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Differential sex effects of systolic blood pressure and LDL-C on Type 2 diabetes: Life-course data from the Bogalusa Heart Study

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Abstract

Background—There may be sex-specific cardiometabolic mechanisms early in life that affect the development of type 2 diabetes (T2DM) through mid-adulthood. Yet, there have been few studies examining whether early life-course interactions between cardiometabolic risk factors and sex are associated with incident T2DM.

Methods—We followed $n=7,725$ children from the Bogalusa Heart Study through mid-adulthood to examine whether low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), body mass index (BMI), or systolic blood pressure (SBP) differentially impact the risk of T2DM for females versus males. A longitudinal, adjusted generalized estimating equations approach was used to test these potential sex interactions after adjustment for age, race, triglycerides, smoking, follow-up time, puberty stage, use of birth control, and enrollment year.

Results—There were 3,834 (49.6%) female participants and 3,891 (50.4%) male participants. Mean(SD) baseline age was 9.4(3.5) years. There were 176 cases of T2DM (cumulative incidence=2.3%) during median follow-up of 9.1 years. LDL-C and SBP were differentially associated with T2DM ($p<.001$ and $p=0.017$, respectively) in females versus males. The relationships of BMI and HDL-C with T2DM were non-differential between females and males ($p=0.79$ and $p=0.27$, respectively).

Conclusions—Our study is the first to show evidence of sex-specific differential effects of LDL-C and SBP on the risk of T2DM from childhood to adulthood. A greater LDL-C places girls at disproportionally higher risk of T2DM as women, whereas a greater SBP differentially exposes boys to a greater risk of T2DM as men. Additional studies within existing child cohorts are needed to confirm and investigate the mechanisms for these differential effects.

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Keywords

Interaction; Life-course Epidemiology; Metabolic Cardiovascular Syndrome; Sex; Type 2 Diabetes Mellitus

Introduction

Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease are known to share many common risk factors, including obesity, hypertension, unbalanced lipid profiles, poor diet, and inadequate physical activity¹⁻³. Although the sex-specific prevalence of T2DM is estimated to be roughly 10–12% among both men and women in the United States, substantial evidence has been summarized by the American Heart Association which indicates worse outcomes, such as increased cardiovascular morbidity and mortality, for women versus men with T2DM⁴. Furthermore, several observational studies have indicated differences in the effects of certain cardiometabolic risk factors on diabetes in women versus men⁵⁻⁷. Specifically, the Framingham Study indicated that increasing high density lipoprotein-cholesterol (HDL-C) reduced the risk of diabetes in elderly men but not women⁵, while the Finnmark⁶ and MONICA⁷ studies found the opposite result in middle-aged adults. Finnmark and MONICA also showed that an increase in body mass index (BMI) differentially increased the risk of diabetes for men versus women. These three studies conflicted on whether systolic blood pressure had a differentially adverse impact on women, men, or neither with regards to the risk of diabetes. Because these studies took place in middle-aged or elderly populations, and because many of the sex-specific differences in diabetes are thought to be driven by interactions between cardiometabolic profiles, obesity, and sex, there may be similar mechanisms involved earlier in life that can be identified or observed prior to clinical diagnosis of T2DM^{4,8}. Therefore, we sought to use early life-course data to explore whether lipoprotein profiles, systolic blood pressure, or obesity differentially affect the development of T2DM by sex beginning in childhood within the Bogalusa Heart Study.

Methods

Study design and population

The Bogalusa Heart Study (BHS) began in 1973 under Dr. Gerald Berenson, and consists of a series of long-term prospective studies of a semi-rural, biracial community in Bogalusa, Louisiana. Summarily, the BHS cohort consists of participants enrolled in childhood through cross-sectional cardiovascular risk factor surveys. After the initial childhood survey, study participants remain enrolled and complete cross-sectional surveys of cardiovascular risk factors every few years. Further details regarding the study population and design are described in greater detail elsewhere⁹. Demographic information, such as age, sex and race, is collected through self-reported survey response or direct interview. Questions on tobacco use were asked for 3rd graders and older from 1974 onward.

We initially considered all participants (n=7,982) of the Bogalusa Heart Study who had at least one follow-up visit after the initial enrollment visit. We then excluded those with

missing information for both diabetes diagnosis and glucose measurements (n=212), those who already had a diabetes diagnosis upon enrollment (n=20), and those with Type 1 diabetes (n=25). For participants who experienced the study outcome of incident T2DM, any subsequent study visits after the visit in which incident diabetes occurred were also excluded. The final study population consisted of n=7,725 participants from 1973 through 2010.

Exposure ascertainment and definitions

Current smoking status was ascertained through self-report and was defined as any use of cigarettes within the past week. Systolic blood pressure levels were recorded as the first Korotkoff phase using mercury sphygmomanometers, and were reported as the mean of six repeated readings from two randomly assigned observers using the right arm of participants seated in a relaxed position. Serum cholesterol levels were obtained and assayed using documented enzymatic procedures¹⁰. Height and weight were also measured and averaged between two observers, with body mass index calculated in the standard format: kilograms body weight per height (in meters) squared.

Outcome ascertainment and definition

Incident Type 2 diabetes was determined to occur at any follow-up visit in which the participant was currently taking oral diabetes medication, had a current diagnosis of Type 2 diabetes, and/or had a fasting blood glucose measurement of greater than 126 mg/dL.

Statistical analysis

Baseline cardiometabolic risk factors were tabulated and differences between female and male participants were compared using Pearson's chi-squared p-values for categorical variables, Student's t-tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for skewed continuous variables.

Based on relationships between sex and diabetes risk factors suggested in previous literature⁵⁻⁷, we tested four plausible interactions with sex: 1.) low-density lipoprotein-cholesterol (LDL-C); 2.) high-density lipoprotein-cholesterol (HDL-C); 3.) body mass index (BMI); and 4.) systolic blood pressure (SBP); for significant associations with incident T2DM over the life-course. Data from each participant visit was combined into a logistic generalized estimating equations (GEE) model adjusted for race, age, triglycerides, current smoking status, time between visits, puberty status (Tanner stages I through V), use of oral contraceptives, and year of first visit (to remove any potential period effect). The outcome (dependent) variable in this model was incident T2DM at time of visit (yes/no), and the exposure variables in the model were sex, HDL-C, LDL-C, BMI, SBP, and the four individual interaction terms between sex and each exposure. All GEE models used an unstructured covariance matrix to allow flexibility and to prevent the introduction of bias from incorrect assumptions of the covariance structure¹¹. Multiple imputation using Markov Chain Monte Carlo estimation was used to impute all missing covariate measurements [n=327 visits (1.1%) were missing at least one covariate measurement].

Results

Of the $n=7,725$ participants, 3,834 (49.6%) were female and 3,891 were male (50.4%). Mean(SD) age of participants at enrollment was 9.4(3.5) years. There were 176 participants with incident T2DM (cumulative incidence = 2.3%) during a median follow-up of 9.1 years in which study participants combined for a total of 30,959 study visits (mean=4.0 per participant). At baseline, boys had significantly higher SBP, HDL-C, and glucose levels, and were more likely to be smokers than girls (Table 1). Conversely, girls had significantly greater LDL-C and triglycerides at baseline. At follow-up, there was no significant difference in cumulative incidence of T2DM for girls (2.4%) versus boys (2.1%) ($p=0.39$), though men and women differed significantly in their risk factor profiles – men had greater SBP and glucose, whereas women had higher BMIs, LDL-C, and HDL-C (Table 1).

In the adjusted GEE model, a majority of the traditional cardiometabolic risk factors were significant predictors of incident diabetes (Table 2). Notably, those of black race had an adjusted Odds Ratio for diabetes of 1.57 (95% Confidence Interval: 1.11, 2.22; $p=0.011$), and each 50 mg/dL increase in triglycerides corresponded to an adjusted Odds Ratio for diabetes of 1.13 (95% Confidence Interval: 1.08, 1.18; $p<0.0001$). The relationship between BMI and diabetes was significant ($p<0.0001$) and non-linear, and is shown in Figure 1A. However, this relationship was non-differential between females and males ($p_{\text{interaction}}=0.79$). Likewise, HDL-C was significantly associated with diabetes ($p<0.001$) in a non-differential ($p_{\text{interaction}}=0.27$), non-linear trend (Figure 1B). In contrast, LDL-C and SBP were both differentially associated with diabetes ($p_{\text{interaction}}<0.001$ and $p_{\text{interaction}}=0.017$, respectively) in females versus males. In males, increasing SBP substantially increased the risk of diabetes, whereas in females an increasing SBP did not change the risk of diabetes (Figure 2). Conversely, an increasing LDL-C increased the risk of diabetes in women, but slightly lowered the risk of diabetes in men (Figure 3).

Discussion

Our large cohort is the first to assess differential sex-specific effects of cardiometabolic risk factors on incident T2DM using a life-course approach from childhood. Our analysis shows strong evidence that early-life interaction between LDL-C and sex is associated with incident T2DM; an increase in LDL-C through adolescence puts women at greater risk of diabetes but may actually reduce the risk of diabetes in men. Additionally, we have shown that increasing systolic blood pressure is an important T2DM risk factor for men, yet has almost no impact on development of T2DM in women. While greater BMI and HDL-C values were also significant life-course risk factors for T2DM in both females and males, we found no evidence of a differential role of these risk factors between sexes.

The most comparable study to date for assessing childhood risk factors of adult diabetes was the Princeton Follow-up Study¹², though results were not stratified nor tested for sex differences. In Princeton, Morrison et al found a marginally significant impact of high SBP (defined as 90th age-height specific percentile) on diabetes (OR=1.82; 95%CI 0.98, 3.41). Conversely, previous studies comparing sex differences in cardiometabolic risk factors for incident diabetes have included the Framingham⁵, Finnmark⁶ and MONICA Augsburg⁷

studies, although these studies were conducted in adult populations without prospective childhood data. In the Framingham study, systolic blood pressure was not significantly associated with diabetes in elderly men or women, whereas SBP was associated with diabetes for women only in the Finnmark study. However, the MONICA investigators found results similar to ours – systolic blood pressure was a significant predictor of diabetes for men, but not for women in their cohort⁷. The authors acknowledged this finding could be due to more women in their study having controlled hypertension than men. Our cohort of is unlikely to be affected by this discrepancy as very few of our participants are taking hypertension medication at young ages. Likewise, there is evidence showing that hypertension is disproportionately associated with metabolic syndrome in men¹³, and that hypertension is more frequently clustered with other metabolic syndrome factors, such as low HDL-C and increased triglycerides in young males¹⁴. Several shared pathways have been identified to link hypertension and diabetes – including genetics, insulin resistance, sex hormones, central obesity, oxidative stress, and physical activity¹⁵, and it is very possible that some combination of these factors behaves differently in adolescents versus adults.

The results of our lipoprotein analysis show that an increase in LDL-C is associated with greater risk of diabetes in young women, while the inverse of this relationship is true for young men. This result is intriguing given the prevailing knowledge that, although increased levels of very small, dense LDL-C particles are associated with diabetes, overall LDL-C levels are not typically associated with diabetes^{16–18}. One reason for this discrepancy may be that most studies have not looked for differential effects by sex. For example, the overall effect of LDL-C on diabetes may be null when both sexes are combined, but this may conceal the increased risk among women and decreased risk among men at high LDL-C that was seen in our cohort due to our intentional search for this interaction. Furthermore, the Princeton study found no difference in risk for those with high LDL-C versus low LDL-C when defined as ≥ 110 mg/dL (OR=0.95, 95% Confidence Interval 0.65–1.44), but this dichotomization of LDL-C may have inhibited their ability to find a true significant effect^{19,20}. Indeed, our study indicates that the lowest risk of diabetes may actually be near this 110 mg/dL cut-off for both men and women, with risks increasing to the extremes at either side for women (Figure 3). In fact, a previous analysis from Bogalusa also showed that a 18mg/dL childhood increase in LDL-C raised the risk of young adult pre-diabetes by 40%²¹. An increase in risk of incident diabetes was seen in our data for both men and women as LDL-C decreased below approximately 90 mg/dL. This is consistent with previous evidence from meta-analyses showing that LDL-lowering therapies and alleles associated with LDL-lowering are associated with increased risk of diabetes^{22,23}. However, in our study this effect was seen in women only at lower LDL-C levels versus across all LDL-C levels in men; the relationship was U-shaped for women and L-shaped for men (Figure 3).

Similar to the Princeton Follow-up Study¹², which indicated 63% higher risk of diabetes for those with a low HDL-C compared to high HDL-C, we also detected a strongly increasing risk of diabetes for both men and women with low HDL-C levels. Most surprising was our result that the effect of HDL-C on the risk of diabetes did not appear to differentiate by sex. Previously, when assessing sex differences, the Finnmark⁶ and MONICA⁷ studies found greater HDL-C to be more beneficial in lowering the risk of diabetes for females, whereas the Framingham⁵ study found HDL-C to be protective of diabetes in males only. Because

the Finnmark⁶, Framingham⁵, and MONICA⁷ studies considered only HDL-C, and did not adjust for LDL-C, however, it is possible that our finding of a strong differential effect of LDL-C overwhelmed a smaller HDL-C interaction effect.

As expected, we found a significant increase in young adult T2DM risk with increasing childhood BMI, which has been regarded as a driving factor in the decades-long increase in the prevalence of childhood diabetes across the nation^{24,25}. In regards to our finding of no differential effects of BMI by sex, our results differ from both MONICA⁷, in which a 4 kg/m² increase in BMI resulted in a twice-greater increase in the risk of diabetes for men as compared to women (OR=1.98 and OR=1.49, respectively) and Finnmark⁶, which also showed a more adverse impact of BMI on diabetes for men. Given the younger nature of our population, however, it is plausible that the cumulative effects of obesity over the life-course become differentiated only after several decades of exposure. A good example of this phenomenon comes from our finding that cigarette smoking among children had virtually no effect on diabetes risk in young adulthood (OR=0.92; 95% CI: 0.64, 1.34). While it has been documented extensively that smoking increases the risk of diabetes in both men and women^{26–30}, the cumulative effect of smoking (e.g. pack-years) on diabetes may be too low, or the latency period may be too long, for smoking to contribute to diabetes in late adolescence or young adulthood. It has been shown that the latent period for smoking and certain types of cancer can exceed 30–40 years, for example³¹.

Our study has some limitations. First, the continuous enrollment period and follow-up schedule of our study necessitates that not all of the study cohort were enrolled as children in the same year. For this reason, we have controlled for the year of enrollment to eliminate the bias from any period effect which likely exists, given the increasing prevalence of childhood and young adult diabetes during the study period. Indeed, we found approximately a 4% increase in risk of diabetes with each successive year of enrollment. Second, although all subjects had at least one subsequent follow-up visit in addition to the enrollment visit, many subjects had several additional visits that were also included in our model to increase power and precision. Thus, it is also possible that differential visits occurred – for instance a greater number of visits for healthier subjects per the healthy user effect. We conducted sensitivity analysis of missing visits by retaining only the enrollment visit and the most recent visit for all subjects, and our results were extremely similar to our main analysis in both effect size and significance (Appendix A), showing that inclusion of multiple visits added precision to our estimates and was unlikely to have biased our results. Third, due to slight differences in cigarette smoking questions asked over several decades of our study, our definition of current smoking as ≥ 1 cigarette per week is open to the potential of residual confounding or misclassification. However, the young age of our cohort and low prevalence of smoking (2.7% at baseline) likely reduces the magnitude that any misclassification could have had on our results. Fourth, our analysis tested four distinct hypotheses; therefore a conservative approach would have been to apply a Bonferroni correction for multiple testing. Nevertheless, given that these tests were not truly independent, but were conducted within the same model and likely to be highly correlated to each other, Bonferroni correction is likely to be too conservative. Therefore, considering this limitation of correction for multiplicity, along with the fact that these four hypothesis tests were specified *a priori*, we chose not to adjust for multiple testing in our main results, which

could have slightly increased the chances of a false positive finding. Lastly, residual confounding is always a possibility in an observational study, and causality cannot be inferred from an observational design regardless of control for confounding. Nevertheless, we have controlled for age, race, BMI, smoking, LDL, HDL, systolic blood pressure, triglycerides, use of contraceptives, pubertal status, and follow-up time in our final model. These variables are inclusive of those most often and most strongly associated with cardiometabolic disease and diabetes. Therefore, additional confounding from unconsidered variables is likely to have a limited effect on these results.

In summary, our study is the first to investigate and provide evidence of sex-specific differential effects of LDL-C and systolic blood pressure on the risk of Type 2 diabetes from childhood to mid-adulthood. A greater LDL-C appears to put girls at disproportionately higher risk of T2DM as women, whereas a higher SBP differentially exposes boys to a greater risk of T2DM as men. On the other hand, greater BMIs and lower HDL-C put both girls and boys at a non-differential but still increased risk of adult diabetes. Additional studies in similar child cardiovascular cohorts are needed to confirm and investigate the mechanisms for these differential effects.

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Appendix A – Sensitivity analyses: Adjusted Odds Ratios and 95% Confidence Intervals

Baseline characteristic:	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Age (per 5 year increase)		
Model 1 ^a	1.54 (1.32, 1.80)	<0.0001
Model 2 ^b	1.44 (1.21, 1.72)	<0.0001
Model 3 ^c	1.39 (1.17, 1.65)	<0.001
Race (Black vs. White)		
Model 1 ^a	1.62 (1.13, 2.34)	0.009
Model 2 ^b	1.58 (1.12, 2.22)	0.009
Model 3 ^c	1.57 (1.11, 2.22)	0.010
BMI		
Model 1 ^a	Non-linear	<0.0001
Model 2 ^b	Non-linear	<0.0001
Model 3 ^c	Non-linear	<0.0001
Systolic blood pressure		
Model 1 ^a	Non-linear	0.080
Model 2 ^b	Non-linear	0.160
Model 3 ^c	Non-linear	0.121
Systolic blood pressure*Sex		
Model 1 ^a	Non-linear	0.033
Model 2 ^b	Non-linear	0.022
Model 3 ^c	Non-linear	0.016
HDL-C		
Model 1 ^a	Non-linear	0.003
Model 2 ^b	Non-linear	0.002
Model 3 ^c	Non-linear	<0.001
LDL-C		
Model 1 ^a	Non-linear	0.037
Model 2 ^b	Non-linear	0.149
Model 3 ^c	Non-linear	0.045
LDL-C*Sex		
Model 1 ^a	Non-linear	0.002
Model 2 ^b	Non-linear	<0.001
Model 3 ^c	Non-linear	<0.001

Baseline characteristic:	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Triglycerides (per 50 mg/dL increase)		
Model 1 ^a	1.15 (1.08, 1.22)	<0.0001
Model 2 ^b	1.15 (1.09, 1.20)	<0.0001
Model 3 ^c	1.13 (1.08, 1.18)	<0.0001
Current smoker (1 cigarette/week)		
Model 1 ^a	0.92 (0.64, 1.33)	0.701
Model 2 ^b	0.99 (0.69, 1.41)	0.935
Model 3 ^c	0.92 (0.64, 1.33)	0.662
Tanner Stage (I–V), per 1 stage increase		
Model 1 ^a	1.15 (0.86, 1.53)	0.355
Model 2 ^b	0.89 (0.66, 1.20)	0.437
Model 3 ^c	0.93 (0.69, 1.24)	0.602
Use of oral contraceptives		
Model 1 ^a	1.12 (0.56, 2.24)	0.742
Model 2 ^b	1.09 (0.58, 2.05)	0.791
Model 3 ^c	0.95 (0.49, 1.83)	0.880
Time between visits (1 year increase)		
Model 1 ^a	1.00 (0.97, 1.03)	0.998
Model 2 ^b	1.03 (0.99, 1.06)	0.166
Model 3 ^c	1.02 (0.99, 1.06)	0.178
Year of enrollment (1 year increase)		
Model 1 ^a	0.97 (0.94, 1.01)	0.134
Model 2 ^b	1.02 (0.98, 1.07)	0.227
Model 3 ^c	1.03 (0.99, 1.08)	0.087
Sex:		
At LDL-C=140 mg/dL and SBP=110 mmHG		
Female vs. Male		
Model 1 ^a	2.03 (0.90, 4.57)	0.069
Model 2 ^b	1.82 (0.98, 3.38)	0.057
Model 3 ^c	1.96 (1.21, 3.16)	0.006
At LDL-C=70 mg/dL and SBP=110 mmHG		
Female vs. Male		
Model 1 ^a	0.73 (0.26, 2.02)	0.396
Model 2 ^b	0.61 (0.28, 1.36)	0.175
Model 3 ^c	0.71 (0.39, 1.30)	0.265
At LDL-C=100 mg/dL and SBP=100 mmHG		
Female vs. Male		
Model 1 ^a	1.45 (0.53, 3.97)	0.325

Baseline characteristic:	Adjusted Odds Ratio (95% Confidence Interval)	<i>p</i> -value
Model 2 ^b	1.24 (0.57, 2.73)	0.507
Model 3 ^c	1.43 (0.78, 2.61)	0.245
At LDL-C=100 mg/dL and SBP=140 mmHG		
Female vs. Male		
Model 1 ^a	0.54 (0.19, 1.52)	0.153
Model 2 ^b	0.47 (0.22, 1.01)	0.052
Model 3 ^c	0.50 (0.27, 0.91)	0.021

^a Identical to main analysis, but includes only first and last visits of each participant (n=7,725);

^b Identical to main analysis, but includes only participants with >2 visits (n=5,846);

^c Identical to main analysis, but with random slope and intercept for number of study visits (n=7,725);

Highlights

From childhood to adulthood, an increase in LDL-C imposes a differentially greater risk for type 2 diabetes (T2DM) for females versus males. Conversely, an increase in systolic blood pressure over the life-course greatly increases males' risk of T2DM, but has no effect in females.

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Figure 1. Non-differential adjusted probabilities of T2DM by HDL-C and BMI

Life-course predicted probabilities of diabetes, by high-density lipoprotein-cholesterol and body mass index with no sex interaction. Adjusted for race, age, triglycerides, current smoking status, time between visits, puberty status, use of oral contraceptives, year of first visit, low-density lipoprotein-cholesterol, and systolic blood pressure.

Figure 2. Differential adjusted probabilities and relative odds of T2DM by SBP

Life-course predicted probabilities and odds ratios (with 95% confidence intervals) comparing females versus males by systolic blood pressure with p-values for sex interaction. Adjusted for race, age, triglycerides, current smoking status, time between visits, puberty status, use of oral contraceptives, year of first visit, body mass index, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol.

Figure 3. Differential adjusted probabilities and relative odds of T2DM by LDL-C
 Life-course predicted probabilities and odds ratios (with 95% confidence intervals) comparing females versus males by low-density lipoprotein-cholesterol with p-values for sex interaction. Adjusted for race, age, triglycerides, current smoking status, time between visits, puberty status, use of oral contraceptives, year of first visit, body mass index, high-density lipoprotein-cholesterol, and systolic blood pressure.

Table 1

Baseline and follow-up characteristics of 7,725 Bogalusa Heart Study participants by sex

Baseline characteristic:	Male (n=3,891, 49.6%)	Female (n=3,834 50.4%)	Unadjusted p-value
Age (years), median(IQR) *	8.9 (6.7,11.6)	8.7 (6.6,11.5)	0.22
Age (years), mean(SD)	9.5(3.6)	9.4(3.5)	
Race			0.83
White	2,455 (63.1%)	2,410 (62.9%)	
Black	1,436 (36.9%)	1,424 (37.1%)	
BMI (kg/m ²), median(IQR) *	16.4 (15.3,18.7)	16.7 (15.1,19.1)	0.68
Systolic blood pressure, (mm Hg)	99.0 ± 10.3	98.3 ± 10.2	<0.01
HDL-C (mg/dL)	63.2 ± 19.9	61.8 ± 19.5	<0.001
LDL-C (mg/dL)	91.3 ± 25.0	95.5 ± 25.8	<0.0001
Triglycerides (mg/dL), median(IQR) *	57 (44,76)	61 (47,82)	<0.0001
Glucose (mg/dL)	83.5 ± 10.0	81.1 ± 9.0	<0.0001
Current smoker (1 cigarette/week)	131 (3.4%)	78 (2.0%)	<0.001
Tanner Stage mean(SD)	1.6(1.2)	1.9(1.4)	<0.001
Use of oral contraceptives	0 (0.0%)	88 (2.3%)	<0.0001
Year of enrollment, median(IQR) *	1977 (1974,1982)	1977 (1974,1982)	0.16
Follow-up characteristic:	Male (n=3,891, 49.6%)	Female (n=3,834 50.4%)	Unadjusted p-value
Age (years), median(IQR) *	17.0 (13.6,26.7)	18.8 (14.0,29.9)	<0.0001
Age (years), mean(SD)	21.1(10.6)	22.8(11.1)	
Race			0.83
White	2,455 (63.1%)	2,410 (62.9%)	
Black	1,436 (36.9%)	1,424 (37.1%)	
BMI (kg/m ²), median(IQR) *	22.3 (19.2,26.8)	22.7 (19.5,28.1)	<0.0001
Systolic blood pressure (mm Hg)	111.7±12.7	108.4 ± 11.4	<0.0001
HDL-C (mg/dL)	51.0 ± 16.9	53.7 ± 15.8	<0.0001
LDL-C (mg/dL)	103.9 ± 32.1	107.1 ± 30.8	<0.0001
Triglycerides (mg/dL), median(IQR) *	75 (54,112)	76 (56,108)	0.67
Glucose (mg/dL)	86.9± 16.2	84.2 ± 15.0	<0.0001

Baseline characteristic:	Male (n=3,891, 49.6%)	Female (n=3,834 50.4%)	Unadjusted p-value
Current smoker (≥ 1 cigarette/week)	835 (21.5%)	759 (19.8%)	0.07
Tanner Stage (I-V), mean(SD)	4.0(1.5)	4.2(1.2)	<0.0001
Use of oral contraceptives	0 (0.0%)	847 (22.1%)	<0.0001
Total follow-up (years), median(IQR) *	8.2 (4.9,16.3)	10.7 (5.1,20.7)	<0.0001
Total follow-up (years), mean(SD)	11.7(10.0)	13.4(10.4)	
Cumulative incidence of diabetes	83 (2.1%)	93 (2.4%)	0.39

* Wilcoxon rank-sum test for skewed distribution;

Table 2

Adjusted Odds Ratios and 95% Confidence Intervals for Incident Type 2 Diabetes

Baseline characteristic:	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Age (per 5 year increase)	1.39 (1.05, 1.64)	<0.001
Race		0.011
White	Reference	
Black	1.57 (1.11, 2.22)	
BMI	Non-linear	<0.0001
Systolic blood pressure	Non-linear	0.163
Systolic blood pressure*Sex	Non-linear	0.017
HDL-C	Non-linear	<0.001
LDL-C	Non-linear	0.031
LDL-C*Sex	Non-linear	<0.001
Triglycerides (per 50 mg/dL increase)	1.13 (1.08, 1.18)	<0.0001
Current smoker (1 cigarette/week)	0.92 (0.64, 1.34)	0.677
Tanner Stage (I-V), per 1 stage increase	0.93 (0.69, 1.25)	0.633
Use of oral contraceptives	0.96 (0.50, 1.86)	0.901
Time between visits (1 year increase)	1.03 (0.99, 1.06)	0.159
Year of enrollment (1 year increase)	1.03 (0.99, 1.08)	0.085
Sex:		
At LDL-C=140 mg/dL and SBP=110 mmHG		
Female vs. Male	1.93 (1.02, 3.62)	0.045
At LDL-C=70 mg/dL and SBP=110 mmHG		
Female vs. Male	0.71 (0.32, 1.57)	0.317
At LDL-C=100 mg/dL and SBP=100 mmHG		
Female vs. Male	1.42 (0.64, 3.13)	0.311
At LDL-C=100 mg/dL and SBP=140 mmHG		
Female vs. Male	0.49 (0.23, 1.08)	0.069