Magnus, M., Lawlor, D., Iliodromiti, S., Padmanabhan, S., Nelson, S. M., & Fraser, A. (2018). Age at menarche and cardiometabolic health: a sibling analysis in the Scottish Family Health Study. *Journal of the American Heart Association*. https://doi.org/10.1161/JAHA.117.007780

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Age at Menarche and Cardiometabolic Health: A Sibling Analysis in the Scottish Family Health Study

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Background—Previous studies of age at menarche and cardiometabolic health report conflicting findings, and only a few could account for childhood characteristics. We aimed to estimate the associations of age at menarche with cardiovascular risk factors in unrelated women and within sister groups, under the assumption that within-sibship estimates will be better adjusted for shared genetics and early life environment.

Methods and Results—Our study included 7770 women, from 5984 sibships, participating in the GS:SFHS (Generation Scotland: Scottish Family Health Study). We used fixed- and between-effects linear regression to estimate the associations within sister groups and between unrelated individuals, respectively. Within sibships, the mean difference between sisters with early menarche (≤11 years) and sisters with menarche at 12 to 13 years was 1.73 mm Hg (95% confidence interval [CI], –0.41 to 3.86) for systolic blood pressure, 1.26 mm Hg (95% CI, –0.02 to 2.55) for diastolic blood pressure, –0.06 mmol/L (95% CI, –0.11 to –0.02) for high-density lipoprotein, 0.20 mmol/L (95% CI, 0.08–0.32) for non–high-density lipoprotein, –0.34% (95% CI, –1.98 to 1.30) for glucose, 1.60 kg/m² (95% CI, 0.92–2.28) for body mass index, and 2.75 cm (95% CI, 1.06–4.44) for waist circumference. There was weak evidence of associations between later menarche (14–15 or ≥16 years) and lower body mass index, waist circumference, and blood pressure. We found no strong evidence that estimates from within- and between-sibship analyses differed (all P values >0.1). The associations with other cardiovascular risk factors were attenuated after adjustment for adult body mass index.

Conclusions—Our results suggest that confounding by shared familial characteristics is unlikely to be a major driver of the association between early menarche and adverse cardiometabolic health but do not exclude confounding by individual-level characteristics. (J Am Heart Assoc. 2018;7:e007780. DOI: 10.1161/JAHA.117.007780.)

Key Words: cardiometabolic health • cardiovascular disease risk factors • menarche • sibships

EarlY menarche is associated with reduced insulin sensitivity and higher glucose,1–9 higher triglycerides and cholesterol levels,2,6,10 higher blood pressure,4,5,11,12 and greater waist circumference and body mass index (BMI).4,5,13–15 In line with these findings, there is some but less consistent evidence of an association between age at menarche and cardiovascular disease (CVD) events.12,16–18 Mendelian randomization studies suggest causal effects of greater childhood BMI on early timing of menarche and of earlier menarche on higher adult BMI and CVD risk,19,20 although genetic pleiotropy may at least partially explain these findings.12 The few observational analyses that were able to adjust for childhood adiposity found that the associations of age at menarche with adult cardiometabolic health were virtually completely attenuated, suggesting that childhood adiposity is a key confounder.4,14 However, studies from populations in which childhood obesity is less prevalent, such as Korea,5,7,8 Bangladesh,6 China,9 and Brazil,10 also indicate an association between early menarche and worse cardiometabolic health.

Sibling studies controls for confounding (measured and unmeasured) by characteristics shared within families.21,22 The underlying assumption of this approach is that siblings...
Clinical Perspective

What Is New?

- Associations of early menarche with cardiovascular risk factors were explained by body mass index in adulthood.
- Adverse cardiometabolic health in women with early menarche is not likely to be explained by shared familial characteristics such as genetics or childhood environment.

What Are the Clinical Implications?

- Earlier age at menarche is characteristic of women with more adverse cardiometabolic health.
- Having a healthy body mass index in adulthood could help diminish differences in cardiometabolic health related to age at menarche.

Methods

Generation Scotland: Scottish Family Health Study

This study included participants in the GS:SFHS (Generation Scotland: Scottish Family Health Study). The data, analytical methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure. Individuals aged 35 to 65 years who were registered with collaborating general practitioners in Glasgow and Tayside (expanded to include Ayrshire, Arran, and northeast Scotland in 2010) were recruited between 2006 and 2011. All volunteers provided written informed consent and had to identify 1 first-degree relative aged ≥18 years who would also consent to participate. Ethics approval was obtained by the National Health Service Tayside committee on research ethics (reference 05/s1401/89). Data collected included self-reported information through questionnaires as well as clinical examinations and blood samples. The response rate was 5%, with 23,703 participants completing a preclinical questionnaire. Of the 13,946 women who completed the preclinical questionnaire, 11,639 had information on parental identification numbers to identify siblings, and 7,770 had information on age at menarche and other covariates necessary for the current analysis (Figure 1). The study sample thus included 5,984 sister groups. The number of women in each sibling group ranged from 1 (no participating sisters for comparison) to 6 (5 participating sisters for comparison). A total of 3,327 women had at least 1 participating sister.

Age at Menarche

The questionnaire used to obtain information about female reproductive health had 2 different versions. One version asked the woman to give her age in whole years when she had her first menstrual period, and the other version asked if her age at her first period was <8, 8 to 9, 10 to 11, 12 to 13, 14 to 15, 16 to 17, 18 to 19, ≥20, or not known. The new questionnaire was introduced in 2009 between July (Tayside) and October (Glasgow). The only difference between the groups that received the different questionnaires was the participation date. To allow for a nonlinear relationship, we categorized age at menarche as ≤11 years (early menarche), 12 to 13, 14 to 15, and ≥16 years (late menarche). The reference group in all analyses comprised those with an age at menarche of 12 to 13 years. There is some variation across studies in the definition of early menarche (≤10, ≤11, or ≤12 years) and late menarche (≥14, ≥15, or ≥16 years), likely influenced by the size and information available in the specific study, but our categorization is in line with commonly used cutoff values.

Cardiometabolic Health Outcomes

Cardiometabolic health was assessed by study nurses at recruitment. Systolic and diastolic blood pressure (mm Hg), calculated as the average of 2 measurements; BMI (weight in kg/height in m²); waist circumference (cm); and 12-lead ECG were recorded (incorporated into a novel CVD risk prediction score). Total cholesterol, high-density lipoprotein (HDL)
cholesterol, and glucose were measured in serum using standard clinical assays. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Overall, 85% of the blood samples procured from participants were fasting (a minimum of 4 hours since the last meal). Furthermore, self-reported information was available regarding diabetes mellitus in addition to the use of antihypertensive, lipid-lowering, and antidiabetic drugs.

We calculated the 10-year risk of CVD using 2 different risk scores. One was the Framingham 10-year risk score, which includes age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes mellitus. The second was a new validated 10-year risk score for CVD from the NHANES (National Health and Nutrition Examination Survey) cohort that uses age and a range of measurements from ECG readings, including positive deflection of the T axis, negative deflection of the T axis, heart rate, and corrected QT interval. The risk scores were calculated only for individuals who were between 30 and 74 years of age (81% of those included in this analysis) because the original risk scores were generated for this age group. Individuals with self-reported history of heart disease or stroke were excluded from the analysis of 10-year risk of CVD.

Potential Confounders

Additional self-reported information on characteristics that could plausibly influence the associations of age at menarche with cardiometabolic health—and confound it—included age at recruitment (continuous), ethnicity (white versus other), qualifications (from none to college/university degree, including 7 categories in total), annual household income in pounds sterling (<10 000, 10 000–30 000, 30 000–50 000, 50 000–70 000, ≥70 000, prefer not to answer), number of pack-years of smoking (none, 1–5, 6–10, >10 units), and number of hours of moderate or vigorous physical activity during the past week (≤1 hour, 1.1–3.0, 3.1–5.0, 5.1–10.0, 10.1–15.0, ≥15.1). Participants’ reports of parental history of CVD (heart disease, stroke, and/or high blood pressure) and diabetes mellitus were also considered.

Statistical Analyses

We used fixed- and between-effects linear regression to evaluate the associations of age at menarche with cardiometabolic health. Fixed-effect linear regression provided the within-sibships association, which is the association between age at menarche and cardiometabolic outcomes controlling for characteristics that are identical or very similar among sisters, including genetics, parental socioeconomic position, and childhood lifestyle and adiposity. The between-sibships estimate was the association of age at menarche with cardiometabolic health in unrelated women. The estimate used data from all individuals but related the mean of the cardiometabolic measures within a cluster (group of sisters) to the mean age at menarche within a cluster (group of sisters). If the within- and between-sibships estimates both provide evidence of an association, this suggests that the association between age at menarche and cardiometabolic health is not explained by unmeasured confounding due to genetic or environmental characteristics shared by siblings. To test whether the between- and within-sibship estimates were different, we used a bootstrapping test with 5000
iterations. We also tested for departure from linearity in the association between age at menarche and cardiometabolic health, using a likelihood ratio test comparing a model with age at menarche as a categorical covariate and a model using age at menarche as a continuum.

We incrementally adjusted for age (model 1), ethnicity, educational qualifications, parental history of CVD, and parental history of diabetes mellitus (model 2). The multivariable analysis further adjusted blood pressure for use of antihypertensive drugs, cholesterol levels for lipid-lowering drugs, and glucose for use of antidiabetic drugs. Potential confounders are common causes of the exposure and outcome. We did not have any direct measures of childhood socioeconomic position in GS:SFHS and thus had to rely on adult educational attainment as a proxy for childhood socioeconomic position. Under the assumption that there are genes that are common determinants of age at menarche and adverse cardiometabolic health, which is clearly the case for obesity-related genes,20,31 parental histories of CVD and diabetes mellitus were also conceptualized as confounders. We then explored further adjustment for adult lifestyle characteristics, including pack-years of smoking, units of alcohol consumed during the past week, and number of hours of moderate or vigorous physical activity during the past week (model 3). These characteristics can be conceptualized as both potential confounders (due to tracking from childhood to adult life) and potential mediators, given evidence of associations between age at menarche and health-related behaviors.32

We also conducted secondary analyses adjusting the other cardiometabolic health outcomes for adult BMI to further explore potential direct associations. Different sensitivity analyses included adjusting for adult household income (not adjusted for in the primary analysis because it also reflects the partner’s contribution), excluding those on medications that could influence the outcomes of interest (for blood pressure, cholesterol, and glucose) and excluding women who had an age difference of ≥4 years with their only sibling for comparison (i.e., restricting the within-sibship analysis to sisters with an age difference of ≤4 years). This sensitivity analysis was done under the assumption that sisters who are closer in age are more likely to have a similar childhood environment. To examine the impact of nonfasting blood sampling on the associations, we reexamined the associations of age at menarche with HDL cholesterol, non-HDL cholesterol, and glucose, excluding women with a nonfasting blood sample (n=1132) and unknown fasting status (n=321). We also conducted a sensitivity analysis excluding women of non-European ethnicity (n=156).

The results presented are from a complete case analysis because it was not possible to conduct multiple imputation accounting for clustering, given the large number and small size of the sibling groups. All analyses were done using Stata version 14 (StataCorp).

Results

Women included in the analyses were younger, were more likely to be white, had higher educational qualifications, had lower annual household income, and were more likely to have a family history of CVD than those excluded because of missing covariate information (Table S1). There was no difference in parental history of diabetes mellitus (Table S1). Of the women included in the analysis, 18% reported menarche at ≤11 years, whereas 52% were 12 to 13 years at menarche, 26% were 14 to 15 years at menarche, and 4% were ≥16 years at menarche. Age at menarche was associated with age at recruitment, qualifications, household income, parental history of diabetes mellitus, current use of antihypertensive medications, and, more weakly, with pack-years of smoking, alcohol intake, and parental history of CVD (Table). A greater proportion of the variation in age at menarche, qualifications, and adult BMI, in addition to other adult lifestyle characteristics, was explained by variation within as opposed to between sibships (Table S2). Looking more closely at the level of concordance of these traits within sibships, there was a moderate to strong concordance for most traits (Table S3).

Associations of Age at Menarche With Cardiometabolic Health Outcomes

There was strong evidence of nonlinear association for most outcomes in both the between- and within-sibship analyses (P values <0.01), with a few exceptions. Women with early menarche (≥11 years) had higher systolic and diastolic blood pressure and BMI and greater waist circumference compared with women with menarche at 12 to 13 years when examined both within and between sibships (Figure 2). Early menarche was also associated with lower HDL cholesterol and increased non-HDL cholesterol both between and within sibships (Figure 3). There was no strong evidence for differences between the estimates from the between- and within-sibship analyses from the bootstrapping tests (Table S4). The only exceptions were the estimates of the associations of age at menarche between 14 and 15 years (versus 12–13) with BMI and waist circumference, for which the inverse association tended to be greater when evaluated within sibships (P=0.02 and P=0.07, respectively; Table S4). Multivariable adjustment caused only modest changes in these associations, including adjustment for adult lifestyle characteristics (Table S4).

Associations of Age at Menarche With 10-Year Risk of CVD

The correlation between the Framingham and NHANES 10-year CVD risk scores was 0.83. The likelihood ratio test
**Table. Distribution of Background Characteristics by Age At Menarche, GS:SFHS, 2006–2011**

| Characteristics                                      | Age At Menarche, y | ≤11 (n=1395) | 12–13 (n=4042) | 14–15 (n=1993) | ≥16 (n=340) | P Value |
|-------------------------------------------------------|-------------------|--------------|----------------|----------------|-------------|---------|
| Age at baseline evaluation, y, mean±SD                |                   | 44.4±13.6    | 43.6±13.7      | 45.2±13.8      | 47.0±12.9   | <0.001  |
| Ethnicity, n (%)                                      |                   |              |                |                |             | 0.566   |
| White                                                 |                   | 1365 (97.9)  | 3967 (98.1)    | 1947 (97.7)    | 335 (98.5)  |         |
| Other                                                 |                   | 30 (2.2)     | 75 (1.9)       | 46 (2.3)       | 5 (1.5)     |         |
| Qualifications, n (%)                                 |                   |              |                |                |             | <0.001  |
| College/university degree                             |                   | 422 (30.3)   | 1451 (35.9)    | 680 (34.1)     | 98 (28.8)   |         |
| Other professional or technical qualification          |                   | 300 (21.5)   | 789 (19.5)     | 394 (19.8)     | 76 (22.4)   |         |
| NVQ/HND/HNC or equivalent                             |                   | 131 (9.4)    | 345 (8.5)      | 154 (7.7)      | 31 (9.1)    |         |
| Higher grade                                          |                   | 177 (12.7)   | 516 (12.8)     | 244 (12.2)     | 24 (7.1)    |         |
| Standard grade/0 level/GCSE                           |                   | 184 (13.2)   | 486 (12.0)     | 248 (12.4)     | 49 (14.4)   |         |
| CSEs, school leavers certificate, other or no qualifications |     | 181 (13.0)   | 455 (11.3)     | 273 (13.7)     | 62 (18.2)   |         |
| Annual household income, £, n (%)                     |                   |              |                |                |             | 0.005   |
| <10 000                                               |                   | 114 (8.2)    | 259 (6.4)      | 112 (5.6)      | 32 (9.4)    |         |
| 10 000–30 000                                         |                   | 414 (29.7)   | 1081 (26.7)    | 546 (27.4)     | 100 (29.4)  |         |
| 30 000–50 000                                         |                   | 335 (24.0)   | 1021 (25.3)    | 507 (25.4)     | 77 (22.7)   |         |
| 50 000–70 000                                         |                   | 172 (12.3)   | 579 (14.3)     | 306 (15.4)     | 37 (10.9)   |         |
| ≥70 000                                               |                   | 132 (9.5)    | 453 (11.2)     | 183 (9.2)      | 32 (9.4)    |         |
| Prefer not to answer                                  |                   | 72 (5.2)     | 201 (5.0)      | 109 (5.5)      | 26 (7.7)    |         |
| Missing                                               |                   | 156 (11.1)   | 448 (11.1)     | 230 (11.5)     | 36 (10.6)   |         |
| Pack-years of smoking, n (%)                          |                   |              |                |                |             | 0.084   |
| None                                                  |                   | 836 (59.9)   | 2566 (63.5)    | 1223 (61.4)    | 208 (61.2)  |         |
| 1–10                                                  |                   | 247 (17.7)   | 703 (17.4)     | 366 (18.4)     | 57 (16.8)   |         |
| 11–20                                                 |                   | 106 (7.6)    | 286 (7.1)      | 128 (6.4)      | 20 (5.9)    |         |
| ≥20                                                   |                   | 206 (14.8)   | 487 (12.1)     | 276 (13.9)     | 55 (16.2)   |         |
| Number of alcohol units consumed during the past week, n (%) |       |              |                |                |             | 0.083   |
| None                                                  |                   | 330 (23.7)   | 813 (20.1)     | 425 (21.3)     | 64 (18.8)   |         |
| 1–5                                                   |                   | 349 (25.0)   | 1001 (24.8)    | 457 (22.9)     | 93 (27.4)   |         |
| 6–10                                                  |                   | 326 (23.4)   | 1039 (25.7)    | 486 (24.4)     | 79 (23.2)   |         |
| ≥10                                                   |                   | 288 (20.7)   | 918 (22.7)     | 483 (24.2)     | 77 (22.7)   |         |
| Missing                                               |                   | 102 (7.3)    | 271 (6.7)      | 142 (7.1)      | 27 (7.9)    |         |
| Number of hours of moderate or vigorous physical activity during the past week, n (%) |       |              |                |                |             | 0.509   |
| ≤1                                                    |                   | 162 (11.6)   | 534 (13.2)     | 232 (11.6)     | 38 (11.2)   |         |
| 1.1–3.0                                               |                   | 296 (21.2)   | 875 (21.7)     | 415 (20.8)     | 65 (19.1)   |         |
| 3.1–5.0                                               |                   | 151 (10.8)   | 463 (11.5)     | 223 (11.2)     | 42 (12.4)   |         |
| 5.1–10.0                                              |                   | 300 (21.5)   | 734 (18.2)     | 383 (19.2)     | 69 (20.3)   |         |
| 10.1–15.0                                             |                   | 148 (10.6)   | 422 (10.4)     | 201 (10.1)     | 41 (12.1)   |         |
| ≥15.1                                                 |                   | 225 (16.1)   | 689 (17.1)     | 360 (18.1)     | 55 (16.2)   |         |
| Missing                                               |                   | 113 (8.1)    | 325 (8.0)      | 179 (9.0)      | 30 (8.8)    |         |
| Parental history of CVD, n (%)                        |                   |              |                |                |             | 0.088   |

Continued
comparing models including age at menarche as a categorical versus a continuous variable supported the presence of a nonlinear association between age at menarche and 10-year risk of CVD ($P<0.01$). Early menarche was associated with higher 10-year CVD risk using both scores compared with age at menarche of 12 to 13 years, which was consistent for both within- and between-sibship estimates (Figure 4). Using the Framingham risk score, but not NHANES, age at menarche of $\geq 16$ years was also associated with higher 10-year CVD risk in models 1 and 2 but not in model 3 (Table S5).

### Sensitivity Analyses
Additional multivariable adjustment for adult household income did not change the associations (results available on request). Excluding those using antihypertensive medications from the analysis of blood pressure, those on lipid-lowering medications from the analysis of cholesterol, and those on antidiabetic medications from the analysis of glucose yielded similar associations with wider confidence intervals (Figure 4). Using the Framingham risk score, but not NHANES, age at menarche of $\geq 16$ years was also associated with higher 10-year CVD risk in models 1 and 2 but not in model 3 (which controlled for adult characteristics; Table S5).

### Discussion
In this sibship study, women who experienced early menarche ($\leq 11$ years) had a more adverse cardiometabolic profile and an increased 10-year CVD risk score compared with women who experienced menarche at 12 to 13 years. The results were similar in unrelated women and within sister groups. Later menarche (14–15 and $\geq 16$ years) was associated with lower BMI and waist circumference (both within and between sister groups) but not with other cardiometabolic health outcomes or the 10-year risk of CVD.

These results suggest that associations found in this study and elsewhere $^{1,6,10,12,13,15}$ between early menarche and CVD risk factors and events are not explained by genetic or other characteristics shared by sisters. This interpretation requires a
strong assumption: that there is little individual-level confounding. If siblings differ to a greater extent with regard to distributions of potential confounders than to the exposure of interest, the within-sibships analysis may be more biased than a standard analysis. Consequently, a key underlying assumption is that childhood adiposity (a key potential confounder in this study), and other lifestyle characteristics, are more similar within sisters than between unrelated individuals, and that the concordance for these potential confounders is greater than the concordance for age at menarche. The GS:SFHS does not have any information on childhood environmental characteristics; therefore, we cannot directly test this assumption. We did find moderate to strong concordance within sibling groups for adult socioeconomic position and lifestyle characteristics, which indicates that the main confounders for this analysis are likely strongly correlated within siblings, since childhood lifestyle is assumed to be even more discordant within siblings than adult lifestyle. When we repeated the within-sibships analyses among sisters with an age difference of up to 4 years, results were similar to the main analysis. Even though we found insufficient evidence to state that the estimates from the within- and between-sibship analyses differed, this might be influenced by the sample size, and we cannot exclude the possibility that a larger sample could provide more conclusive evidence for, or against, an unconfounded causal effect of age at menarche with adverse cardiometabolic risk.

Figure 2. Adjusted associations of age at menarche with blood pressure and adiposity, GS:SFHS (Generation Scotland: Scottish Family Health Study), 2006–2011. The comparison group comprises women with an age at menarche of 12 or 13 years. A, Systolic blood pressure (mm Hg). B, Diastolic blood pressure (mm Hg). C, Body mass index. D, Waist circumference (cm). Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, and parental history of diabetes mellitus. Blood pressure was further adjusted for use of antihypertensive drugs. CI indicates confidence interval.
heritable component during adolescence\(^3\),\(^4\),\(^5\) and that family-level characteristics play a more important role in determining children’s sedentary time compared with school-level characteristics.\(^3\),\(^6\) There is also a strong correlation in childhood adiposity among siblings, and having an obese elder sibling is associated with a 5-fold increase in obesity in the younger sibling; the similarity is even greater among siblings of the same sex.\(^3\),\(^7\),\(^8\)

Our results could be influenced by selection bias due to the low participation rate in the GS:SFHS; however, the mean age at menarche in the cohort (13.1 years) is fairly similar to the average reported for women born between 1950 and 1980 from the Breakthrough Generations Study (\(\approx 12.7\) years).\(^3\)

Notably, we had information on age at menarche only in years and not months in GS:SFHS, and this could have resulted in a slight overestimation of the mean. It is also important to keep in mind that the low participation rate also reflects the unique sampling strategy of the cohort because participants were required to identify a family member who was also willing to participate. We cannot exclude the possibility that

**Figure 3.** Adjusted associations of age at menarche with cholesterol and glucose, GS:SFHS (Generation Scotland: Scottish Family Health Study), 2006–2011. The comparison group comprises women with an age at menarche of 12 or 13 years. A, HDL cholesterol (mmol/L). B, Non-HDL cholesterol (mmol/L). C, Glucose (mmol/L). Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, and parental history of diabetes mellitus. Cholesterol levels further adjusted for lipid-lowering drugs and glucose adjusted for use of antidiabetic drugs. CI indicates confidence interval; HDL, high-density lipoprotein.

**Figure 4.** Adjusted association between age at menarche and 10-year risk score of overall cardiovascular disease, GS:SFHS (Generation Scotland: Scottish Family Health Study), 2006–2011. The comparison group comprises women with an age at menarche of 12 or 13 years. A, Framingham risk score. B, NHANES (National Health and Nutrition Examination Survey) ECG risk score. The variables included in the Framingham risk score are age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes mellitus. The information included in the NHANES ECG risk score included age, positive deflection of the T axis, negative deflection of the T axis, heart rate, and corrected QT interval. The associations are adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, and parental history of diabetes mellitus. CI indicates confidence interval.
participation could be influenced by background characteristics associated with both the exposure and the outcome, such as childhood socioeconomic position and/or lifestyle characteristics. For example, the proportion of women who had a university degree in our analysis sample was greater than the national average identified in the 2011 Scottish census (34% versus 25%). This might have resulted in underestimation of the associations of interest.

We relied on self-report of age at menarche a long time after the event occurred (median: 32 years; range: 5.5–59 years). This should not have resulted in substantial misclassification because previous studies have shown good validity of retrospectively recalled age at menarche. However, any misclassification in the exposure tends to exaggerate effects in within-sibling analyses. Consequently, if there were substantial misclassification of age at menarche, it would have caused overestimation of the association with cardiometabolic health within sister groups, and contributed to the weak evidence of a difference in the associations within sister groups and between unrelated individuals. This possibility cannot be excluded. Finally, our study had limited power to evaluate associations with late menarche, given the relatively modest size of this group in the cohort.

Whether childhood adiposity is the sole driver of the associations of age at menarche with cardiometabolic health and CVD events, related to its strong inverse relationship with age at menarche, remains to be determined. A limited number of studies were able to adjust for childhood characteristics when studying the associations of age at menarche with cardiometabolic health. Two studies that had data on BMI before menarche indicated that adjustment for childhood BMI virtually completely attenuated the association between age at menarche and adult BMI. In this study and elsewhere, the associations of age at menarche with cardiometabolic outcomes were attenuated after adjustment for adult BMI. However, because BMI tracks across the life course, it is difficult to truly distinguish confounding (childhood BMI) from mediation (adult BMI) of the associations of age at menarche with other cardiometabolic health outcomes.

Greater confidence in causal inference from observational studies stems from consistent evidence across different studies and the use of different analytical approaches to address confounding and selection bias. The sibling comparison used in the current study is one such study-design, but it is important to note that if its assumptions are violated, it may result in greater bias than conventional multivariable adjustment. Another increasingly popular approach is Mendelian randomization, which addresses unmeasured and residual confounding by using genetic polymorphisms as instrumental variables for the exposure of interest, based on their random allocation at conception resulting in their independence of confounding factors. However, the potential to use Mendelian randomization to study age at menarche in relation to cardiometabolic health is hampered by the number of overlapping genes associated with both age at menarche and adiposity. Longitudinal studies with measures of adiposity before and after puberty have the potential to contribute valuable insight into the role of childhood adiposity in the associations of age at menarche with cardiometabolic health, with studies that have been able to do this suggesting that childhood BMI before puberty confounds any associations with adult BMI and thus, potentially, with cardiometabolic risk.

In conclusion, early menarche is associated with an overall adverse cardiometabolic profile and a higher 10-year risk score for CVD. The associations were similar when evaluated within sisters and between unrelated individuals, suggesting that confounding by shared familial characteristics is unlikely to be a major driver of the association; but, this does not exclude confounding by individual-level characteristics.

Acknowledgments

We are grateful to all the families who took part, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants, and nurses.

Sources of Funding

The data collection in Generation Scotland (http://www.generationscotland.org) is funded by the Chief Scientist Office (CZD/16/6) and the Scottish Family Funding Council (HR03006). Drs Magnus, Lawlor, and Fraser work in at the MRC Integrative Epidemiology Unit, which receives infrastructure funding from the UK Medical Research Council (MRC) (MC_UU_12013/5). Dr Fraser and Dr Magnus are funded by a UK MRC Fellowship awarded to Dr Fraser (MR/M009351/1). Dr Iliodromiti is funded by UK MRC a fellowship (MR/N015177/1). This study was also supported by the Research Council of Norway Centres of Excellence funding scheme (project number 262700). These funding sources had no role in the...
design, collection, analysis, and interpretation of data; the writing of the article; or the decision to submit the article for publication.

Disclosures
Dr Lawlor has received funding for biomarker research unrelated to this article from Roche Diagnostics and Ferring Pharmaceuticals. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL
Table S1. Background Characteristics Among Individuals Included and Excluded from Analyses Due to Missing Data, the Scottish Family Health Study, 2006-2011.

| Characteristics                                                                 | Excluded (n=6,176) | Included (n=7,770) | P-value |
|---------------------------------------------------------------------------------|-------------------|--------------------|---------|
|                                                                                | n/mean            | %/SD               | n/mean  | %/SD   | <0.001 |<0.001 |<0.001 |
| Age at baseline evaluation                                                      | 52.1              | 16.1               | 44.3    | 13.7   |         |       |       |
| Ethnicity                                                                       |                   |                    |         |        | <0.001 |       |       |
| White                                                                           | 5,691             | 95.9               | 7,614   | 98.0   |         |       |       |
| Other                                                                           | 246               | 4.1                | 156     | 2.0    |         |       |       |
| Missing                                                                          | 239               | 0                  |         |        |         |       |       |
| Qualifications                                                                  |                   |                    |         |        | <0.001 |       |       |
| College/University degree                                                       | 1,594             | 31.0               | 2,651   | 34.1   |         |       |       |
| Other professional or technical qualification                                   | 826               | 16.1               | 1,559   | 20.1   |         |       |       |
| NVQ/HND/HNC or equivalent                                                       | 472               | 9.2                | 661     | 8.5    |         |       |       |
| Higher Grade                                                                    | 465               | 9.1                | 961     | 12.4   |         |       |       |
| Standard Grade/O Level/GCSE                                                     | 590               | 11.5               | 967     | 12.5   |         |       |       |
| CSEs, School leavers certificate, other or no qualifications                    | 1,193             | 23.2               | 971     | 12.5   |         |       |       |
| Missing                                                                         | 1,036             | 0                  |         |        |         |       |       |
| Annual household income, pounds                                                |                   |                    |         |        | <0.001 |       |       |
| <10,000                                                                         | 509               | 10.4               | 517     | 7.5    |         |       |       |
| 10,000-30,000                                                                  | 1,591             | 32.4               | 2,141   | 31.0   |         |       |       |
| 30,000-50,000                                                                  | 1,151             | 23.5               | 1,940   | 28.1   |         |       |       |
| 50,000-70,000                                                                  | 627               | 12.8               | 1,094   | 15.9   |         |       |       |
| 70,000+                                                                         | 510               | 10.4               | 800     | 11.6   |         |       |       |
| Prefer not to answer                                                            | 516               | 10.5               | 408     | 5.9    |         |       |       |
| Missing                                                                         | 1,272             | 870                |         |        |         |       |       |
| Parental history of CVD                                                          |                   |                    |         |        | <0.001 |       |       |
| No                                                                              | 1,260             | 32.0               | 2,749   | 35.4   |         |       |       |
| Yes                                                                             | 2,673             | 68.0               | 5,021   | 64.6   |         |       |       |
| Missing                                                                         | 2,243             | 0                  |         |        |         |       |       |
| Parental history of diabetes                                                     |                   |                    |         |        | 0.143  |       |       |
| No                                                                              | 3,365             | 85.6               | 6,568   | 84.5   |         |       |       |
| Yes                                                                             | 568               | 14.4               | 1,202   | 15.5   |         |       |       |
| Missing                                                                         | 2,243             | 0                  |         |        |         |       |       |

CVD=cardiovascular disease.

Percentages and test of differences in distributions among those with and without the necessary follow-up information are based on observed values and missing categories are not included.
Table S2. Proportion of the Variation in Traits Explained by Variation Between and Within Sibships/Groups of Sisters, the Scottish Family Health Study, 2006-2011.

| Characteristics                                      | Proportion explained by variation between sibships | Proportion explained by variation within sibships |
|------------------------------------------------------|---------------------------------------------------|--------------------------------------------------|
| Age (years)                                          |                                                   |                                                  |
| Age at menarche (years)                              | 0.27                                              | 0.73                                             |
| Qualifications (ordered from CSE/school leavers to college/university degree) | 0.40                                              | 0.60                                             |
| Current smoking at recruitment (yes versus no)       | 0.37                                              | 0.63                                             |
| Hours of moderate/vigorous physical activity in the past week | 0.48                                              | 0.52                                             |
| Units of alcohol consumed in the past week           | 0.07                                              | 0.93                                             |
| Adult BMI                                            | 0.31                                              | 0.69                                             |

BMI=body-mass index.

The proportion of variation explained by variation between sibships/groups of sisters estimated using the intra-class correlation coefficient from a random effects linear/logistic regression model.
Table S3. Pairwise Discordance in Traits Between Sibships, the Scottish Family Health Study, 2006-2011.

| Characteristics                                           | Number of pairs | %  |
|-----------------------------------------------------------|-----------------|----|
| Difference in age (years)                                 |                 |    |
| Number of sibling groups=1,541 (Number of women=3,327)     |                 |    |
| 0-2                                                       | 584             | 37.9|
| 3-4                                                       | 464             | 30.1|
| 5-6                                                       | 219             | 14.2|
| More than 6                                               | 274             | 17.8|
| Difference in age at menarche (years)                     |                 |    |
| Number of sibling groups=1,541 (Number of women=3,327)     |                 |    |
| 0                                                         | 582             | 37.8|
| 1                                                         | 331             | 21.5|
| 2                                                         | 440             | 28.6|
| 3                                                         | 93              | 6.0 |
| More than 3.0                                             | 95              | 6.2 |
| Discordance in college/university degree                  |                 |    |
| Number of sibling groups=1,541 (Number of women=3,327)     |                 |    |
| No                                                        | 1,139           | 73.9|
| Yes                                                       | 402             | 26.1|
| Discordance in current smoking at recruitment              |                 |    |
| Number of groups= 1,520 (Number of women= 3,280)           |                 |    |
| No                                                        | 1,235           | 81.3|
| Yes                                                       | 285             | 18.7|
| Difference in hours of moderate/vigorous physical activity in the past week |     |    |
| Number of sibling groups= 1,332 (Number of women= 2,863)   |                 |    |
| 0-2.9                                                     | 524             | 39.3|
| 3.0-5.9                                                   | 310             | 23.2|
| 6.0 or more                                               | 498             | 37.4|
| Difference in units of alcohol consumed in the past week   |                 |    |
| Number of sibling groups= 1,378 (Number of women= 2,961)   |                 |    |
| 0-1                                                       | 304             | 22.1|
| 2-3                                                       | 297             | 21.6|
| 4-5                                                       | 204             | 14.8|
| 6 or more                                                 | 573             | 41.6|
| Difference in adult body-mass index                       |                 |    |
| Number of sibling groups=1,513 (Number of women= 3,265)    |                 |    |
| 0-2                                                       | 582             | 38.5|
| 3-4                                                       | 318             | 21.0|
| 5-6                                                       | 233             | 15.4|
| More than 6                                               | 380             | 25.1|
Table S4. Association Between Age at Menarche and Cardiometabolic Health Outcomes, the Scottish Family Health Study, 2006–2011.

| Outcome                           | Model | Age at menarche | N    | Mean/Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|-----------------------------------|-------|-----------------|------|-------------|----------|-----------------------------|-----------------------------|--------------------------------------------------------------------------------|
| Systolic blood pressure (mmHg)    | Model 1 | 11 or younger | 1,392 | 127.5       | 17.2     | 1.97 | -0.16, 4.10 | 2.08 | 1.06, 3.10 | 0.99 |
|                                   | 12-13 | 4,034           |       | 124.9       | 16.5     | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,989           |       | 125.6       | 17.6     | -0.02 | -1.67, 1.62 | -0.47 | -1.37, 0.44 | 0.67 |
|                                   | 16 or higher | 339   |       | 126.6       | 18.0     | -2.50 | -5.98, 0.97 | 0.76 | -1.18, 2.69 | 0.33 |
| Model 2                           | 11 or younger | 1,392 |       | 127.5       | 17.2     | 1.73 | -0.41, 3.86 | 1.71 | 0.71, 2.72 | 0.94 |
|                                   | 12-13 | 4,034           |       | 124.9       | 16.5     | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,989           |       | 125.6       | 17.6     | -0.01 | -1.66, 1.64 | -0.38 | -1.28, 0.51 | 0.74 |
|                                   | 16 or higher | 339   |       | 126.6       | 18.0     | -2.62 | -6.10, 0.86 | 0.81 | -1.10, 2.73 | 0.31 |
| Model 3                           | 11 or younger | 1,189 |       | 127.3       | 17.2     | 2.26 | -0.26, 4.78 | 1.74 | 0.68, 2.80 | 0.78 |
|                                   | 12-13 | 3,474           |       | 124.7       | 16.3     | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,687           |       | 125.1       | 17.3     | 0.44 | -1.45, 2.32 | -0.41 | -1.35, 0.53 | 0.54 |
|                                   | 16 or higher | 285   |       | 126.1       | 17.4     | -2.74 | -6.52, 1.04 | 0.31 | -1.69, 2.32 | 0.34 |
| Diastolic blood pressure (mmHg)   | Model 1 | 11 or younger | 1,392 | 79.2        | 10.1     | 1.39 | 0.11, 2.67 | 1.48 | 0.83, 2.12 | 0.98 |
|                                   | 12-13 | 4,034           |       | 77.5        | 9.9      | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,989           |       | 77.1        | 10.0     | -0.62 | -1.64, 0.41 | -0.86 | -1.44, -0.28 | 0.70 |
|                                   | 16 or higher | 339   |       | 77.8        | 10.1     | -0.38 | -2.49, 1.73 | -0.38 | -1.62, 0.85 | 0.86 |
| Model 2                           | 11 or younger | 1,392 |       | 79.2        | 10.1     | 1.26 | -0.02, 2.55 | 1.32 | 0.68, 1.96 | 0.99 |
|                                   | 12-13 | 4,034           |       | 77.5        | 9.9      | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,989           |       | 77.1        | 10.0     | -0.62 | -1.64, 0.40 | -0.83 | -1.40, -0.25 | 0.75 |
|                                   | 16 or higher | 339   |       | 77.8        | 10.1     | -0.45 | -2.57, 1.67 | -0.36 | -1.58, 0.87 | 0.89 |
| Model 3                           | 11 or younger | 1,189 |       | 79.2        | 10.1     | 1.74 | 0.22, 3.25 | 1.39 | 0.71, 2.08 | 0.75 |
|                                   | 12-13 | 3,474           |       | 77.4        | 9.8      | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,687           |       | 77.0        | 10.1     | -0.37 | -1.52, 0.78 | -0.66 | -1.27, -0.05 | 0.67 |
|                                   | 16 or higher | 285   |       | 77.8        | 10.3     | -0.93 | -3.40, 1.54 | -0.06 | -1.36, 1.24 | 0.74 |
| HDL cholesterol, (mmol/L)         | Model 1 | 11 or younger | 1,338 | 1.537      | 0.404    | -0.064 | -0.109, -0.019 | -0.045 | -0.074, -0.017 | 0.65 |
|                                   | 12-13 | 3,851           |       | 1.591      | 0.418    | Ref                         | Ref                         | NA                                                                              |
|                                   | 14-15 | 1,897           |       | 1.627      | 0.405    | -0.009 | -0.050, 0.033 | 0.040 | 0.014, 0.065 | 0.13 |
|                                   | 16 or higher | 326   |       | 1.646      | 0.432    | -0.025 | -0.109, 0.060 | 0.058 | 0.004, 0.113 | 0.21 |
| Non-HDL cholesterol (mmol/L) | Model 1 | 11 or younger | 1,338 | 3.638 | 1.065 | 0.196 | 0.073 | 0.319 | 0.063 | -0.004 | 0.131 | 0.20 |
| Model 2 | 11 or younger | 1,338 | 3.638 | 1.065 | 0.202 | 0.084 | 0.321 | 0.051 | -0.015 | 0.117 | 0.13 |
| Model 3 | 11 or younger | 1,146 | 3.629 | 1.068 | 0.142 | 0.009 | 0.274 | 0.068 | -0.002 | 0.137 | 0.49 |
| Glucose, (mmol/L) | Model 1 | 11 or younger | 1,317 | 4.6 | 4.3 | 4.9 | -0.732 | -2.418 | 0.954 | 1.349 | 0.456 | 2.241 | 0.11 |
| Model 2 | 11 or younger | 1,317 | 4.6 | 4.3 | 4.9 | -0.338 | -1.975 | 1.298 | 1.143 | 0.287 | 1.999 | 0.23 |
| Model 3 | 11 or younger | 1,126 | 4.6 | 4.3 | 4.9 | -0.022 | -2.002 | 1.958 | 1.006 | 0.125 | 1.888 | 0.43 |
| Body-mass index (kg/m²) | Model 1 | 11 or younger | 1,374 | 28.081 | 6.170 | 1.687 | 0.997 | 2.377 | 1.871 | 1.509 | 2.232 | 0.64 |
| Model 2 | 11 or younger | 1,374 | 28.081 | 6.170 | 1.687 | 0.997 | 2.377 | 1.871 | 1.509 | 2.232 | 0.64 |
| Model 3 | 11 or younger | 1,374 | 28.081 | 6.170 | 1.687 | 0.997 | 2.377 | 1.871 | 1.509 | 2.232 | 0.64 |
| Model   | 11 or younger | 12-13 | 14-15 | 16 or higher | 12-13 | 14-15 | 16 or higher |
|---------|---------------|-------|-------|-------------|-------|-------|-------------|
| Model 2 | 1,374         | 3,997 | 1,975 | 334         | 1,146 | 3,915 | 1,615       |
|         | 28.081        | 26.107| 25.048| 25.424      | 3.629 | 3.491 | 3.462       |
|         | 6.170         | 5.195 | 4.771 | 5.398       | 1.068 | 1.021 | 1.021       |
|         | 0.919, 2.278  | Ref   | Ref   | Ref         | 1.691 | 1.611 | 1.865       |
|         | 1.742         |       |       |             | 1.665 |       |             |
|         | 1.386, 2.098  |       |       |             | 1.295 |       |             |
|         | 0.70          |       |       |             | 0.94  |       |             |
| Waist circumference, (cm) | Model 1 | 11 or younger | 1,364 | 3,981 | 1,966 | 335 |
|         | 88.20         | 84.48 | 82.53 | 83.66      | 88.20 | 84.48 | 82.53       |
|         | 15.30         | 13.80 | 12.71 | 14.49      | 15.30 | 13.80 | 12.71       |
|         | 2.907         |       |       | -1.903     | 2.907 |       | -1.903      |
|         | 1.200, 4.614  |       |       | -4.576, 0.770 | 1.200 |       | -4.576, 0.770 |
|         | 3.530         |       |       | -1.665     | 3.530 |       | -1.665      |
|         | 2.590, 4.472  |       |       | -3.455, 0.124 | 2.590 |       | -3.455, 0.124 |
|         | 0.55          |       |       | 0.83       | 0.55  |       | 0.83        |
|         | Model 2       | 11 or younger | 1,364 | 3,981 | 1,966 | 335 |
|         | 88.20         | 84.48 | 82.53 | 83.66      | 88.20 | 84.48 | 82.53       |
|         | 15.30         | 13.80 | 12.71 | 14.49      | 15.30 | 13.80 | 12.71       |
|         | 2.907         |       |       | -1.903     | 2.907 |       | -1.903      |
|         | 1.200, 4.614  |       |       | -4.576, 0.770 | 1.200 |       | -4.576, 0.770 |
|         | 3.530         |       |       | -1.665     | 3.530 |       | -1.665      |
|         | 2.590, 4.472  |       |       | -3.455, 0.124 | 2.590 |       | -3.455, 0.124 |
|         | 0.55          |       |       | 0.83       | 0.55  |       | 0.83        |
| Model 3 | 11 or younger | 1,146 | 3,915 | 1,615      | 276  | 3,437 | 282     |
|         | 3.629         | 3.491 | 3.539 | 3.539      | 1.691 | 8.749 | 83.02    |
|         | 1.068         | 1.039 | 1.001 | 1.001      | 1.691 | 14.97 | 13.90    |
|         | 0.942, 2.440  |       |       | -1.902     | 0.942 |       | -1.902    |
|         | 1.663         |       |       | -4.569, 0.765 | 1.663 |       | -4.569, 0.765 |
|         | 1.295, 2.031  |       |       | -2.056     | 1.295 |       | -2.056    |
|         | 0.94          |       |       | -3.817, -0.294 | 1.295 |       | -3.817, -0.294 |
|         | 0.56          |       |       | 0.98       | 0.56  |       | 0.98       |

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Model 1 Adjusted for age
Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.
Model 3 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.

*Outcome log transformed and the coefficients reflect the percent change in the outcome.
Table S5. Association Between Age at Menarche and 10-Year Risk for Overall Cardiovascular Disease, the Scottish Family Health Study, 2006-2011.

| Risk score            | Model | Age at menarche | N  | Mean  | SD  | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|-----------------------|-------|-----------------|----|-------|-----|----------------------------|-------------------------------|--------------------------------------------------------------------------------|
|                       |       |                 |    |       |     | β                            | β                            | CI=confidence interval; ECG=electrocardiogram; SD=standard deviation. |
| Framingham risk score *| Model 1 | 11 or younger  | 1,076 | 26.06 | 0.91 | 0.09 | 0.02, 0.17 | 0.10 | 0.06, 0.14 | 0.80 |
|                       |       | 12-13           | 3,014 | 25.94 | 0.90 | Ref | Ref | NA |
|                       |       | 14-15           | 1,543 | 25.97 | 0.92 | 0.02 | -0.04, 0.08 | -0.03 | -0.07, 0.00 | 0.24 |
|                       |       | 16 or higher    | 272 | 26.07 | 0.87 | -0.03 | -0.15, 0.09 | 0.04 | -0.04, 0.12 | 0.54 |
|                       | Model 2 | 11 or younger | 1,076 | 26.06 | 0.91 | 0.08 | 0.00, 0.16 | 0.09 | 0.05, 0.13 | 0.85 |
|                       |       | 12-13           | 3,014 | 25.94 | 0.90 | Ref | Ref | NA |
|                       |       | 14-15           | 1,543 | 25.97 | 0.92 | 0.02 | -0.04, 0.08 | -0.04 | -0.07, 0.00 | 0.20 |
|                       |       | 16 or higher    | 272 | 26.07 | 0.87 | -0.03 | -0.15, 0.09 | 0.02 | -0.05, 0.09 | 0.68 |
|                       | Model 3 | 11 or younger | 922 | 26.04 | 0.90 | 0.08 | -0.01, 0.17 | 0.08 | 0.04, 0.13 | 0.85 |
|                       |       | 12-13           | 2,591 | 25.92 | 0.89 | Ref | Ref | NA |
|                       |       | 14-15           | 1,312 | 25.94 | 0.91 | 0.02 | -0.05, 0.09 | -0.02 | -0.06, 0.01 | 0.40 |
|                       |       | 16 or higher    | 231 | 26.01 | 0.84 | -0.04 | -0.18, 0.10 | 0.01 | -0.07, 0.08) | 0.71 |
| NHANES ECG risk equation score † | Model 1 | 11 or younger | 1,076 | 7.963 | 0.847 | 0.030 | -0.004, 0.064 | 0.018 | 0.001, 0.035 | 0.62 |
|                       |       | 12-13           | 3,054 | 7.928 | 0.845 | Ref | Ref | NA |
|                       |       | 14-15           | 1,581 | 7.970 | 0.880 | 0.002 | -0.025, 0.030 | -0.020 | -0.035, -0.005 | 0.27 |
|                       |       | 16 or higher    | 265 | 8.061 | 0.819 | 0.003 | -0.056, 0.063 | 0.027 | -0.005, 0.059 | 0.82 |
|                       | Model 2 | 11 or younger | 1,076 | 7.963 | 0.847 | 0.031 | -0.003, 0.065 | 0.015 | -0.002, 0.032 | 0.52 |
|                       |       | 12-13           | 3,054 | 7.928 | 0.845 | Ref | Ref | NA |
|                       |       | 14-15           | 1,581 | 7.970 | 0.880 | 0.004 | -0.024, 0.031 | -0.020 | -0.035, -0.005 | 0.24 |
|                       |       | 16 or higher    | 265 | 8.061 | 0.819 | 0.003 | -0.057, 0.064 | 0.025 | -0.007, 0.057 | 0.85 |
|                       | Model 3 | 11 or younger | 919 | 7.957 | 0.846 | 0.044 | 0.005, 0.083 | 0.023 | 0.006, 0.041 | 0.43 |
|                       |       | 12-13           | 2,625 | 7.914 | 0.845 | Ref | Ref | NA |
|                       |       | 14-15           | 1,336 | 7.928 | 0.865 | -0.015 | -0.047, 0.017 | -0.014 | -0.030, 0.001 | 0.93 |
|                       |       | 16 or higher    | 224 | 8.025 | 0.783 | -0.001 | -0.073, 0.071 | 0.027 | -0.005, 0.060 | 0.79 |

* The variables included in the Framingham risk score are age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking and diabetes.
† The information included in the NHANES ECG risk score included age, positive deflection of T axis, negative deflection of the T axis, heart rate and corrected QT interval.
Model 1 Adjusted for age
Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes.
Model 3 Adjusted for all of the covariates in Model 2 in addition to smoking (not adjusted for in the analysis of the Framingham risk score since part of the risk calculation), alcohol intake and leisure time physical activity.
| Outcome                              | Model | Age at menarche | N     | Mean/Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|-------------------------------------|-------|-----------------|-------|-------------|----------|-----------------------------|-----------------------------|--------------------------------------------------------------------------------|
| **Systolic blood pressure (mmHg)** | Model 1 | 11 or younger  | 1,249 | 126.34      | 16.66    | 1.81                        | -0.40, 4.02                      | 2.21                           | 1.19, 3.24                      | 0.80                           |
|                                     |       | 12-13          | 3,728 | 123.79      | 15.72    | Ref                         | Ref                          | NA                             | NA                             | NA                             |
|                                     | 14-15 | 1,853          | 124.56 | 16.80      | -0.07   | -1.79, 1.65                 | -0.26, -1.17, 0.64               | 0.03                           | -1.89, 1.96                     | 0.39                           |
|                                     | 16 or higher | 313          | 125.04 | 16.20      | -2.69   | -6.23, 0.85                 | 0.03                           | -1.89, 1.96                     | 0.39                           |
| Model 2                             | 11 or younger | 1,249      | 126.34 | 16.66      | 1.55    | -0.67, 3.77                 | 2.00                           | 0.98, 3.01                      | 0.79                           |
|                                     | 12-13 | 3,728          | 123.79 | 15.72      | Ref     | Ref                         | Ref                          | NA                             | NA                             | NA                             |
|                                     | 14-15 | 1,853          | 124.56 | 16.80      | -0.08   | -1.79, 1.63                 | -0.28, -1.18, 0.62               | 0.08                           | -2.09, 1.74                     | 0.40                           |
|                                     | 16 or higher | 313        | 125.04 | 16.20      | -2.84   | -6.39, 0.70                 | -0.18                          | -2.09, 1.74                     | 0.40                           |
| Model 3                             | 11 or younger | 1,076      | 126.27 | 16.75      | 2.12    | -0.53, 4.77                 | 2.05                           | 0.98, 3.13                      | 0.97                           |
|                                     | 12-13 | 3,221          | 123.63 | 15.55      | Ref     | Ref                         | Ref                          | NA                             | NA                             | NA                             |
|                                     | 14-15 | 1,580          | 124.13 | 16.55      | 0.50    | -1.44, 2.44                 | -0.30                          | -1.25, 0.65                     | 0.56                           |
|                                     | 16 or higher | 268     | 124.74 | 15.83      | -2.46   | -6.15, 1.23                 | -0.46                          | -2.47, 1.56                     | 0.54                           |
| **Diastolic blood pressure (mmHg)** | Model 1 | 11 or younger | 1,249 | 78.76      | 9.99    | 1.29                        | -0.10, 2.67                     | 1.43                           | 0.77, 2.09                      | 0.88                           |
|                                     |       | 12-13          | 3,728 | 77.12      | 9.68    | Ref                         | Ref                          | Ref                            | Ref                            | Ref                            |
|                                     | 14-15 | 1,853          | 76.82  | 10.0       | -0.49   | -1.57, 0.60                 | -0.79                          | -1.38, -0.21                    | 0.67                           |
|                                     | 16 or higher | 313      | 77.60  | 9.86       | -0.08   | -2.37, 2.21                 | -0.39                          | -1.64, 0.85                     | 0.79                           |
| Model 2                             | 11 or younger | 1,249      | 78.76  | 9.99       | 1.14    | -0.25, 2.53                 | 1.30                           | 0.65, 1.96                      | 0.86                           |
|                                     | 12-13 | 3,728          | 77.12  | 9.68       | Ref     | Ref                         | Ref                          | Ref                            | Ref                            | Ref                            |
|                                     | 14-15 | 1,853          | 76.82  | 10.0       | -0.49   | -1.57, 0.59                 | -0.78                          | -1.36, -0.20                    | 0.70                           |
|                                     | 16 or higher | 313      | 77.60  | 9.86       | -0.19   | -2.49, 2.11                 | -0.43                          | -1.66, 0.81                     | 0.81                           |
| Model 3                             | 11 or younger | 1,076      | 78.71  | 10.02      | 1.51    | -0.13, 3.15                 | 1.34                           | 0.64, 2.04                      | 0.92                           |
|                                     | 12-13 | 3,221          | 76.99  | 9.65       | Ref     | Ref                         | Ref                          | NA                             | NA                             | NA                             |
|                                     | 14-15 | 1,580          | 76.72  | 10.05      | -0.20   | -1.41, 1.00                 | -0.64                          | -1.26, -0.01                    | 0.57                           |
|                                     | 16 or higher | 268      | 77.65  | 10.03      | -0.24   | -2.81, 2.33                 | -0.11                          | -1.42, 1.20                     | 0.98                           |
| **HDL cholesterol, (mmol/L)**      | Model 1 | 11 or younger | 1,266 | 1.540      | 0.408   | -0.056                      | -0.102, -0.010                  | -0.050                         | -0.079, -0.021                  | 0.93                           |
|                                     |       | 12-13          | 3,675 | 1.595      | 0.415   | Ref                         | Ref                          | Ref                            | Ref                            | Ref                            |
|                                     | 14-15 | 1,806          | 1.626  | 0.404      | -0.013  | -0.056, 0.030               | 0.032                          | 0.006, 0.058                    | 0.18                           |
|                                     | 16 or higher | 308     | 1.658  | 0.436      | -0.023  | -0.116, 0.070              | 0.055                          | 0.000, 0.110                    | 0.25                           |
| Model 2                             | 11 or younger | 1,266     | 1.540  | 0.408      | -0.054  | -0.100, -0.008             | -0.042                         | -0.071, -0.013                  | 0.78                           |
|                                     | 12-13 | 3,675          | 1.595  | 0.415      | Ref     | Ref                         | Ref                          | NA                             | NA                             | NA                             |
| Model 3 | 11 or younger, CI | 12-13, CI | 14-15, CI | 16 or higher, CI |
|---|---|---|---|---|
| 14-15 | 1.806 (0.404, 0.014) | 1.626 (0.436, 0.022) | 1.070 (0.410, 0.034) | 1.070 (0.442, 0.009) |
| 16 or higher | 1.101 (0.410, 0.034) | 1.658 (0.436, 0.022) | 1.070 (0.410, 0.034) | 1.070 (0.442, 0.009) |

Non-HDL cholesterol (mmol/L)

| Model 1 | 11 or younger, CI | 12-13, CI | 14-15, CI | 16 or higher, CI |
|---|---|---|---|---|
| 14-15 | 1.266 (1.070, 0.201) | 1.658 (1.070, 0.201) | 1.070 (1.001, -0.077) | 1.070 (1.001, -0.077) |
| 16 or higher | 1.101 (1.001, -0.077) | 1.658 (1.070, 0.201) | 1.070 (1.001, -0.077) | 1.070 (1.001, -0.077) |

Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes.

Model 3 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity.

* Outcome log transformed and the coefficients reflect the percent change in the outcome.

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Glucose, (mmol/L)*
| Outcome | Model | Age at Menarche | N   | Mean/Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|---------|-------|-----------------|-----|-------------|----------|-----------------------------|-------------------------------|--------------------------------------------------------------------------------|
| Systolic blood pressure (mmHg) | Model 1 | 11 or younger | 1,189 | 127.3 | 17.2 | 2.26 | -0.26, 4.78 | 1.74 | 0.68, 2.80 | 0.78 |
|         |       | 12-13 | 3,474 | 124.7 | 16.3 | Ref | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,687 | 125.1 | 17.3 | 0.44 | -1.45, 2.32 | -0.41 | -1.35, 0.53 | 0.54 |
|         |       | 16 or higher | 285 | 126.1 | 17.4 | -2.74 | -6.52, 1.04 | 0.31 | -1.69, 2.32 | 0.34 |
|         | Model 2 | 11 or younger | 1,174 | 127.3 | 17.19 | 0.62 | -1.88, 3.12 | 0.55 | -0.48, 1.58 | 0.94 |
|         |       | 12-13 | 3,448 | 124.7 | 16.26 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,674 | 125.14 | 17.32 | 1.10 | -0.71, 2.92 | 0.53 | -0.38, 1.45 | 0.65 |
|         |       | 16 or higher | 280 | 126.25 | 17.50 | -1.38 | -5.10, 2.34 | 1.05 | -0.90, 2.99 | 0.48 |
| Diastolic blood pressure (mmHg) | Model 1 | 11 or younger | 1,392 | 79.2 | 10.1 | 1.74 | -0.22, 3.25 | 1.39 | 0.71, 2.08 | 0.75 |
|         |       | 12-13 | 4,034 | 77.5 | 9.9 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,989 | 77.1 | 10.0 | -0.37 | -1.52, 0.78 | -0.66 | -1.27, -0.05 | 0.67 |
|         |       | 16 or higher | 339 | 77.8 | 10.1 | -0.93 | -3.40, 1.54 | -0.06 | -1.36, 1.24 | 0.74 |
|         | Model 2 | 11 or younger | 1,174 | 79.2 | 10.0 | 0.52 | -0.96, 1.99 | 0.34 | -0.30, 0.99 | 0.84 |
|         |       | 12-13 | 3,448 | 77.4 | 9.8 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,674 | 77.0 | 10.1 | 0.14 | -0.96, 1.23 | 0.14 | -0.43, 0.72 | 0.91 |
|         |       | 16 or higher | 280 | 78.0 | 10.2 | 0.55 | -1.76, 2.86 | 0.58 | -0.64, 1.80 | 0.87 |
| HDL cholesterol, (mmol/L) | Model 1 | 11 or younger | 1,338 | 1,537 | 0.404 | -0.042 | -0.093, 0.008 | -0.038 | -0.067, -0.009 | 0.96 |
|         |       | 12-13 | 3,851 | 1,591 | 0.418 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,897 | 1,627 | 0.405 | -0.009 | -0.057, 0.039 | 0.037 | 0.011, 0.063 | 0.22 |
|         |       | 16 or higher | 326 | 1,646 | 0.432 | -0.017 | -0.105, 0.071 | 0.061 | 0.005, 0.116 | 0.24 |
|         | Model 2 | 11 or younger | 1,132 | 1,549 | 0.404 | -0.005 | -0.054, 0.045 | 0.002 | -0.026, 0.030 | 0.87 |
|         |       | 12-13 | 3,292 | 1,605 | 0.415 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,602 | 1,639 | 0.408 | -0.026 | -0.071, 0.020 | 0.007 | -0.018, 0.032 | 0.38 |
|         |       | 16 or higher | 271 | 1,673 | 0.438 | -0.037 | -0.126, 0.052 | 0.030 | -0.023, 0.083 | 0.30 |
| Non-HDL cholesterol (mmol/L) | Model 1 | 11 or younger | 1,338 | 3.638 | 1.065 | 0.142 | 0.009, 0.274 | 0.068 | -0.002, 0.137 | 0.49 |
|         |       | 12-13 | 3,851 | 3.517 | 1.050 | Ref | Ref | Ref | NA |
|         |       | 14-15 | 1,897 | 3.498 | 1.031 | -0.013 | -0.132, 0.105 | -0.092 | -0.154, -0.030 | 0.37 |
|         |       | 16 or higher | 326 | 3.583 | 1.008 | 0.071 | -0.281, 0.139 | -0.070 | -0.201, 0.061 | 0.96 |
|         | Model 2 | 11 or younger | 1,132 | 3.631 | 1.067 | 0.038 | -0.091, 0.167 | -0.006 | -0.074, 0.062 | 0.68 |
|         |       | 12-13 | 3,292 | 3.491 | 1.039 | Ref | Ref | Ref | NA |
| Glucose, (mmol/L)* | Model 1 |        |        |        |        |        |        |
|------------------|---------|--------|--------|--------|--------|--------|
|                  | 14-15   | 1,602  | 3.460  | 1.023  | 0.010  | -0.106, 0.126 | -0.041  | -0.102, 0.020 | 0.55 |
|                  | 16 or higher | 271    | 3.544  | 1.005  | 0.005  | -0.202, 0.212 | -0.028  | -0.157, 0.100 | 0.78 |
|                  | 11 or younger | 1,317  | 4.6    | 4.3, 4.9 | -0.022 | -2.002, 1.958 | 1.006  | 0.125, 1.888 | 0.43 |
|                  | 12-13 | 3,814  | 4.5    | 4.3, 4.8 | Ref   | Ref   | NA |
|                  | 14-15 | 1,876  | 4.6    | 4.3, 4.8 | 1.534 | 0.021, 3.047 | -0.212 | -0.999, 0.576 | 0.17 |
|                  | 16 or higher | 327    | 4.6    | 4.3, 4.8 | -2.585 | -6.208, 1.038 | -0.721 | -2.396, 0.953 | 0.54 |
|                  | 11 or younger | 1,112  | 4.6    | 4.3, 4.9 | -1.125 | -3.057, 0.808 | 0.516  | -0.372, 1.403 | 0.26 |
|                  | 12-13 | 3,259  | 4.5    | 4.3, 4.8 | Ref   | Ref   | NA |
|                  | 14-15 | 1,586  | 4.6    | 4.3, 4.8 | 1.500 | 0.047, 2.953 | 0.108  | -0.681, 0.897 | 0.27 |
|                  | 16 or higher | 271    | 4.6    | 4.3, 4.8 | -2.023 | -5.570, 1.524 | -0.230 | -1.902, 1.443 | 0.58 |

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Model 1 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs (Model 3 from Supplement Table 4).

Model 2 Adjusted for all covariates in model 1 in addition to adult body-mass index.

*Outcomes log transformed and the coefficients reflect the percent change in the outcome.
Table S8. Association Between Age at Menarche and 10-Year Risk for Cardiovascular Disease After Adjustment for Adult Body-Mass Index, the Scottish Family Health Study, 2006-2011.

| Risk score | Model | Age at menarche | N   | Mean | SD  | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|------------|-------|----------------|-----|------|-----|----------------------------|-----------------------------|------------------------------------------------------------------|
|            |       |                |     |      |     | β                           | 95% CI                      | β                             | 95% CI               |
| Framingham risk score * | Model 1 | 11 or younger | 922 | 26.04 | 0.90 | 0.08 | -0.01, 0.17 | 0.08 | 0.04, 0.13 | 0.85 |
|            |       | 12-13         | 2,591 | 25.92 | 0.89 | Ref | Ref | Ref | Ref | NA |
|            |       | 14-15         | 1,312 | 25.94 | 0.91 | 0.02 | -0.05, 0.09 | -0.02 | -0.06, 0.01 | 0.40 |
|            |       | 16 or higher  | 231 | 26.01 | 0.84 | -0.04 | -0.18, 0.10 | 0.01 | -0.07, 0.08 | 0.71 |
|            | Model 2 | 11 or younger | 913 | 26.04 | 0.90 | 0.00 | -0.08, 0.09 | 0.02 | -0.02, 0.06 | 0.78 |
|            |       | 12-13         | 2,575 | 25.92 | 0.89 | Ref | Ref | Ref | Ref | NA |
|            |       | 14-15         | 1,304 | 25.94 | 0.91 | 0.04 | -0.02, 0.11 | 0.02 | -0.01, 0.06 | 0.67 |
|            |       | 16 or higher  | 227 | 26.02 | 0.84 | 0.02 | -0.11, 0.14 | 0.04 | -0.03, 0.11 | 0.91 |
| NHANES ECG risk equation † | Model 1 | 11 or younger | 919 | 7.957 | 0.846 | 0.044 | 0.005, 0.083 | 0.023 | 0.006, 0.041 | 0.43 |
|            |       | 12-13         | 2,625 | 7.914 | 0.845 | Ref | Ref | Ref | Ref | NA |
|            |       | 14-15         | 1,336 | 7.928 | 0.865 | -0.015 | -0.047, 0.017 | -0.014 | -0.030, 0.001 | 0.93 |
|            |       | 16 or higher  | 224 | 8.025 | 0.783 | -0.001 | -0.073, 0.071 | 0.027 | -0.005, 0.060 | 0.79 |
|            | Model 2 | 11 or younger | 909 | 7.961 | 0.848 | 0.022 | -0.016, 0.059 | 0.004 | -0.014, 0.021 | 0.45 |
|            |       | 12-13         | 2,607 | 7.913 | 0.844 | Ref | Ref | Ref | Ref | NA |
|            |       | 14-15         | 1,328 | 7.929 | 0.864 | -0.006 | -0.037, 0.026 | 0.000 | -0.015, 0.015 | 0.94 |
|            |       | 16 or higher  | 220 | 8.029 | 0.786 | 0.005 | -0.064, 0.074 | 0.034 | 0.002, 0.065 | 0.75 |

CI=confidence interval; ECG=electrocardiogram; SD=standard deviation.

* The variables included in the Framingham risk score is age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking and diabetes.
† The information included in the NHANES ECG risk score included age, positive deflection of T axis, negative deflection of the T axis, heart rate and corrected QT interval.
Model 1 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity (Model 3 from Table 2).
Model 2 Adjusted for all covariates in model 1 in addition to adult body-mass index.
Table S9. Association Between Age at Menarche and Cardiometabolic Health After Restricting the Analysis to Sibships With up to Four Years Age Difference Between Sisters, the Scottish Family Health Study, 2006-2011.

| Outcome | Model | Age at menarche | N     | Mean/Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|---------|-------|----------------|-------|-------------|----------|-----------------------------|-----------------------------|------------------------------------------------------------------|
|         |       |                |       |             |          | β                           | β                            | 95% CI                            | 95% CI                       |                                                                  |
| Systolic blood pressure (mmHg) | Model 1 | 11 or younger | 1,276 | 127.4       | 17.1     | 2.67                        | 0.14, 5.20                   | 1.87                              | 0.84, 2.90                | 0.69                                                            |
|         |       | 12-13         | 3,757 | 124.9       | 16.6     | Ref                         | Ref                         | Ref                               | NA                        | 0.25                                                            |
|         |       | 14-15         | 1,855 | 125.9       | 17.8     | 1.20                        | -0.76, 3.15                  | -0.26                             | -1.17, 0.65              | 0.25                                                            |
|         |       | 16 or higher  | 313   | 126.6       | 18.4     | -2.46                       | -6.58, 1.67                   | 0.28                              | -1.67, 2.22             | 0.41                                                            |
|         | Model 2 | 11 or younger | 1,276 | 127.4       | 17.1     | 2.35                        | -0.19, 4.88                  | 1.53                              | 0.52, 2.55              | 0.70                                                            |
|         |       | 12-13         | 3,757 | 124.9       | 16.6     | Ref                         | Ref                         | Ref                               | NA                        | 0.27                                                            |
|         |       | 14-15         | 1,855 | 125.9       | 17.8     | 1.24                        | -0.71, 3.20                  | -0.20                             | -1.09, 0.70            | 0.27                                                            |
|         |       | 16 or higher  | 313   | 126.6       | 18.4     | -2.50                       | -6.65, 1.66                   | 0.26                              | -1.66, 2.18            | 0.41                                                            |
|         | Model 3 | 11 or younger | 1,090 | 127.2       | 17.1     | 3.01                        | 0.09, 5.93                   | 1.60                              | 0.53, 2.67              | 0.58                                                            |
|         |       | 12-13         | 3,235 | 124.7       | 16.3     | Ref                         | Ref                         | Ref                               | NA                        | 0.19                                                            |
|         |       | 14-15         | 1,569 | 125.4       | 17.5     | 1.75                        | -0.45, 3.93                  | -0.24                             | -1.20, 0.71            | 0.19                                                            |
|         |       | 16 or higher  | 266   | 126.2       | 17.8     | 1.74                        | -0.45, 3.93                  | 0.05                              | -1.98, 2.08            | 0.29                                                            |
| Diastolic blood pressure (mmHg) | Model 1 | 11 or younger | 1,276 | 79.2        | 10.0    | 1.53                        | 0.03, 3.03                   | 1.38                              | 0.72, 2.03              | 0.89                                                            |
|         |       | 12-13         | 3,757 | 77.5        | 9.9     | Ref                         | Ref                         | Ref                               | NA                        | 0.27                                                            |
|         |       | 14-15         | 1,855 | 77.1        | 10.1    | 0.06                        | -1.15, 1.26                  | -0.77                             | -1.34, 0.19            | 0.27                                                            |
|         |       | 16 or higher  | 313   | 77.6        | 10.2    | -0.27                       | -2.94, 2.40                  | -0.56                             | -1.79, 0.68            | 0.79                                                            |
|         | Model 2 | 11 or younger | 1,276 | 79.2        | 10.0    | 1.30                        | -0.19, 2.79                  | 1.22                              | 0.57, 1.87              | 0.95                                                            |
|         |       | 12-13         | 3,757 | 77.5        | 9.9     | Ref                         | Ref                         | Ref                               | NA                        | 0.27                                                            |
|         |       | 14-15         | 1,855 | 77.1        | 10.1    | 0.07                        | -1.13, 1.28                  | -0.74                             | -1.32, 0.17            | 0.27                                                            |
|         |       | 16 or higher  | 313   | 77.6        | 10.2    | -0.30                       | -2.98, 2.37                  | -0.55                             | -1.78, 0.68            | 0.80                                                            |
|         | Model 3 | 11 or younger | 1,090 | 79.1        | 10.1    | 1.93                        | 0.21, 3.66                   | 1.31                              | 0.62, 2.00              | 0.67                                                            |
|         |       | 12-13         | 3,235 | 77.3        | 9.9     | Ref                         | Ref                         | Ref                               | NA                        | 0.27                                                            |
|         |       | 14-15         | 1,569 | 77.0        | 10.2    | 0.30                        | -1.03, 1.63                  | -0.63                             | -1.24, 0.01            | 0.27                                                            |
|         |       | 16 or higher  | 266   | 77.7        | 10.5    | -1.08                       | -4.10, 1.93                  | -0.18                             | -1.49, 1.14            | 0.75                                                            |
| HDL cholesterol, (mmol/L) | Model 1 | 11 or younger | 1,228 | 1.534       | 0.405  | -0.061                      | -0.114, -0.008               | -0.049                            | -0.078, -0.020       | 0.81                                                            |
|         |       | 12-13         | 3,591 | 1.589       | 0.414  | Ref                         | Ref                         | Ref                               | NA                        | 0.08                                                            |
|         |       | 14-15         | 1,768 | 1.625       | 0.406  | -0.022                      | -0.069, 0.026                | 0.038                             | 0.013, 0.064         | 0.08                                                            |
|         |       | 16 or higher  | 300   | 1.661       | 0.436  | -0.037                      | -0.139, 0.061                | 0.073                             | 0.018, 0.127         | 0.14                                                            |
|         | Model 2 | 11 or younger | 1,228 | 1.534       | 0.405  | -0.061                      | -0.114, -0.007               | -0.042                            | -0.070, -0.014       | 0.68                                                            |
|         |       | 12-13         | 3,591 | 1.589       | 0.414  | Ref                         | Ref                         | Ref                               | NA                        | 0.08                                                            |
|         |       | 14-15         | 1,768 | 1.625       | 0.406  | -0.02                       | -0.071, 0.024                | 0.039                             | 0.014, 0.065         | 0.07                                                            |
|                      | Model 3 |     |     |     |     |     |     |
|----------------------|---------|-----|-----|-----|-----|-----|-----|
|                      | 16 or younger | 11 or younger | 12-13 | 14-15 | 16 or higher | 16 or younger | 11 or younger |
|                      | 300 | 1,053 | 3,089 | 1,500 | 257 | 1,228 | 3,591 |
|                      | 1.661 | 1.546 | 1.603 | 1.638 | 1.684 | 3.630 | 3.518 |
|                      | 0.436 | 0.406 | 0.410 | 0.409 | 0.441 | 1.056 | 1.057 |
|                      | -0.036 | -0.036 | -0.097 | -0.022 | -0.024 | 0.159 | Ref |
|                      | -0.137 | -0.097 | -0.025 | -0.122 | -0.132 | 0.009 | Ref |
|                      | 0.065 | 0.025 | 0.074 | 0.032 | 0.073 | 0.309 | Ref |
|                      | 0.083 | -0.040 | 0.008 | -0.049 | 0.017 | 0.070 | NA |
|                      | 0.029 | -0.069 | 0.061 | -0.149 | 0.017 | 0.002 | 0.128 |
|                      | 0.137 | -0.010 | 0.15 | -0.028 | 0.128 | 0.138 | 0.20 |
|                      | 0.12 | 0.88 | 0.15 | 0.27 | 0.20 | 0.49 | 0.26 |

| Non-HDL cholesterol (mmol/L) | Model 1 |     |     |     |     |     |     |
|------------------------------|---------|-----|-----|-----|-----|-----|-----|
|                              | 16 or younger | 11 or younger | 12-13 | 14-15 | 16 or higher | 16 or younger | 11 or younger |
|                              | 300 | 1,053 | 3,089 | 1,500 | 257 | 1,228 | 3,591 |
|                              | 1.661 | 1.546 | 1.603 | 1.638 | 1.684 | 3.630 | 3.518 |
|                              | 0.436 | 0.406 | 0.410 | 0.409 | 0.441 | 1.056 | 1.057 |
|                              | -0.036 | -0.036 | -0.097 | -0.022 | -0.024 | 0.159 | Ref |
|                              | -0.137 | -0.097 | -0.025 | -0.122 | -0.132 | 0.009 | Ref |
|                              | 0.065 | 0.025 | 0.074 | 0.032 | 0.073 | 0.309 | Ref |
|                              | 0.083 | -0.040 | 0.008 | -0.049 | 0.017 | 0.070 | NA |
|                              | 0.029 | -0.069 | 0.061 | -0.149 | 0.017 | 0.002 | 0.128 |
|                              | 0.137 | -0.010 | 0.15 | -0.028 | 0.128 | 0.138 | 0.20 |
|                              | 0.12 | 0.88 | 0.15 | 0.27 | 0.20 | 0.49 | 0.26 |

| Glucose, (mmol/L)* | Model 1 |     |     |     |     |     |     |
|---------------------|---------|-----|-----|-----|-----|-----|-----|
|                     | 16 or younger | 11 or younger | 12-13 | 14-15 | 16 or higher | 16 or younger | 11 or younger |
|                     | 300 | 1,053 | 3,089 | 1,500 | 257 | 1,228 | 3,591 |
|                     | 1.661 | 1.546 | 1.603 | 1.638 | 1.684 | 3.630 | 3.518 |
|                     | 0.436 | 0.406 | 0.410 | 0.409 | 0.441 | 1.056 | 1.057 |
|                     | -0.036 | -0.036 | -0.097 | -0.022 | -0.024 | 0.159 | Ref |
|                     | -0.137 | -0.097 | -0.025 | -0.122 | -0.132 | 0.009 | Ref |
|                     | 0.065 | 0.025 | 0.074 | 0.032 | 0.073 | 0.309 | Ref |
|                     | 0.083 | -0.040 | 0.008 | -0.049 | 0.017 | 0.070 | NA |
|                     | 0.029 | -0.069 | 0.061 | -0.149 | 0.017 | 0.002 | 0.128 |
|                     | 0.137 | -0.010 | 0.15 | -0.028 | 0.128 | 0.138 | 0.20 |
|                     | 0.12 | 0.88 | 0.15 | 0.27 | 0.20 | 0.49 | 0.26 |

| Body-mass index (kg/m²) | Model 1 |     |     |     |     |     |     |
|------------------------|---------|-----|-----|-----|-----|-----|-----|
|                       | 16 or younger | 11 or younger | 12-13 | 14-15 | 16 or higher | 16 or younger | 11 or younger |
|                       | 300 | 1,053 | 3,089 | 1,500 | 257 | 1,228 | 3,591 |
|                       | 1.661 | 1.546 | 1.603 | 1.638 | 1.684 | 3.630 | 3.518 |
|                       | 0.436 | 0.406 | 0.410 | 0.409 | 0.441 | 1.056 | 1.057 |
|                       | -0.036 | -0.036 | -0.097 | -0.022 | -0.024 | 0.159 | Ref |
|                       | -0.137 | -0.097 | -0.025 | -0.122 | -0.132 | 0.009 | Ref |
|                       | 0.065 | 0.025 | 0.074 | 0.032 | 0.073 | 0.309 | Ref |
|                       | 0.083 | -0.040 | 0.008 | -0.049 | 0.017 | 0.070 | NA |
|                       | 0.029 | -0.069 | 0.061 | -0.149 | 0.017 | 0.002 | 0.128 |
|                       | 0.137 | -0.010 | 0.15 | -0.028 | 0.128 | 0.138 | 0.20 |
|                       | 0.12 | 0.88 | 0.15 | 0.27 | 0.20 | 0.49 | 0.26 |
| Waist circumference, (cm) | Model 3 | 11 or younger | 1,078 | 27.8 | 6.0 | 1.95 | 1.09, 2.82 | 1.68 | 1.31, 2.05 | 0.70 |
|--------------------------|---------|----------------|-------|------|-----|------|-------------|-----|-------------|-----|
| 12-13                    | 3,213   | 25.9           | 5.0   | Ref  | Ref | Ref  | Ref         | NA  | NA          |     |
| 14-15                    | 1,559   | 24.9           | 4.6   | -0.75| -1.39, -0.12 | -1.12 | -1.45, -0.79 | 0.43 |
| 16 or higher             | 263     | 25.0           | 5.2   | -1.73| -2.97, -0.49 | -1.13 | -1.83, -0.44 | 0.45 |
| Model 1                  | 11 or younger | 1,249 | 88.1 | 15.2 | 3.07 | 0.98, 5.18 | 3.66 | 2.71, 4.60 | 0.67 |
| 12-13                    | 3,707   | 84.4           | 13.8  | Ref  | Ref  | Ref  | Ref         | NA  | NA          |     |
| 14-15                    | 1,833   | 82.5           | 12.8  | -0.64| -2.37, 1.09 | -2.53 | -3.36, -1.70 | 0.13 |
| 16 or higher             | 309     | 83.2           | 14.1  | -2.67| -5.75, 0.40 | -1.87 | -3.64, -0.09 | 0.71 |
| Model 2                  | 11 or younger | 1,249 | 88.1 | 15.2 | 2.89 | 0.79, 4.99 | 3.30 | 2.37, 4.23 | 0.76 |
| 12-13                    | 3,707   | 84.4           | 13.8  | Ref  | Ref  | Ref  | Ref         | NA  | NA          |     |
| 14-15                    | 1,833   | 82.5           | 12.8  | -0.67| -2.41, 1.06 | -2.58 | -3.40, -1.77 | 0.13 |
| 16 or higher             | 309     | 83.2           | 14.1  | -2.65| -5.70, 0.40 | -2.26 | -4.01, -0.51 | 0.84 |
| Model 3                  | 11 or younger | 1,067 | 87.7 | 14.9 | 3.30 | 1.15, 5.45 | 3.16 | 2.19, 4.13 | 0.92 |
| 12-13                    | 3,200   | 83.9           | 13.4  | Ref  | Ref  | Ref  | Ref         | NA  | NA          |     |
| 14-15                    | 1,555   | 82.0           | 12.3  | -1.23| -2.95, 0.50 | -2.43 | -3.29, -1.58 | 0.33 |
| 16 or higher             | 263     | 82.5           | 13.5  | -3.72| -6.63, -0.81 | -2.18 | -4.00, -0.35 | 0.48 |

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Model 1 Adjusted for age
Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.
Model 3 Adjusted for all the characteristics in Model 2 in addition to smoking, alcohol intake and leisure time physical activity.

* Outcome log transformed and the coefficients reflect the percent change in the outcome.
### Table S10. Association Between Age at Menarche and 10-Year Risk of Cardiovascular Disease After Restricting the Analysis to Sibships With up to Four Years Age Difference Between Sisters, the Scottish Family Health Study, 2006-2011

| Risk score | Model 1 | Model 2 | Model 3 |
|------------|---------|---------|---------|
| Framingham risk score † | 11 or younger | 12-13 | 14-15 | 16 or higher |
| N | 982 | 2,795 | 1,430 | 248 |
| Mean | 26.06 | 25.95 | 25.98 | 26.07 |
| SD | 0.90 | 0.90 | 0.93 | 0.90 |
| Within-sibships association | β | 0.13 | -0.04 | -0.90 |
| 95% CI | 0.05, 0.22 | -0.03, 0.11 | -0.21, 0.05 | -0.05, 0.11 |
| Between-sibships association | β | 0.09 | 0.04 | 0.03 |
| 95% CI | 0.05, 0.13 | -0.06, 0.01 | -0.05, 0.11 | 0.28 |
| Bootstrap p-value for the difference in the within and between sibship association | | | | NA |

| NHANES ECG risk equation † | 11 or younger | 12-13 | 14-15 | 16 or higher |
| N | 981 | 2,830 | 1,464 | 243 |
| Mean | 7.97 | 7.93 | 7.98 | 8.08 |
| SD | 0.86 | 0.85 | 0.89 | 0.83 |
| Within-sibships association | β | 0.04 | -0.01 | -0.02 |
| 95% CI | 0.00, 0.08 | -0.04, 0.02 | -0.09, 0.06 | 0.00, 0.06 |
| Between-sibships association | β | 0.02 | -0.01 | 0.03 |
| 95% CI | 0.00, 0.04 | -0.03, 0.00 | 0.00, 0.06 | 0.00, 0.11 |
| Bootstrap p-value for the difference in the within and between sibship association | | | | NA |

CI=confidence interval; ECG=electrocardiogram; SD=standard deviation.

† The variables included in the Framingham risk score is age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking and diabetes.

† The information included in the NHANES ECG risk score included age, positive deflection of T axis, negative deflection of the T axis, heart rate and corrected QT interval.

The estimates are from a mixed effects linear regression analysis.

Model 1 Adjusted for age

Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes.

Model 3 Adjusted for all of the covariates in Model 2 in addition to smoking (not adjusted for in the analysis of the NHANES risk score since part of the risk calculation), alcohol intake and leisure time physical activity.
Table S11. Association Between Age at Menarche and Cardiometabolic Health Outcomes Excluding Individuals of Non-European Ethnicity, the Scottish Family Health Study, 2006-2011.

| Outcome                          | Model | Age at menarche | N   | Mean/Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|---------------------------------|-------|-----------------|-----|-------------|----------|-------------------------------|-------------------------------|------------------------------------------------------------------|
|                                 |       |                 |     |             |          | β                             | 95% CI                        | β                                 | 95% CI                                                                 |
| Systolic blood pressure (mmHg)  | Model 1 | 11 or younger   | 1,362 | 127.7     | 17.2     | 1.95                          | -0.19, 4.08                   | 2.15                             | 1.12, 3.18                                                                | 0.98                                                                |
|                                 |       | 12-13           | 3,959 | 124.9     | 16.5     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,943 | 125.7     | 17.6     | -0.05                         | -1.71, 1.61                   | -0.45                            | -1.36, 0.47                                                               | 0.69                                                                |
|                                 |       | 16 or higher    | 334  | 126.6     | 18.0     | -2.56                         | -6.09, 0.96                   | 0.87                             | -1.08, 2.82                                                               | 0.33                                                                |
|                                 | Model 2 | 11 or younger   | 1,362 | 127.7     | 17.2     | 1.82                          | -0.33, 3.97                   | 1.82                             | 0.75, 2.89                                                                | 0.91                                                                |
|                                 |       | 12-13           | 3,959 | 124.9     | 16.5     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,943 | 125.7     | 17.6     | -0.03                         | -1.70, 1.64                   | -0.34                            | -1.29, 0.62                                                               | 0.75                                                                |
|                                 |       | 16 or higher    | 334  | 126.6     | 18.0     | -2.63                         | -6.16, 0.90                   | 0.45                             | -1.57, 2.48                                                               | 0.32                                                                |
|                                 | Model 3 | 11 or younger   | 1,165 | 127.4     | 17.3     | 2.35                          | -0.19, 4.88                   | 1.74                             | 0.68, 2.80                                                                | 0.74                                                                |
|                                 |       | 12-13           | 3,408 | 124.7     | 16.3     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,649 | 125.2     | 17.3     | 0.35                          | -1.57, 2.26                   | -0.41                            | -1.35, 0.53                                                               | 0.58                                                                |
|                                 |       | 16 or higher    | 281  | 126.2     | 17.4     | -3.02                         | -6.85, 0.81                   | 0.31                             | -1.69, 2.32                                                               | 0.29                                                                |
| Diastolic blood pressure (mmHg) | Model 1 | 11 or younger   | 1,362 | 79.2      | 10.1    | 1.42                          | 0.14, 2.70                    | 1.49                             | 0.84, 2.15                                                                | 0.98                                                                |
|                                 |       | 12-13           | 3,959 | 77.5      | 9.9     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,943 | 77.1      | 10.0    | -0.62                         | -1.64, 0.41                   | -0.84                            | -1.43, -0.26                                                              | 0.69                                                                |
|                                 |       | 16 or higher    | 334  | 77.8      | 10.1    | -0.41                         | -2.55, 1.73                   | -0.22                            | -1.47, 1.02                                                               | 0.97                                                                |
|                                 | Model 2 | 11 or younger   | 1,362 | 79.2      | 10.1    | 1.38                          | 0.09, 2.66                    | 1.33                             | 0.69, 1.98                                                                | 0.89                                                                |
|                                 |       | 12-13           | 3,959 | 77.5      | 9.9     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,943 | 77.1      | 10.0    | -0.62                         | -1.64, 0.41                   | -0.80                            | -1.38, -0.22                                                              | 0.74                                                                |
|                                 |       | 16 or higher    | 334  | 77.8      | 10.1    | -0.45                         | -2.61, 1.70                   | -0.20                            | -1.44, 1.03                                                               | 0.99                                                                |
|                                 | Model 3 | 11 or younger   | 1,165 | 79.2      | 10.1    | 1.81                          | 0.29, 3.33                    | 1.41                             | 0.72, 2.10                                                                | 0.67                                                                |
|                                 |       | 12-13           | 3,408 | 77.4      | 9.8     | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,649 | 77.0      | 10.1    | -0.47                         | -1.63, 0.69                   | -0.60                            | -1.21, 0.02                                                               | 0.77                                                                |
|                                 |       | 16 or higher    | 281  | 77.9      | 10.3    | -1.02                         | -3.52, 1.48                   | -0.09                            | -1.22, 1.40                                                               | 0.65                                                                |
| HDL cholesterol, (mmol/L)       | Model 1 | 11 or younger   | 1,309 | 1.538     | 0.405  | -0.065                        | -0.110, -0.019                | -0.045                           | -0.074, -0.016                                                            | 0.62                                                                |
|                                 |       | 12-13           | 3,779 | 1.592     | 0.418  | Ref                           | Ref                           | Ref                              | NA                                                                             |
|                                 |       | 14-15           | 1,854 | 1.631     | 0.402  | -0.009                        | -0.051, 0.033                 | 0.044                            | 0.018, 0.070                                                              | 0.10                                                                |
|                                 |       | 16 or higher    | 321  | 1.645     | 0.433  | -0.032                        | -0.118, 0.053                 | 0.059                            | 0.004, 0.114                                                               | 0.18                                                                |
| Non-HDL cholesterol (mmol/L) | Model 1 | 11 or younger | 1,309 | 3.636 | 1.064 | 0.209 | 0.086 | 0.033 | 0.065 | -0.003, 0.132 | 0.17 |
| Model 2 | 11 or younger | 1,309 | 3.636 | 1.064 | 0.213 | 0.094 | 0.331 | 0.053 | -0.014, 0.119 | 0.11 |
| Model 3 | 11 or younger | 1,122 | 3.625 | 1.067 | 0.152 | 0.021 | 0.284 | 0.067 | -0.003, 0.137 | 0.42 |
| Glucose, (mmol/L) | Model 1 | 11 or younger | 1,289 | 4.6 | 4.3, 4.9 | -0.721 | -2.422 | 0.980 | 1.376 | 0.474, 2.277 | 0.11 |
| Model 2 | 11 or younger | 1,289 | 4.6 | 4.3, 4.9 | -0.562 | -2.165 | 0.429 | -1.237 | 0.380 | 0.32 |
| Model 3 | 11 or younger | 1,103 | 4.6 | 4.3, 4.9 | 0.008 | -1.986 | 2.001 | 1.010 | 0.121, 1.890 | 0.44 |
| Body-mass index (kg/m²) | Model 1 | 11 or younger | 1,344 | 28.080 | 6.176 | 1.710 | 1.018 | 2.401 | 1.848 | 1.481, 2.214 | 0.74 |
| Model 2 | 11 or younger | 1,344 | 28.080 | 6.176 | 1.710 | 1.018 | 2.401 | 1.848 | 1.481, 2.214 | 0.74 |
| Model 3 | 11 or younger | 1,103 | 4.6 | 4.3, 4.9 | 0.008 | -1.986 | 2.001 | 1.010 | 0.121, 1.890 | 0.44 |
Model 2

| Age Group          | Waist Circumference (cm) | Model 1 | Model 2 | Model 3 |
|--------------------|--------------------------|---------|---------|---------|
| 11 or younger      | 1,344                    | 28.080  | 1,653   | 0.970   |
| 12-13              | 3,922                    | 26.115  | Ref     | Ref     |
| 14-15              | 1,929                    | 25.061  | -0.452  | -0.961  |
| 16 or higher       | 329                      | 25.423  | -0.672  | -1.724  |

Outcome log transformed and the coefficients reflect the percent change in the outcome.

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Model 1 Adjusted for age
Model 2 Adjusted for age, qualifications, parental history of cardiovascular disease and parental history of diabetes. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.
Model 3 Adjusted for age, qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.

* Outcome log transformed and the coefficients reflect the percent change in the outcome.
**Table S12.** Association Between Age at Menarche and 10-Year Risk For Overall Cardiovascular Disease Excluding Individuals of Non-European ethnicity, the Scottish Family Health Study, 2006-2011.

| Risk score                              | Model     | Age at menarche | N    | Mean    | SD    | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|----------------------------------------|-----------|-----------------|------|---------|-------|----------------------------|-----------------------------|---------------------------------------------------------------------------------|
|                                        |           |                 |      |         |       | β              | 95% CI               | β              | 95% CI               |
| Framingham risk score                  | Model 1   |                 |      |         |       |                |                      |                |                      |
|                                        |           | 11 or younger   | 1,051| 26.07   | 0.90  | 0.10           | 0.02, 0.17           | 0.11           | 0.06, 0.15           | 0.80               |
|                                        |           | 12-13           | 2,956| 25.94   | 0.90  | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,504| 25.97   | 0.92  | 0.02           | -0.04, 0.08          | -0.03          | -0.07, 0.003         | 0.24               |
|                                        |           | 16 or older     | 267  | 26.07   | 0.86  | -0.03          | -0.15, 0.09          | 0.05           | -0.03, 0.13          | 0.48               |
|                                        | Model 2   | 11 or younger   | 1,051| 26.07   | 0.90  | 0.09           | 0.01, 0.16           | 0.09           | 0.05, 0.13           | 0.88               |
|                                        |           | 12-13           | 2,956| 25.94   | 0.90  | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,504| 25.97   | 0.92  | 0.02           | -0.04, 0.08          | -0.04          | -0.07, -0.002        | 0.20               |
|                                        |           | 16 or older     | 267  | 26.07   | 0.86  | -0.03          | -0.15, 0.10          | 0.03           | -0.04, 0.10          | 0.63               |
|                                        | Model 3   | 11 or younger   | 902  | 26.04   | 0.90  | 0.08           | -0.01, 0.17          | 0.09           | 0.05, 0.13           | 0.88               |
|                                        |           | 12-13           | 2,538| 25.92   | 0.89  | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,280| 25.94   | 0.91  | 0.02           | -0.05, 0.09          | -0.02          | -0.06, 0.01          | 0.39               |
|                                        |           | 16 or older     | 227  | 26.02   | 0.83  | -0.04          | -0.18, 0.10          | 0.02           | -0.06, 0.09          | 0.66               |
| NHANES ECG risk equation score         | Model 1   | 11 or younger   | 1,051| 7.971   | 0.846 | 0.030          | -0.004, 0.064        | 0.018          | 0.001, 0.035         | 0.59               |
|                                        |           | 12-13           | 2,994| 7.931   | 0.847 | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,544| 7.976   | 0.882 | 0.005          | -0.023, 0.032        | -0.019         | -0.034, -0.004       | 0.24               |
|                                        |           | 16 or older     | 260  | 8.056   | 0.803 | 0.004          | -0.057, 0.065        | 0.024          | -0.008, 0.056        | 0.85               |
|                                        | Model 2   | 11 or younger   | 1,051| 7.971   | 0.846 | 0.031          | -0.004, 0.065        | 0.016          | -0.002, 0.033        | 0.50               |
|                                        |           | 12-13           | 2,994| 7.931   | 0.847 | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,544| 7.976   | 0.882 | 0.006          | -0.022, 0.033        | -0.019         | -0.034, -0.004       | 0.22               |
|                                        |           | 16 or older     | 260  | 8.056   | 0.803 | 0.004          | -0.057, 0.066        | 0.022          | -0.010, 0.054        | 0.89               |
|                                        | Model 3   | 11 or younger   | 899  | 7.966   | 0.846 | 0.043          | 0.004, 0.082         | 0.023          | 0.006, 0.041         | 0.46               |
|                                        |           | 12-13           | 2,571| 7.918   | 0.847 | Ref            | Ref                  | NA             |                      |                    |
|                                        |           | 14-15           | 1,306| 7.935   | 0.866 | -0.016         | -0.048, 0.016        | -0.013         | -0.029, 0.003        | 1.00               |
|                                        |           | 16 or higher    | 220  | 8.024   | 0.765 | -0.002         | -0.075, 0.071        | 0.024          | -0.008, 0.057        | 0.80               |

CI=confidence interval; ECG=electrocardiogram; SD=standard deviation.

† The variables included in the Framingham risk score are age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking and diabetes.

Model 1 Adjusted for age
Model 2 Adjusted for age, qualifications, parental history of cardiovascular disease and parental history of diabetes.
Model 3 Adjusted for all of the covariates in Model 2 in addition to smoking (not adjusted for in the analysis of the Framingham risk score since part of the risk calculation), alcohol intake and leisure time physical activity.
### Table S13. Association Between Age at Menarche and Cardiometabolic Health Outcomes Excluding Non-fasting Individuals, the Scottish Family Health Study, 2006-2011.

| Outcome                        | Model  | Age at menarche | N   | Mean/ Median | SD/Range | Within-sibships association | Between-sibships association | Bootstrap p-value for the difference in the within and between sibship association |
|--------------------------------|--------|-----------------|-----|-------------|----------|----------------------------|------------------------------|--------------------------------------------------------------------------------|
| **HDL cholesterol, (mmol/L)**  | Model 1| 11 or younger   | 1,139 | 1.543        | 0.411    | -0.075                     | -0.127, -0.024              | -0.038                           | -0.069, -0.008 | 0.37 |
|                                |        | 12-13           | 3,275 | 1.591        | 0.414    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,599 | 1.623        | 0.403    | -0.030                     | -0.078, 0.018               | 0.039                           | 0.011, 0.066 | 0.07 |
|                                |        | 16 or higher    | 274   | 1.631        | 0.429    | -0.027                     | -0.117, 0.062               | 0.048                           | -0.009, 0.105 | 0.30 |
|                                | Model 2| 11 or younger   | 1,139 | 1.543        | 0.411    | -0.077                     | -0.128, -0.025              | -0.029                          | -0.059, 0.001 | 0.24 |
|                                |        | 12-13           | 3,275 | 1.591        | 0.414    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,599 | 1.623        | 0.403    | -0.031                     | -0.079, 0.017               | 0.039                           | 0.012, 0.066 | 0.06 |
|                                |        | 16 or higher    | 274   | 1.631        | 0.429    | -0.028                     | -0.118, 0.062               | 0.057                           | 0.001, 0.114 | 0.25 |
|                                | Model 3| 11 or younger   | 971   | 1.556        | 0.411    | -0.065                     | -0.125, -0.006              | -0.024                          | -0.055, 0.007 | 0.39 |
|                                |        | 12-13           | 2,809 | 1.602        | 0.411    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,367 | 1.635        | 0.408    | -0.040                     | -0.095, 0.015               | 0.042                           | 0.014, 0.069 | 0.05 |
|                                |        | 16 or higher    | 272   | 1.652        | 0.431    | -0.045                     | -0.143, 0.054               | 0.054                           | -0.004, 0.112 | 0.21 |
| **Non-HDL cholesterol, (mmol/L)** | Model 1| 11 or younger   | 1,139 | 3.630        | 1.058    | 0.202                      | 0.064, 0.341                | 0.047                           | -0.025, 0.119 | 0.18 |
|                                |        | 12-13           | 3,275 | 3.530        | 1.050    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,599 | 3.511        | 1.021    | 0.059                      | -0.066, 0.184               | -0.099                          | -0.163, -0.034 | 0.08 |
|                                |        | 16 or higher    | 274   | 3.589        | 1.006    | -0.057                     | -0.320, 0.188               | -0.028                          | -0.163, 0.107 | 0.92 |
|                                | Model 2| 11 or younger   | 1,139 | 3.630        | 1.058    | 0.204                      | 0.072, 0.337                | 0.033                           | -0.038, 0.103 | 0.11 |
|                                |        | 12-13           | 3,275 | 3.530        | 1.050    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,599 | 3.511        | 1.021    | 0.046                      | -0.075, 0.168               | -0.101                          | -0.164, -0.039 | 0.10 |
|                                |        | 16 or higher    | 274   | 3.589        | 1.006    | -0.043                     | -0.267, 0.182               | -0.044                          | -0.176, 0.088 | 0.98 |
|                                | Model 3| 11 or younger   | 971   | 3.619        | 1.062    | 0.155                      | 0.003, 0.306                | 0.042                           | -0.032, 0.116 | 0.34 |
|                                |        | 12-13           | 2,809 | 3.510        | 1.042    | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,367 | 3.472        | 1.014    | 0.055                      | -0.083, 0.193               | -0.104                          | -0.170, -0.038 | 0.11 |
|                                |        | 16 or higher    | 234   | 3.560        | 1.009    | -0.075                     | -0.328, 0.178               | -0.046                          | -0.185, 0.093 | 0.96 |
| **Glucose, (mmol/L)***         | Model 1| 11 or younger   | 1,125 | 4.6          | 4.3, 4.9 | -1.351                     | -2.916, 0.213               | 1.229                           | 0.398, 2.059 | 0.04 |
|                                |        | 12-13           | 3,248 | 4.5          | 4.3, 4.8 | Ref                        | Ref                          | Ref                              | NA                     |
|                                |        | 14-15           | 1,583 | 4.6          | 4.3, 4.8 | -0.095                     | -1.577, 1.387               | -0.504                          | -1.246, 0.238 | 0.80 |
|                                |        | 16 or higher    | 275   | 4.6          | 4.3, 4.8 | -0.560                     | -4.375, 3.256               | -0.589                          | -2.153, 0.975 | 0.87 |
| Model 2 | 11 or younger | 1.125 | 4.6 | 4.3, 4.9 | -0.865 | -2.382, 0.653 | 1.209 | 0.398, 2.020 | 0.10 |
|--------|---------------|-------|-----|----------|--------|--------------|-------|-------------|-----|
|        | 12-13         | 3.248 | 4.5 | 4.3, 4.8 | Ref    | Ref          |       | NA          |     |
|        | 14-15         | 1.583 | 4.6 | 4.3, 4.8 | 0.006  | -1.385, 1.398 | -0.294 | -1.019, 0.430 | 0.81 |
|        | 16 or higher  | 275   | 4.6 | 4.3, 4.8 | -0.682 | -4.505, 3.141 | -0.437 | -1.964, 1.090 | 0.80 |
| Model 3| 11 or younger | 958   | 4.6 | 4.3, 4.9 | -0.263 | -1.966, 1.440 | 1.087  | 0.244, 1.930 | 0.29 |
|        | 12-13         | 2.785 | 4.5 | 4.3, 4.8 | Ref    | Ref          |       | NA          |     |
|        | 14-15         | 1.355 | 4.6 | 4.3, 4.8 | 0.479  | -1.024, 1.983 | -0.332 | -1.084, 0.420 | 0.54 |
|        | 16 or higher  | 234   | 4.6 | 4.3, 4.8 | -3.115 | -7.624, 1.394 | -0.155 | -1.740, 1.430 | 0.41 |

CI=confidence interval; HDL=high-density lipoprotein; SD=standard deviation.

Model 1 Adjusted for age
Model 2 Adjusted for age, ethnicity, qualifications, parental history of cardiovascular disease and parental history of diabetes. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.
Model 3 Adjusted for age, ethnicity qualifications, parental history of cardiovascular disease, parental history of diabetes, smoking, alcohol intake and leisure time physical activity. Blood pressure further adjusted for use of antihypertensive drugs, cholesterol levels adjusted for lipid lowering drugs and glucose adjusted for use of antidiabetic drugs.

* Outcome log transformed and the coefficients reflect the percent change in the outcome.
Age at Menarche and Cardiometabolic Health: A Sibling Analysis in the Scottish Family Health Study
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J Am Heart Assoc. 2018;7:e007780; originally published February 10, 2018;
doi: 10.1161/JAHA.117.007780
The Journal of the American Heart Association is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

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