

Gender differences in cardiovascular risk: Testing the impact of Androgen exposure and the Y chromosome using human experiments of nature.

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On average, men experience ischaemic heart disease (IHD) approximately ten years before women. Factors accounting for this 'gender gap' are not fully understood. There are sex differences in cardiac risk markers such as HDL cholesterol and waist measurements, these parameters do not fully account for the gender gap. We have studied human experiments of nature to characterise 'testosterone' or 'Y chromosome' effects on cardiovascular disease risk markers. We have recruited cohorts of specific conditions: including Complete Androgen Insensitivity (CAIS), 46XY Gonadal Dysgenesis (XYGD), and primary ovarian failure (XXGD), which differ in their sensitivity and exposure to testosterone, and in the presence of a Y chromosome. Serum HDL cholesterol concentrations are higher in two groups with Y chromosome (CAIS & XYGD) and low in normal males. Regression analysis shows that the Y chromosome has no significant independent association with HDL concentration and that testosterone accounts for 51% of the variation of this parameter. LDL shows no association with testosterone or the Y chromosome. Both Y chromosome and testosterone exposure independently contribute to the variability of waist hip ratio. Insulin resistance (HOMA-R) suggests a trend to opposite effects from Y chromosome and testosterone. In conclusion, this model enables segregation of gender differences in CVD risk to those that are 'testosterone sensitive' and those that are associated with the presence of a Y chromosome. The latter group may lead to identification of Y chromosome CVD risk genes.