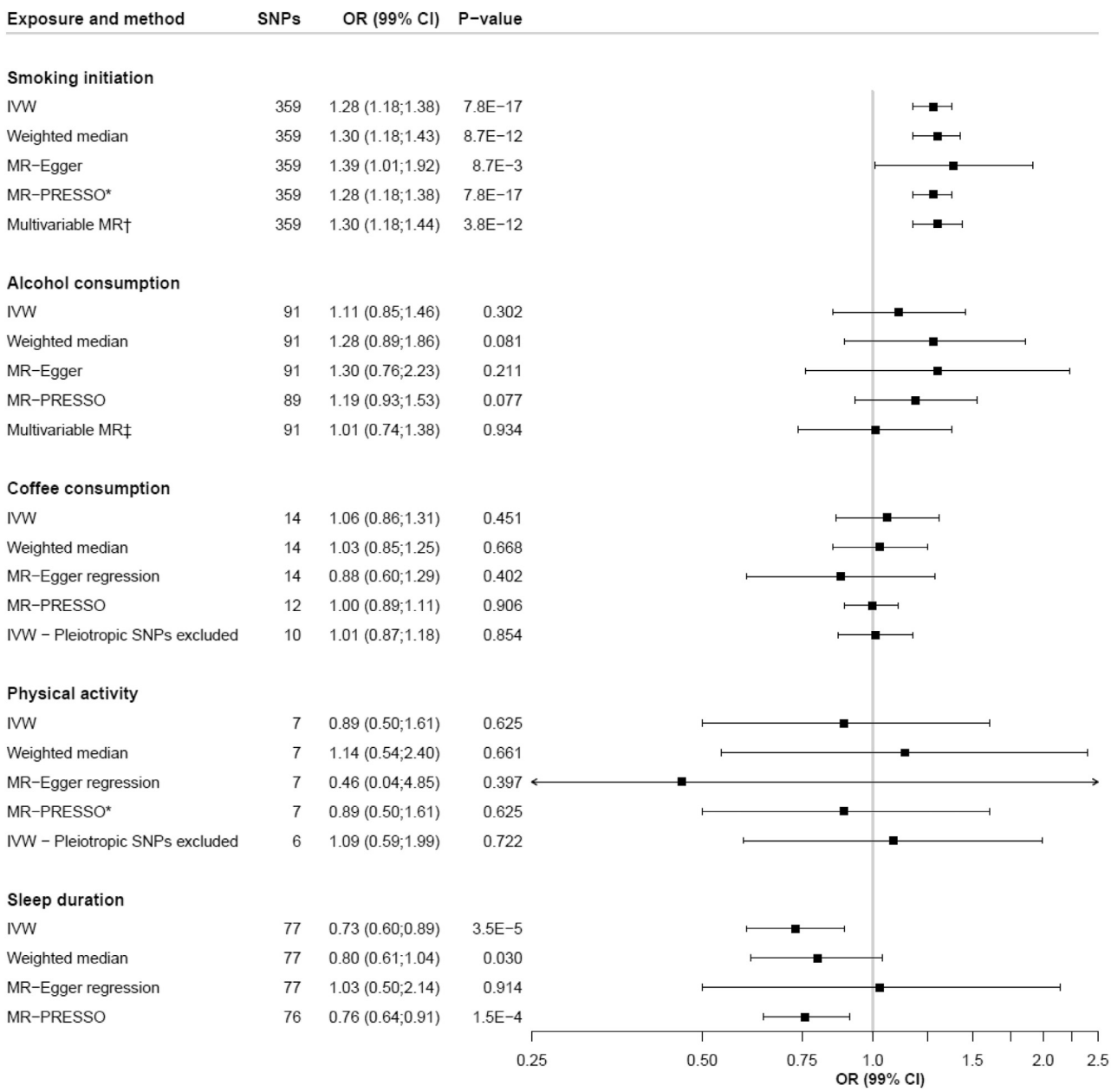
Genetically predicted sleep duration was associated with lower odds of heart failure (OR per 1-hour sleep per day: 0.73; 99% CI: 0.60-0.89) (Figure 2 and Supplementary Figure V). Similar results were observed for the weighted median method. The MR-Egger regression's estimate deviated toward a null association (OR per 1-hour sleep per day: 1.03; 99% CI: 0.50-2.14), but the intercept did not indicate pleiotropy (−0.006; 95% CI: −0.015 to 0.003). MR-PRESSO identified rs9940646 (close to the *FTO* gene) as an outlier. Exclusion of this SNP did not alter the findings (distortion test *P* value: .455).

The complementary analyses revealed a trend toward a beneficial effect of long sleep duration (≥9 h/d) and a harmful effect of short sleep duration (<7 h/d) on heart failure compared to a sleep duration of 7-8 h/d (Figure 5). The MR-Egger regression of the long sleep trait indicated pleiotropy (intercept: −0.035; 95% CI: −0.067 to −0.003). Exclusion of potentially pleiotropic SNPs (rs17817288 and rs17688916) slightly attenuated the protective trend of long sleep duration on heart failure.

Discussion

In this large MR study on multiple lifestyle factors and heart failure, we found evidence that smoking increases the risk of heart failure, whereas longer sleep duration may reduce the risk of heart failure. We found no support for causal associations of alcohol consumption, coffee consumption, and physical activity with heart failure, but the precision was low in these analyses.

Figure 2

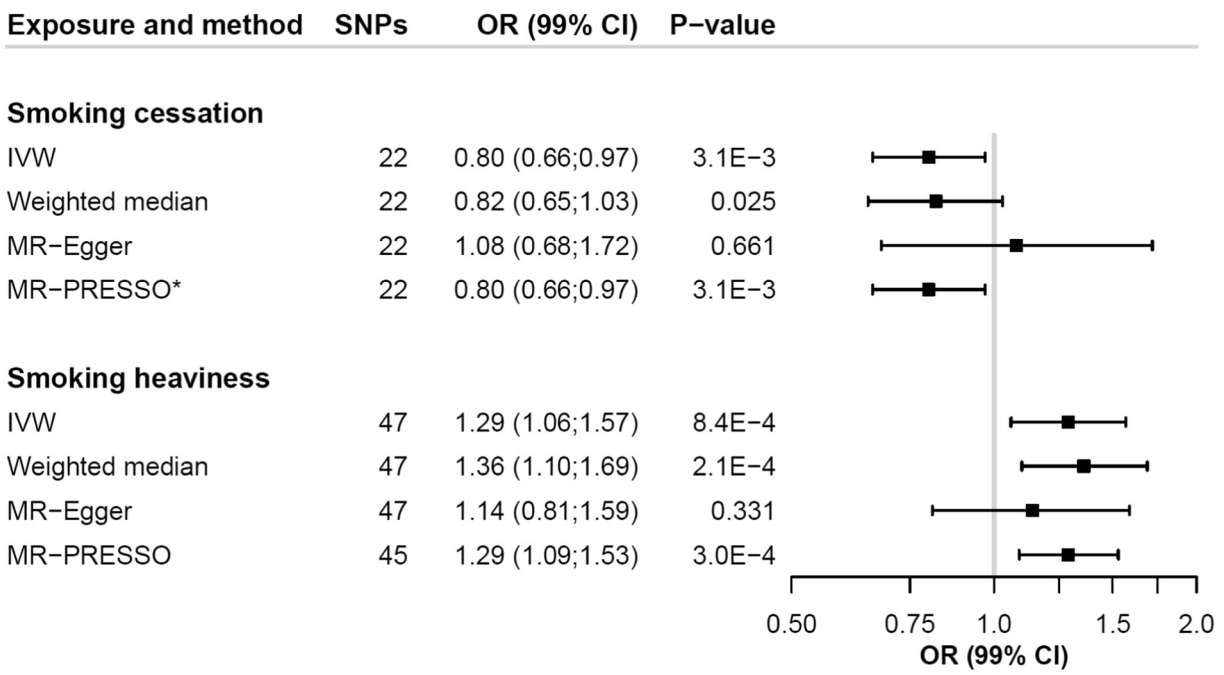


Associations between the lifestyle factors and heart failure using the MR approach.ORs display the association with heart failure of, respectively, ever smoked regularly compared with never smoked regularly, an SD increase in log-transformed alcoholic drinks per week, a 50% change in coffee consumption, an SD increase in MET min/wk of moderate to vigorous physical activity, and an hour increase in sleep duration.The IVW random effects method was used as main analysis, and the other methods were used as sensitivity analyses. Pleiotropic SNPs were identified with PhenoScanner.*MR-PRESSO did not identify any outlying SNPs,†Adjusted for alcohol consumption,‡Adjusted for smoking initiation

The observed association between smoking initiation and heart failure is likely to be causal given the robust results across sensitivity analyses. Furthermore, evidence from prospective observational studies pointed toward the same direction.[2-4] A summary of relevant prospective observational studies on the investigated lifestyle factors and heart failure has been provided in Supplementary Table IV.

Deducing the causality in the effect of sleep duration on heart failure is less straightforward. The evidence from observational studies has been inconsistent with regard to the direction and magnitude of the association

Figure 3



Complementary MR analyses of smoking cessation and smoking heaviness in relation to heart failure.ORs represent the association between smoking cessation (former smoker compared with current smoker) and smoking heaviness (per SD increase in number of cigarettes smoked daily). The IVW random effects method was used as main analysis, and the other methods were used as sensitivity analyses.*MR-PRESSO did not identify any outlying SNPs.

between sleep duration and heart failure (Supplementary Table IV).[4,15,16] Although we observed an inverse association between genetically predicted sleep duration and heart failure in the present MR study, more evidence from larger or combined observational and MR studies with objective methods to measure sleep duration would strengthen causal inference.

Results from meta-analyses of observational studies of the association between alcohol consumption and risk of heart failure are conflicting, with both an inverse association related to light drinking and a dose-response positive association reported (Supplementary Table IV).[11,12] Although we found no indication of a protective or detrimental effect of alcohol consumption on heart failure risk after adjustment for genetic predisposition to smoking, we cannot rule out a weak causal association in either direction given the low power in our MR analysis (~6%) due to the small phenotypic variance explained by the genetic instrument for alcohol consumption (~0.2%).

It is not yet possible to draw conclusions on the causal role of coffee consumption in heart failure. The weak *U*-shaped association found in observational studies[13,14] (Supplementary Table IV) might be the result of residual confounding or reverse causation bias. Our MR analysis was not designed to reveal *U*-shaped relations but provided no indication of a strong linear association between coffee consumption and heart failure risk.

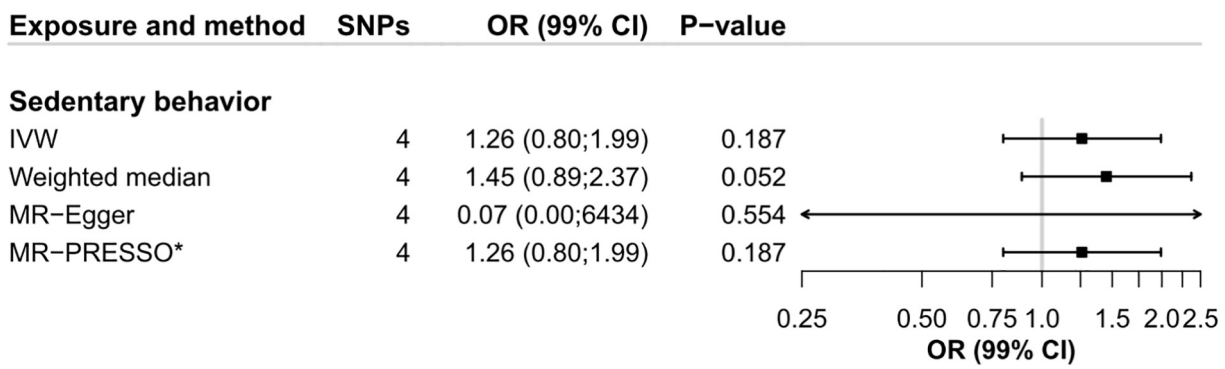
The lack of evidence for a causal effect of physical activity in this MR study, whereas previous prospective observational studies consistently reported that higher physical activity was associated with lower heart failure risk,[4-10] is probably due to weak instrument bias. The variance explained by the genetic instrument for both moderate-to-vigorous physical activity and sedentary behavior was very small (0.073% and 0.08%, respectively), which was also reflected in the very wide CIs for the physical activity estimates across all analyses and in the low power according to our post hoc power calculation (~3%).

Underlying mechanisms

The increased heart failure risk in smokers is thought to be mediated via several pathways.[32] These pathways include effects on atherosclerosis, hypertension, and myocardial infarction, which are risk factors for heart failure with reduced ejection fraction. On the other hand, smoking also has effects on cardiometabolic risk factors, such as diabetes and inflammation, which are related to heart failure with preserved ejection fraction.

Although the definition of insomnia generally does not include sleep duration as criterion, there has been genetic

Figure 4



Complementary MR analyses of sedentary behavior with heart failure.ORs represent the association between an SD increase in sedentary behavior and heart failure.The IVW random effects method was used as main analysis, and the other methods were used as sensitivity analyses.*MR-PRESSO did not identify any outlying SNPs

overlap between the sleep duration trait and the insomnia trait.[33] A recent MR study showed that genetic liability to insomnia was associated with an increased heart failure risk.[19] As such, it is complex to determine if either 1 of the 2 traits is most important or the effect of both traits is cumulative, as previously suggested.[16] Several mechanisms could link sleep disturbances to higher heart failure risk. A recent MR study reported that genetically longer sleep duration was associated with a lower myocardial infarction risk.[34] In observational studies, short sleep duration has been associated with subclinical atherosclerosis,[35] coronary heart disease,[36] type 2 diabetes,[37] and obesity.[38] Obstructive sleep apnea syndrome—which leads to sleep disturbances—might also play a role, as it has been associated with increased heart failure risk in men.[39] As our results were not altered by removing variants with potentially pleiotropic associations with cardiometabolic traits, a combination of these pathways is most likely, and probably, other pathways are involved as well.

Implications

The 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease already emphasizes the importance of lifestyle counseling and interventions with focus on smoking cessation and prevention, healthy diet, weight loss, and physical activity.[40] The current guidelines do not yet provide advice on sleep duration as risk factor of cardiovascular disease. Our study implicates a role of longer sleep duration in the prevention of heart failure, with a lifetime causal protective effect that was of similar size as the harmful effect of smoking initiation on heart failure risk.

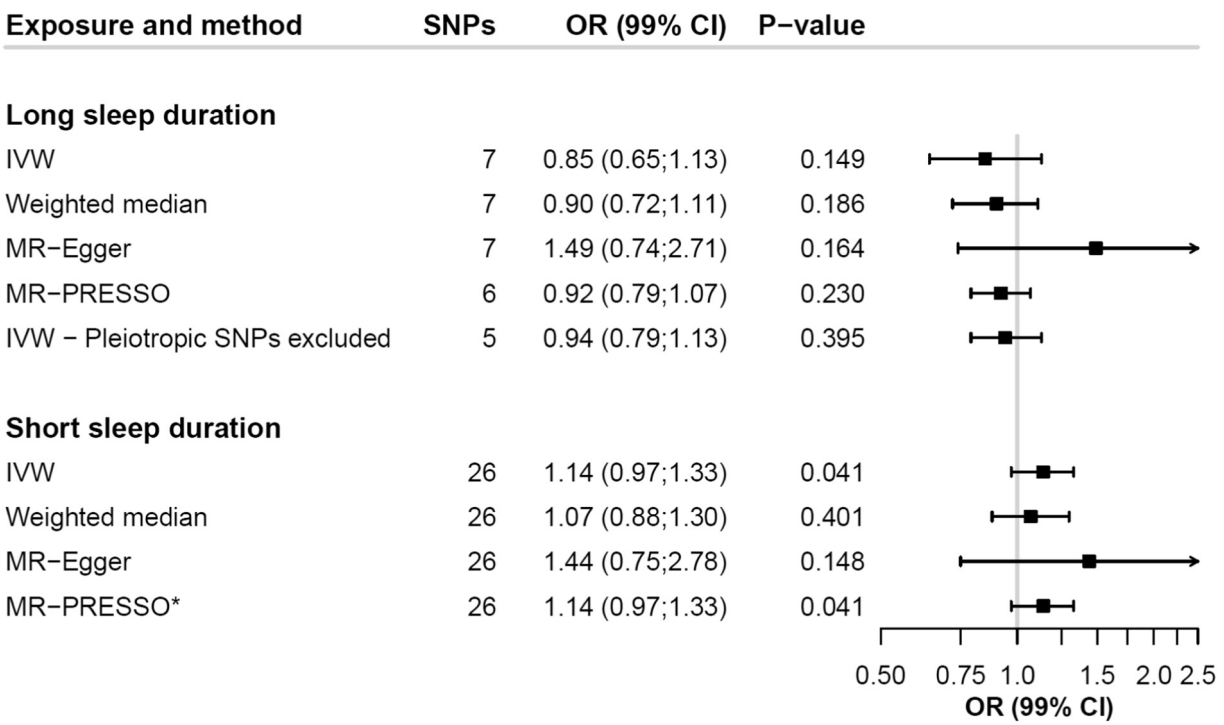
To draw conclusions on whether alcohol consumption, coffee consumption, and physical activity play a causal role in the pathophysiology of heart failure, larger GWASs for the lifestyle factors with objective assessment methods are needed to identify more variants, explaining a larger proportion of the phenotypic variance. Larger GWASs for heart failure will also contribute to improved power. Current developments in genetic epidemiology including data sharing and worldwide collaborations will support attaining these required large sample sizes. Moreover, future MR studies on lifestyle and heart failure subtypes could help distinguish hypothesized differences in pathophysiology between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Finally, as it has become increasingly clear in the past years that there are sex-specific differences in the pathophysiology of heart failure, future GWASs and MR studies could focus on obtaining separate estimates for men and women.

Strengths and limitations

This study had several strengths. Multiple SNPs were used as instruments for the different lifestyle factors, which enabled the detection of potential horizontal pleiotropy and led to strong genetic instruments for smoking initiation and sleep duration. Furthermore, our main findings were robust across sensitivity analyses that assessed potential violations of the instrumental variable assumptions. This supports the validity of causal inference from this study.

A limitation of this study was the partial overlap in the data sets of the gene-lifestyle factor and gene-outcome associations (Supplementary Table I), which potentially inflated the type 1 error rate. Another shortcoming was that we were not able to assess potential nonlinear associations of alcohol and coffee consumption with heart failure. Despite the large sample size, the small variation in exposure explained by the genetic instruments for alcohol consumption, coffee consumption, and physical activity resulted in low precision. Thus, the null associations cannot be interpreted as no causal effect of these lifestyle factors on heart failure risk. Additionally, it was not possible to specify the effects of lifestyle factors

Figure 5



Complementary MR analyses of long and short sleep duration with heart failure.ORs represent the association long sleep duration (≥9 h/d) and short sleep duration (<7 h/d) compared to a sleep duration of 7-8 h/d with heart failure.The IVW random effects method was used as main analysis, and the other methods were used as sensitivity analyses. Pleiotropic SNPs were identified with PhenoScanner.*MR-PRESSO did not identify any outlying SNPs

on heart failure subtypes because information on heart failure subtypes was lacking. It is also important to acknowledge that our effect estimates might have been biased in either direction by survival bias because people had to reach a certain age to be included in the GWASs. Nevertheless, our observed effect estimates for smoking initiation and sleep duration were quite large, which make them less vulnerable to a reversal of the effect due to selection bias.[41] Therefore, it is unlikely that survivor bias completely explained our findings. Finally, the generalizability of our findings is limited to populations of European ancestry. However, smoking initiation is most likely a robust risk factor for all ethnic groups.

Conclusions

This Mendelian randomization study showed that smoking initiation increases heart failure risk, whereas longer sleep duration decreases the risk of heart failure. Sleep duration should be regarded as novel risk factor in heart failure prevention guidelines. The potential causal role of alcohol and coffee consumption and physical activity for heart failure warrants further investigation in future larger MR analyses.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.06.007.

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