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ARTICLE

# Causal effects of risky behaviours on heart failure: a two-sample Mendelian randomisation study

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## Abstract

**Aims/Background** Previous studies have indicated correlations between various risky behaviours, increased risk tolerance, and the likelihood of heart failure. However, the causative nature of these correlations remains to be established. Therefore, our research aims to explore the causality between phenotypes of risky behaviour and the incidence of heart failure.

**Methods** To assess causality, a two-sample Mendelian randomisation analysis was employed. Genetic variants of risky behaviours and risk tolerance (n=251,151–939,908) were sourced from existing genome-wide association summary statistics. For heart failure, genetic links were derived from a separate genome-wide association summary statistics dataset involving 977,323 individuals, comprising 47,309 heart failure cases and 930,014 controls. The primary method for this analysis was the inverse variance weighted technique.

**Results** Mendelian randomisation analysis indicated a positive association between the number of offspring an individual has and the likelihood of heart failure (odds ratio, 1.841; 95% confidence interval, 1.528–2.217, $p=1.26 \times 10^{-10}$). Additionally, a modest statistically significant link was found between overall risk tolerance and heart failure (odds ratio, 1.249; 95% confidence interval, 1.003–1.556, $p=0.047$). Conversely, a genetic predisposition towards frequent automobile speeding showed a protective effect against heart failure (odds ratio, 0.732; 95% confidence interval, 0.545–0.982, $p=0.037$).

**Conclusion** This Mendelian randomisation study confirmed genetically that risky behaviours are causally linked to the likelihood of heart failure. This finding may offer fresh perspectives on the pathogenic mechanisms underlying the progression of heart failure.

Key words: Heart failure; Mendelian randomization; Risk tolerance; Risky behaviours

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## Introduction

Heart failure (HF), characterised by substantial morbidity and mortality rates, is increasingly emerging as a prominent global public health concern (Savarese et al, 2023). Epidemiological data suggest that in Europe, the median yearly incidence rate of HF stands at 3.2 cases per, 1000 person-years (Seferović et al, 2021). The economic burden imposed by HF on global healthcare systems is substantial and projected to escalate due to the increasing prevalence of this disease (Savarese et al, 2023).

Relevant clinical risk factors, such as diabetes (Lehrke and Marx, 2017), renal dysfunction (Schefold et al, 2016), and hypertension (Joseph et al, 2023), have been extensively documented to contribute significantly to the pathogenesis and exacerbation of HF. Moreover, numerous large-scale meta-analyses and observational studies have consistently demonstrated the substantial impact of lifestyle exposure factors on the development of HF (Zyriax and Windler, 2023).

A nationwide population-based study comprising 18,346 Finnish men and 19,729 women without pre-existing HF at baseline demonstrated that adherence to a healthier lifestyle profile is significantly linked to a reduced risk of HF in both genders (Wang et al, 2011). Nevertheless, earlier observational studies potentially suffered from unresolved

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confounding factors, which could have obstructed the identification of causal links between specific risky behaviours and HF.

Mendelian randomisation (MR) utilises genetic variants as instrumental variables (IVs) to deduce the causal effects of risk factors on health outcomes (Emdin et al, 2017). The genetic variants linked to this exposure are allocated randomly, thereby eliminating concerns of reverse causation (Sekula et al, 2016). Genome-wide association studies (GWASs) have yielded robust and reliable IVs for MR analyses. Recently, findings from an MR analysis indicated that genetic predisposition towards starting to smoke and increased overall exposure to smoking throughout life correlate with an increased risk of HF (Lu et al, 2021). This investigation conducted a two-sample MR approach to assess the causal relationship between six hazardous behaviours and HF, employing summary-level data from GWASs.

## Methods

### Study design

Figure 1 illustrates the configuration of our two-sample MR approach. We chose single nucleotide polymorphisms (SNPs) linked to six hazardous behaviours as IVs. Initially, these genetic IVs must exhibit a strong correlation with exposure ($p < 5 \times 10^{-8}$). Furthermore, these IVs should affect the outcome solely through their interaction with the risky behaviours. Lastly, genetic IVs were not related to any potential confounding factors (Holmes et al, 2017). Proxy SNPs exhibiting high linkage disequilibrium ($r^2 > 0.8$) were designated as IVs in cases where a specific SNP was not available in the dataset of the outcomes (https://ldlink.nci.nih.gov/).

### Genetic instruments selection

The genetic instruments for traits related to risky behaviours were obtained from a comprehensive GWAS conducted on participants of the UK Biobank and the 23andMe study (Karlsson Linnér et al, 2019). This GWAS pinpointed a variety of independent genetic loci linked to different dimensions of risky behaviours, including general risk tolerance, adventurousness, and activities involving risks associated with driving, alcohol consumption, tobacco use, and sexual behaviours.

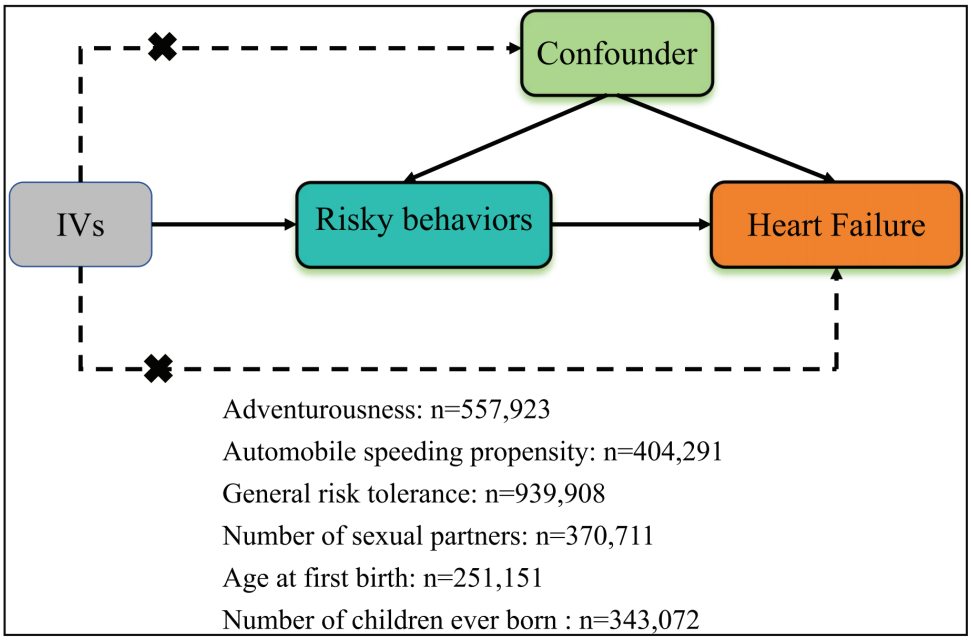


**Figure 1.** Design of Mendelian randomisation study. IVs, instrumental variables.

Our study operationalised general risk tolerance as the inclination to engage in risky behaviours, adventurousness as the self-reported propensity for novelty-seeking and risk-taking compared to caution, and automobile speeding propensity as the disposition to exceed speed limits while driving.

The genetic variations of reproductive traits, namely age at first birth (AFB) and number of children ever born (NEB), were derived from a large GWAS encompassing 251,151 individuals for AFB and 343,072 individuals for NEB (Barban et al, 2016).

The data link for exposure was provided in **Supplementary Table 1**.

### Data source

Statistical summaries for HF were extracted from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) dataset, which includes 47,309 cases and 930,014 control participants of European descent (Shah et al, 2020). The analysis considered covariates such as age, sex, and up to 12 genetic principal components (Shah et al, 2020).

### Statistical analyses

In our analysis, we employed the random-effects inverse-variance weighted (IVW) approach as the primary statistical model to assess the causal relationships between risky behaviours and HF risk. Effect estimates were calculated using the Wald estimator and then synthesised through a random-effects IVW meta-analysis to generate a consolidated effect estimate (Burgess et al, 2013). Additionally, for sensitivity analysis, we utilised the Weighted Median method, MR-Egger regression, and the Mendelian Randomisation Pleiotropy Residual Sum and Outlier (MR-PRESSO) approach as supplementary analytical tools. Notably, the Weighted Median method can yield reliable causal estimates even if up to 50% of the data are derived from invalid SNPs (Bowden et al, 2016). Mendelian randomisation-Egger regression enables the detection of potential pleiotropy among associations through intercept tests, thereby providing a more accurate estimation of the causal effect by adjusting for pleiotropy (Burgess and Thompson, 2017). The application of the MR-PRESSO method facilitated the identification and exclusion of potential outliers, enhancing the precision and reliability of the causal estimates that support the study's conclusions. The Cochran Q-derived *p*-value was used to assess heterogeneity in the IVW analysis, while the *p*-value for the MR-Egger intercept was employed to evaluate potential pleiotropy. Furthermore, we created comprehensive visualisations using scatter plots, and robustness checks were conducted through leave-one-out analyses to vividly illustrate and confirm the relationships between risky behaviours and the incidence of HF.

The Multivariable MR (MVMR) analyses were carried out sequentially for each exposure. The multivariable IVW (MV-IVW) method served as the primary analysis, while the MVMR-Egger method was utilised as a sensitivity analysis.

Statistical power calculations for MR analyses were conducted using the specialised web application mRnd (https://shiny.cnsgenomics.com/mRnd/). The MR analyses were performed using R packages 'TwoSampleMR' and 'MRPRESSO' in R software (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

## Results

In the MR analysis, **Supplementary Tables 1–6** present the IVs for six risky behaviours. Specifically, we identified 80 SNPs for general risk tolerance, 108 SNPs for adventurousness, 31 SNPs for automobile speeding propensity, 77 SNPs for number of sexual partners, 9 SNPs for AFB, and 2 SNPs for nicotine experimentation behaviour (NEB). The F-statistics of these IVs exceeded 10 (**Supplementary Tables 2–7**).

Figure 2 depicts the main results from primary MR studies evaluating the connections between various risky behaviours and susceptibility to HF. Detailed IVW analysis provided initial support for the hypothesis that genetic inclinations towards accepting general risks might correlate with heightened HF risk (odds ratio (OR) 1.249; 95% confidence interval (95% CI) 1.003–1.556; $p$=0.047). Additionally, the genetic propensity for NEB appeared to similarly predict an increased HF risk (OR 1.841; 95% CI 1.528–2.217; $p=1.26 \times 10^{-10}$). In contrast, our data also pointed to a potential causal relationship wherein a predisposition

to automobile speeding propensity might actually lower the risk of HF (OR 0.732; 95% CI 0.545–0.982; $p$=0.037). No other risky behaviours demonstrated statistically significant causal links with HF occurrence, as outlined in Figure 2. Moreover, the consistency of these associations was further confirmed in sensitivity analyses, showing stable directionality across most statistical models detailed in Table 1.

The $p$-value derived from the Cochran Q test suggested a moderate degree of heterogeneity in the primary analyses. Additionally, only slight pleiotropy was detected during the MR-Egger intercept evaluations (Table 2). Furthermore, our study exhibited a statistical power exceeding 80% in detecting the causal associations of automobile speeding propensity, general risk tolerance, and NEB with HF (**Supplementary Table 8**).

The scatter plots visually depicted the associations between risky behaviours and HF (**Supplementary Figures 1–6**). The leave-one-out sensitivity analyses revealed that none of the single SNP had a significant effect on the causality in our primary analysis (**Supplementary Figures 7–11**). The causal relationships between automobile speeding propensity and risk of HF remained consistent after adjusting for other exposures (**Supplementary Table 9**). Additionally, the causality between general risk tolerance and risk of HF remained consistent after adjusting for automobile speeding propensity (**Supplementary Table 9**).

## Discussion

In this comprehensive MR analysis, summary-level statistics from large consortia were utilised to explore the causal relationship between several risky behaviours and HF. Our study revealed that a genetic predisposition to self-reported general risk tolerance and NEB was linked to a higher likelihood of HF. We observed an unexpected inverse correlation between automobile speeding propensity and HF. However, limited evidence was found to support causality between other behaviours and HF.

Earlier research exploring the association between NEB and HF has yielded varied and conflicting outcomes. A comprehensive meta-analysis, which included 10 separate studies with a participant range from 867 to 1,332,062 individuals, demonstrated a notable correlation between NEB and the incidence of cardiovascular diseases (Li et al, 2019). Furthermore, an increasing NEB was found to be positively correlated with the risk of developing cardiovascular disease, which aligns with our findings. Moreover, a retrospective cohort study based on population data involving, 8583 White and African American women

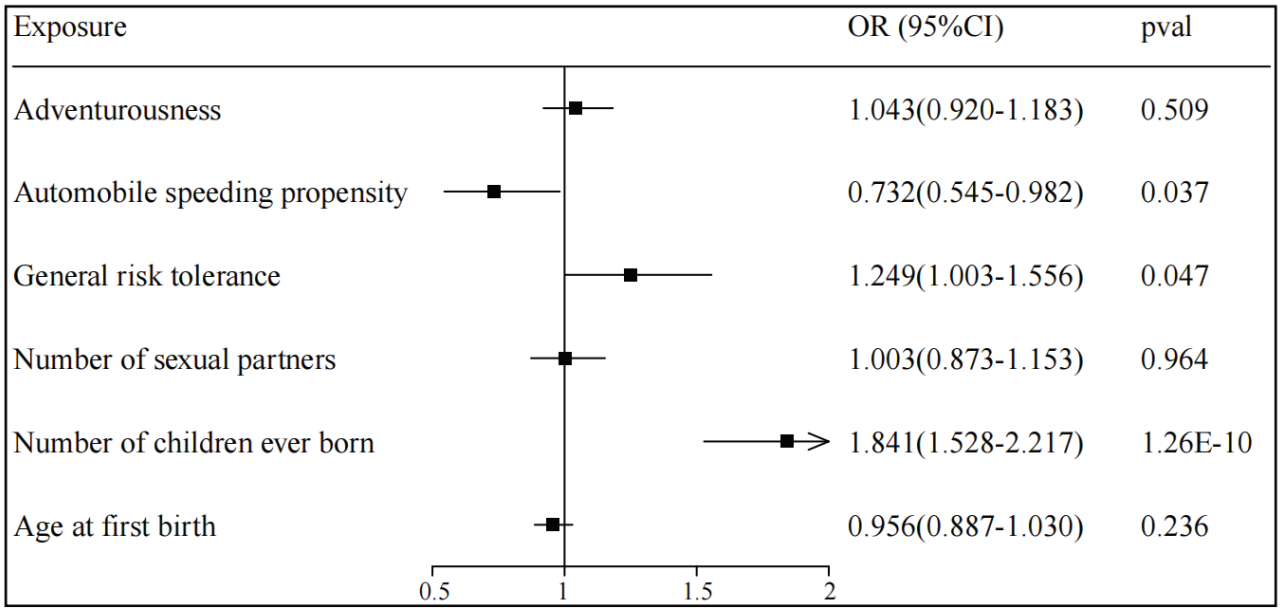


**Figure 2.** Mendelian randomisation analysis estimates of risky behaviours and the risk of heart failure. OR, odds ratio; CI, confidence interval.

**Table 1. Sensitivity analysis of risky behaviours with heart failure**

| Exposure | Method | OR (95% CI) | *p*-value |
|---|---|---|---|
| Adventurousness | Weighted median | 1.052 (0.880–1.258) | 0.575 |
| | MR-Egger | 1.488 (0.915–2.420) | 0.112 |
| | MR-PRESSO | 1.043 (0.920–1.183) | 0.510 |
| Automobile speeding propensity | Weighted median | 0.667 (0.496–0.897) | 0.007 |
| | MR-Egger | 0.739 (0.603–0.907) | 0.004 |
| | MR-PRESSO | 0.692 (0.530–0.905) | 0.012 |
| General risk tolerance | Weighted median | 1.314 (0.998–1.731) | 0.051 |
| | MR-Egger | 2.157 (0.071–6.551) | 0.179 |
| | MR-PRESSO | 1.289 (1.045–1.591) | 0.020 |
| Number of sexual partners | Weighted median | 0.967 (0.813–1.150) | 0.702 |
| | MR-Egger | 0.807 (0.392–1.662) | 0.563 |
| | MR-PRESSO | 1.003 (0.873–1.153) | 0.964 |
| Age at first birth | Weighted median | 0.956 (0.881–1.038) | 0.283 |
| | MR-Egger | 0.664 (0.318–1.386) | 0.311 |
| | MR-PRESSO | 0.956 (0.887–1.030) | 0.270 |

*MR-PRESSO, Mendelian Randomisation Pleiotropy Residual Sum and Outlier; OR, odds ratio; CI, confidence interval.*

**Table 2. Heterogeneity and pleiotropic statistics of risky behaviours on heart failure**

| Outcome | Q-value | $P_Q$ | Intercept | $P_{intercept}$ |
|---|---|---|---|---|
| Adventurousness | 128.39 | 0.078 | –0.005 | 0.142 |
| Automobile speeding propensity | 65.89 | 1.68E-04 | –0.004 | 0.705 |
| General risk tolerance | 120.06 | 0.002 | –0.006 | 0.328 |
| Number of sexual partners | 107.98 | 0.009 | 0.004 | 0.550 |
| Number of children ever born | 0.11 | 0.737 | NA | NA |
| Age at first birth | 89.18 | 0.030 | –0.010 | 0.591 |

*Q-value: the statistics of Cochran Q test; $P_Q$, p-value corresponding to Cochran Q test; $P_{intercept}$, p-value corresponding to MR-Egger intercept test; NA, not applicable.*

revealed that women with five or more childbirths exhibited an elevated risk of HF (hazard ratio [HR] 1.25; 95% CI 1.09–1.43) compared to those with one to two births (Oliver-Williams et al, 2019). However, conflicting findings have been reported by other studies indicating that parity may not be a significant risk factor for certain subtypes of HF (Bolijn et al, 2017). The results of an observational study involving 161,808 participants indicated that there was no significant association between higher parity and the risk of HF, even after adjusting for confounders related to cardiovascular health and sociodemographic characteristics (Hall et al, 2017). A retrospective analysis encompassing, 3931 participants suggested that women with 5 or more live births had a lower risk of developing future HFpEF (Heart failure with preserved ejection fraction) compared to nulliparous women (Sarma

et al, 2023). Therefore, this MR study is timely in directing attention toward assessing the causal relationship between NEB and HF. Possible explanations for the lack of association in previous observational studies may stem from the failure to consider pregnancy-related cardiometabolic conditions in their medical histories, as well as the persistent influence of socioeconomic confounding factors.

The causal effect of NEB on HF could potentially be elucidated through several possible mechanisms. Pregnancy represents a significant physiological challenge to all bodily systems. During pregnancy, the ability of insulin to phosphorylate insulin receptors decreases, leading to a reduction in the expression of IRS-1 (insulin receptor substrate 1) and impaired responsiveness of PI3 kinase (phosphoinositide 3-kinase) to insulin (Barbour et al, 2007). These processes may exacerbate glycaemic control in pregnant women, leading to insulin resistance, and even causing gestational hypertension (Seely and Solomon, 2003; Vejrazkova et al, 2014). Moreover, multiple putative biological mechanisms have been documented, encompassing deleterious alterations in lipids and weight during each gestation period, alongside endothelial dysfunction and haemostatic processes (Cowan et al, 1997; Stewart et al, 2007; Brown and Smith, 2020; Hanna and Frangogiannis, 2020). These cardiometabolic alterations may potentially exert long-lasting effects on the cardiovascular system, thereby increasing the susceptibility of women to HF in later stages. Additionally, research suggests that various social aspects of childrearing, including increased exposure to physical and psychological stressors along with reduced physical activity, are linked to a higher risk of developing HF (Celano et al, 2018; Ogunmoroti et al, 2019; Harris et al, 2020). This MR study further elucidates the enduring impact of parity on the risk of HF, thereby corroborating the findings of observational studies.

Driving is a multifaceted yet ubiquitous activity. We have identified an inverse causal association between automobile speeding propensity and HF. Interpretation of such an unexpectedly beneficial effect should be approached cautiously. To a certain extent, driving speed can serve as an indicator of cognitive abilities, educational attainment, and intellectual aptitude (Aksan et al, 2015; Navarro et al, 2018). Recent findings from an MR study indicate that elevated levels of education and intelligence may confer a protective benefit against the risk of HF (Liao et al, 2021). Presently, there is a notable shortage of population-based epidemiological studies that explore the link between the propensity for automobile speeding and the risk of HF. The elucidation of the mechanisms underlying this association necessitates further investigations.

Risk tolerance, which refers to the extent to which an individual is willing to accept risk in pursuit of a higher anticipated return, plays a pivotal role in shaping a wide range of financial decisions and health-related behaviours (Jung et al, 2018). Previous studies have identified an association between risk tolerance and various health behaviours, such as smoking (Lejuez et al, 2005; Schepis et al, 2011), which has been recognised as a contributing factor for HF (Dunlay et al, 2009; Kamimura et al, 2018). However, additional corroborative evidence from independent sources is imperative to substantiate the veracity of these findings.

This study showcases numerous strengths. Primarily, it applied MR analysis for the inaugural exploration of the causal connections between various risk behaviours and HF, thereby significantly reducing the effects of confounders. Additionally, through meticulous screening of a vast array of genetic associations to identify suitable genetic instruments, the compilation of comprehensive data ensured a precise estimation of the causal effect based on substantial sample sizes. Lastly, multiple sensitivity analyses were conducted to ensure the robustness of causal relationships.

However, this study is not without its limitations. Initially, the definition of HF varied across the different studies within the HERMES Consortium, which could affect the consistency of results. Second, varying levels of heterogeneity detected through Cochrane's Q tests suggest the potential influence of pleiotropy on our findings. Third, although limited evidence of horizontal pleiotropy was detected in the pleiotropy tests, it is important to acknowledge that the potential influence of pleiotropy cannot be completely disregarded. Fourth, the generalizability of our findings to diverse populations is limited, as the HF cases studied were exclusively of European descent. Lastly, the availability of only two

genetic instruments for NEB constrained our ability to apply a comprehensive sensitivity analysis to ensure the stability and reliability of our findings.

## Conclusion

This research contributes genetic proof that underscores the causal linkage between risk tolerance, engaging in risky behaviours, and the likelihood of developing HF. Such evidence could shed new light on the pathogenic processes involved in the onset of HF. Therefore, emphasising the potential significance of managing risky behaviours is essential in combating HF.

### Key points

- Evidence from observational studies regarding the association between risky behaviours and HF remains controversial.
- Genetically predicted general risk tolerance and NEB significantly contribute to HF.
- Genetically predicted automobile speeding propensity was associated with a reduced risk of HF.
- Requiring further investigations to explore the benefits of targeting risky behaviours in the prevention of HF.

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## Availability of data and materials

All data included in this study are available upon request by contact with the corresponding author.

## Author contributions

YC conducted the study and analysed the data. YC drafted the manuscript and HBC edited the manuscript. HBC interpreted the data and provided constructive feedback on the manuscript. The final version of the manuscript has undergone a comprehensive review and obtained unanimous approval from both authors. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics approval and consent to participate

Not applicable.

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## Conflict of interest

The authors disclose that they have no competing interests.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0185.

## References

Aksan N, Anderson SW, Dawson J, Uc E, Rizzo M. Cognitive functioning differentially predicts different dimensions of older drivers' on-road safety. Accid Anal Prev. 2015;75:236–244. https://doi.org/10.1016/j.aap.2014.12.007

Barban N, Jansen R, de Vlaming R et al. Genome-wide analysis identifies 12 loci influencing human reproductive behavior. Nat Genet. 2016;48(12):1462–1472. https://doi.org/10.1038/ng.3698

Barbour LA, McCurdy CE, Hernandez TL et al. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(Supplement_2):S112–S119. https://doi.org/10.2337/dc07-s202

Bolijn R, Onland-Moret NC, Asselbergs FW, van der Schouw YT. Reproductive factors in relation to heart failure in women: a systematic review. Maturitas. 2017;106:57–72. https://doi.org/10.1016/j.maturitas.2017.09.004

Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–314. https://doi.org/10.1002/gepi.21965

Brown HL, Smith GN. Pregnancy complications, cardiovascular risk factors, and future heart disease. Obstet Gynecol Clin North Am. 2020;47(3):487–495. https://doi.org/10.1016/j.ogc.2020.04.009

Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–665. https://doi.org/10.1002/gepi.21758

Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377–389. https://doi.org/10.1007/s10654-017-0255-x

Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and anxiety in heart failure: a review. Harv Rev Psychiatry. 2018;26(4):175–184. https://doi.org/10.1097/hrp.0000000000000162

Cowan LD, Go OT, Howard BV et al. Parity, postmenopausal estrogen use, and cardiovascular disease risk factors in American Indian women: the Strong Heart Study. J Womens Health. 1997;6(4):441–449. https://doi.org/10.1089/jwh.1997.6.441

Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. Am J Med. 2009;122(11):1023–1028. https://doi.org/10.1016/j.amjmed.2009.04.022

Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA. 2017;318(19):1925–1926. https://doi.org/10.1001/jama.2017.17219

Hall PS, Nah G, Howard BV et al. Reproductive factors and incidence of heart failure hospitalization in the women's health initiative. J Am Coll Cardiol. 2017;69(20):2517–2526. https://doi.org/10.1016/j.jacc.2017.03.557

Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. Cardiovasc Drugs Ther. 2020;34(6):849–863. https://doi.org/10.1007/s10557-020-07071-0

Harris KM, Gottdiener JS, Gottlieb SS et al. Impact of mental stress and anger on indices of diastolic function in patients with heart failure. J Card Fail. 2020;26(11):1006–1010. https://doi.org/10.1016/j.cardfail.2020.07.008

Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. Nat Rev Cardiol. 2017;14(10):577–590. https://doi.org/10.1038/nrcardio.2017.78

Joseph P, Roy A, Lonn E et al. Global variations in heart failure etiology, management, and outcomes. JAMA. 2023;329(19):1650–1661. https://doi.org/10.1001/jama.2023.5942

Jung WH, Lee S, Lerman C, Kable JW. Amygdala functional and structural connectivity predicts individual risk tolerance. Neuron. 2018;98(2):394–404.e4. https://doi.org/10.1016/j.neuron.2018.03.019

Kamimura D, Cain LR, Mentz RJ et al. Cigarette smoking and incident heart failure: insights from the Jackson Heart Study. Circulation. 2018;137(24):2572–2582. https://doi.org/10.1161/circulationaha.117.031912

Karlsson Linnér R, Biroli P, Kong E et al. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet. 2019;51(2):245–257. https://doi.org/10.1038/s41588-018-0309-3

Lehrke M, Marx N. Diabetes mellitus and heart failure. Am J Med. 2017;130(6):S40–S50. https://doi.org/10.1016/j.amjmed.2017.04.010

Lejuez CW, Aklin W, Bornovalova M, Moolchan ET. Differences in risk-taking propensity across inner-city adolescent ever- and never-smokers. Nicotine Tob Res. 2005;7(1):71–79. https://doi.org/10.1080/14622200412331328484

Li W, Ruan W, Lu Z, Wang D. Parity and risk of maternal cardiovascular disease: a dose-response meta-analysis of cohort studies. Eur J Prev Cardiolog. 2019;26(6):592–602. https://doi.org/10.1177/2047487318818265

Liao LZ, Zhuang XD, Zhang SZ, Liao XX, Li WD. Education and heart failure: new insights from the atherosclerosis risk in communities study and Mendelian randomization study. Int J Cardiol. 2021;324:115–121. https://doi.org/10.1016/j.ijcard.2020.09.068

Lu Y, Xu Z, Georgakis MK et al. Smoking and heart failure: a Mendelian randomization and mediation analysis. ESC Heart Fail. 2021;8(3):1954–1965. https://doi.org/10.1002/ehf2.13248

Navarro J, Reynaud E, Osiurak F. Neuroergonomics of car driving: a critical meta-analysis of neuroimaging data on the human brain behind the wheel. Neurosci Biobehav Rev. 2018;95:464–479. https://doi.org/10.1016/j.neubiorev.2018.10.016

Ogunmoroti O, Osibogun O, Kolade OB et al. Multiparity is associated with poorer cardiovascular health among women from the Multi-Ethnic Study of Atherosclerosis. Am J Obstet Gynecol. 2019;221(6):631.e631–631.e616. https://doi.org/10.1016/j.ajog.2019.07.001

Oliver-Williams C, Vladutiu CJ, Loehr LR, Rosamond WD, Stuebe AM. The association between parity and subsequent cardiovascular disease in women: the atherosclerosis risk in communities study. J Womens Health (Larchmt). 2019;28(5):721–727. https://doi.org/10.1089/jwh.2018.7161

Sarma AA, Paniagua SM, Lau ES et al. Multiple prior live births are associated with cardiac remodeling and heart failure risk in women. J Card Fail. 2023;29(7):1032–1042. https://doi.org/10.1016/j.cardfail.2022.12.014

Savarese G, Becher PM, Lund LH et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272–3287. https://doi.org/10.1093/cvr/cvac013

Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol. 2016;12(10):610–623. https://doi.org/10.1038/nrneph.2016.113

Schepis TS, McFetridge A, Chaplin TM, Sinha R, Krishnan-Sarin S. A pilot examination of stress-related changes in impulsivity and risk taking as related to smoking status and cessation outcome in adolescents. Nicotine Tob Res. 2011;13(7):611–615. https://doi.org/10.1093/ntr/ntr022

Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. J Clin Endocrinol Metab. 2003;88(6):2393–2398. https://doi.org/10.1210/jc.2003-030241

Seferović PM, Vardas P, Jankowska EA et al. The heart failure association atlas: heart failure epidemiology and management statistics 2019. Eur J Heart Fail. 2021;23(6):906–914. https://doi.org/10.1002/ejhf.2143

Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. JASN. 2016;27(11):3253–3265. https://doi.org/10.1681/asn.2016010098

Shah S, Henry A, Roselli C et al. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun. 2020;11(1):163. https://doi.org/10.1038/s41467-019-13690-5

Stewart FM, Freeman DJ, Ramsay JE et al. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. J Clin Endocrinol Metab. 2007;92(3):969–975. https://doi.org/10.1210/jc.2006-2083

Vejrazkova D, Vcelak J, Vankova M et al. Steroids and insulin resistance in pregnancy. J Steroid Biochem Mol Biol. 2014;139:122–129. https://doi.org/10.1016/j.jsbmb.2012.11.007

Wang Y, Tuomilehto J, Jousilahti P et al. Lifestyle factors in relation to heart failure among Finnish men and women. Circ Heart Fail. 2011;4(5):607–612. https://doi.org/10.1161/circheartfailure.111.962589

Zyriax BC, Windler E. Lifestyle changes to prevent cardio- and cerebrovascular disease at midlife: a systematic review. Maturitas. 2023;167:60–65. https://doi.org/10.1016/j.maturitas.2022.09.003