Testing causality in the association of plasma cortisol with risk of coronary heart disease: a Mendelian randomisation study

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Introduction

Coronary heart disease (CHD) is one of the leading causes of death in the developed world. Morning plasma cortisol provides a reliable marker of the activation of the HPA axis which accompanies risk factors for CHD such as high blood pressure, hyperglycaemia and dyslipidemia (1-2). Although epidemiological studies have reported positive associations between plasma cortisol and CHD (3-5), they have included a relatively small number of events and so suffer from a lack of power. More importantly, observational studies are unable to infer causality and results may be confounded.

Methods

A two-sample Mendelian randomisation approach, using publicly available data, was used to estimate the causal effect of plasma cortisol on risk of CHD.
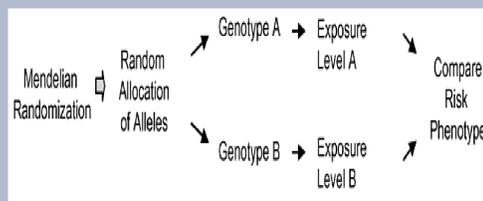
Figure 1. According to Mendel's First Law of segregation (genotypes are assigned randomly when passed from parents to offspring in meiosis) and Second Law of independent assortment (inheritance of one trait is independent of inheritance of other traits) Mendelian Randomisation is similar to an RCT
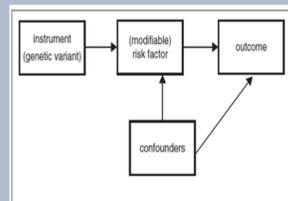
Figure 2. A valid instrument must be: 1) reliably associated with risk factor; 2) Associated with the outcome only through the risk factor; and 3) Independent of confounders.

CORNET performed a meta-analysis of genome-wide association studies of morning plasma cortisol in 12,597 subjects from 11 western European population-based cohorts (6).

CORtisol NETwork
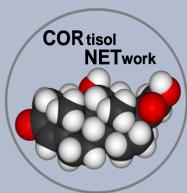
Replication was tested in 2,795 subjects from three independent cohorts. Our genetic instrument for plasma cortisol comprised of three independent ($r^2 < 0.2$) SNPs

Cortisol was measured by immunoassay in blood samples collected from study participants between 0700 and 1100 h. Inclusion criteria were morning plasma cortisol from Caucasian populations; exclusion criteria were current glucocorticoid use, pregnant or breast feeding women, and twins (exclusion of one).

We investigated the association between this genetic instrument for plasma cortisol and risk of CHD in up to 22,223 cases/64,762 controls from the publicly available CARDIOGRAM consortium.

CARDIoGRAMplusC4D

Objective

To investigate whether plasma cortisol is causally associated with CHD using Mendelian randomisation.

Results

Each standard deviation change in genetically elevated plasma cortisol was associated with an odds ratio of 1.27 (95% CI: 1.01 to 1.60) for CHD. These results are compatible with causality for the observational association between plasma cortisol and CHD.
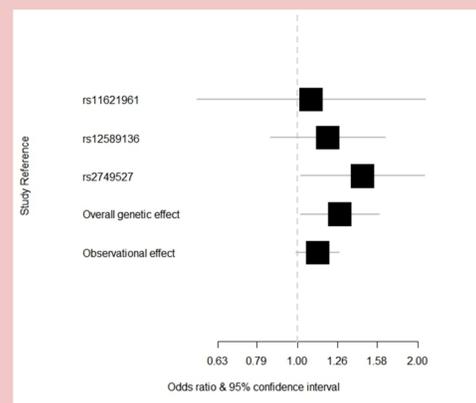
Fig 2. Mendelian randomisation and observational estimates of the association of plasma cortisol with CHD. The forest plot shows odds ratio per standard deviation increase in plasma cortisol. The overall genetic effect was estimated using fixed effects meta-analysis. The observational effect was taken from the Caerphilly cohort (3).

Discussion

These results are compatible with a causal effect for the observational association between plasma cortisol and CHD. The inconsistent results from observational studies may be explained by: the inverse association between cortisol and obesity, which confounded the positive association of cortisol with other cardiovascular risk factors; and the use of single 'snapshot' plasma cortisol measurement rather than cumulative measure of cortisol exposure provided by genetic prediction.

Future work

A bidirectional Mendelian randomisation analysis between plasma cortisol and BMI may yield greater clarity to the confounding effects of obesity. To improve the strength of our genetic instrument an expanded CORNET GWAMA is currently underway with the aim of recruiting 30,000 individuals. A large scale prospective study would provide a more precise estimate of the observational association between plasma cortisol and CHD.

Conclusion

Measurements of cortisol may add value to predictions of CHD risk.

References
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