NIH Public Access
Author Manuscript

Ann Epidemiol. Author manuscript; available in PMC 2009 December 1.

Parity and cardiovascular disease risk among older women: how do pregnancy complications mediate the association?

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Abstract

Purpose—To determine if parity is associated with increased risk of cardiovascular disease (CVD) after accounting for perinatal complications.

Methods—CVD prevalence, number of births, and a history of preeclampsia, term low birth weight, preterm or stillbirth were evaluated among 540 women (mean age 80 years; 47% black) enrolled in the Pittsburgh, PA site of the Health, Aging and Body Composition Study. Biomarkers were measured and CVD status was determined by self-report and hospital records.

Results—Nulliparous women (n=89) had lower CVD prevalence compared to parous women (18.0% vs. 30.2%). Parous women without perinatal complications of interest (n=321) had higher statin use compared to nulliparas, a trend accompanied by lower HDL and higher triglycerides among women with perinatal complications (n=130). After adjustment, parous women with no complicated births had a 1.95-fold (95% CI 1.03–3.7) higher CVD prevalence compared to nulliparas. Among women with ≥1 pregnancy complication, CVD prevalence was 2.67 times (1.34–5.33) higher. Women with ≥5 births had the highest CVD prevalence (OR 2.60, 1.17–5.76) that was attenuated to 2.27 (1.00–5.15) after adjustment for complications of interest.

Conclusions—History of pregnancy complications and higher statin use accounted for some but not all of the excess CVD prevalence among older, parous women.

Keywords

Parity; cardiovascular disease; pregnancy complications

Parity evaluated cross sectionally has been associated with increased risk of cardiovascular disease in women in many but not all studies. Some studies indicate that each live birth confers

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additional, albeit modest, risk for prevalent maternal cardiovascular disease[1] or athlerosclerosis.[2] Alternatively, other studies have found a threshold effect such that women with more than five or six children have excess cardiovascular disease risk.[3][4] Risks associated with nulliparity are contradictory. Some studies indicate that nulliparous women are at lower risk compared to parous women;[2–5] others have found nulliparous women to be at higher risk for cardiovascular disease compared to parous women with one or two births.[1, 6, 7]

Separate studies have also found that certain pregnancy complications, including preeclampsia, [8–11] preterm delivery,[12, 13] and low birth weight[14, 15] have been associated with excess maternal cardiovascular risk. Only one study to date has attempted to disaggregate the effects of parity and pregnancy complications on women's long term cardiovascular risk. Hannaford found that nulliparaous women at an average age of 56 had an increased risk for developing hypertension or stroke compared to parous women whose births had been without complications from hypertension.[6]

We set out to assess the effect of parity on CVD prevalence, and determine if this effect was mediated by pregnancy complications. In particular, we sought to determine if parity was associated with higher prevalence of cardiovascular disease among older women after excluding those who had experienced at least one pregnancy complicated by preeclampsia, low birth weight, or preterm delivery. A secondary aim was to investigate how cardiovascular risk factors, including body composition, vascular, metabolic or inflammatory markers were related to parity, pregnancy complications, and maternal cardiovascular disease risk.

Methods

Participants

This was a cross sectional study nested within the Health, Aging and Body Composition (Health ABC) Study. The Health ABC study is a large on-going epidemiologic study of how changes in body composition affect morbidity, disability, and mortality. A total of 3,075 community dwelling participants (50% female) were enrolled in Pittsburgh, Pennsylvania and Memphis, Tennessee in 1997–1998. Recruitment procedures have been described elsewhere in detail. [16] All participants signed an informed consent approved by the institutional review boards at the University of Pittsburgh and University of Tennessee. Eligibility criteria for the main study included: age 70 to 79; self-report of no difficulty walking one quarter mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no use of assistive devices to ambulate; no history of active treatment for cancer in the prior three years; and no plans to move out of the area in the next three years. Based on these criteria participants were considered well functioning.[17]

Pregnancy characteristics

Among 608 women in the Pittsburgh cohort who were interviewed in 2003 and 2004 as part of on-going follow-up, 596 also answered questions about pregnancy history. On average, 56.6 years (SD 5 years) had elapsed between delivery of the first pregnancy and age at the time of the interview. Parity was defined as the number of births lasting at least 6 months gestation. A total of 507 women (85%) reported 1560 births >6 months and 89 women reported no births. Births were reported as live or still born. Women in this analysis included those who reported complete birth information (number of births with outcomes, and birth weight for each live birth; n=540, 91%).

We previously validated the accuracy of the recall of infant birth weight among a randomly selected group of women in our study (intraclass correlation coefficient 0.96 for first births and 0.59 for subsequent births), and demonstrated that these older women reported birth weight

data reliably at two time points across race, age, income and education strata.[18] In addition, our validation study indicated that mothers underestimated the birth weight of their children by an average of 44–86 g. when compared to actual birth certificate or hospital records,[18] and these results were remarkably consistent with other studies of maternal recall of infant birth weight among younger women.[19, 20]

Term low birth weight infants were those reported as born ≥37 weeks and <2500 g; preterm births were those reported as born <37 weeks. Women were also asked if each pregnancy was complicated by preeclampsia or hypertension. Gestational diabetes was not routinely assessed at the time these women gave birth, and therefore we were unable to evaluate this complication. Women were characterized into three distinct parity groups: nulliparous (no births > 6 months); parous, no reported pregnancy complications of interest; and parous, with ≥1 pregnancy complicated by preeclampsia/hypertension, term LBW, preterm birth, or stillbirth. Parity was also evaluated as 0, 1–2, 3–4, and ≥5 births with or without perinatal complications of interest.

CVD status

Prevalent cardiovascular disease was ascertained at baseline (1997 to 1998) via self-report and was validated with algorithms that included selected medications and ECG results.[21] There were 118 participants with the following prevalent conditions: myocardial infarction, angina, coronary artery bypass surgery, percutaneous transluminal angioplasty, stroke, or peripheral vascular disease. Incident events that occurred after baseline (n=34) were ascertained by phone contact or at the clinic examination every six months (1998 to 2002), and validated by medical record review.[22] Overall, 152 women (28.2%) were identified as having cardiovascular disease from baseline through the time of the interview.

Covariates

Potential confounders included characteristics with an established association with adverse pregnancy outcomes or cardiovascular disease. These were all assessed at baseline. Sociodemographic and lifestyle variables included age, race, education, income, marital status and smoking status (characterized as ever vs. never ; and measured in pack years [the average packs of cigarettes smoked daily multiplied by years smoking]). Participants reported annual family income at study baseline, and also described how well their income fit their needs (poorly, fairly well, very well). Due to the high number of missing values for family income (n=63, 14%), a low socioeconomic indicator variable was calculated for women who reported either the lowest quartile of family income or the lowest level of income adequacy.

Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured on fasting serum by a colorimetric technique on a Johnson and Johnson Vitros 950 analyzer, New Brunswick, NJ. Low-density lipoprotein cholesterol was estimated with the Friedewald calculation. Vascular measures included systolic and diastolic blood pressures[21] and pulse wave velocity[23] (measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries by use of nondirectional transcutaneous Doppler flow probes). Hypertension was defined via self report and medication use, or systolic blood pressure above 135 and diastolic blood pressure above 85. Presence of diabetes mellitus (self-report and medication) or metabolic syndrome (NCEP III definition[24] as three or more of the following: abdominal circumference > 88; blood pressure >=130/85 or taking anti-hypertensive medication; fasting glucose >= 110 or taking insulin or oral antidiabetic agents; HDL cholesterol < 50; or triglycerides >= 150) were also considered. Other metabolic markers were serum insulin (non-diabetics only) and glucose (determined using a radioimmunoassay kit [Pharmacia, Uppsala, Sweden]. Insulin resistance was estimated with the homeostasis model assessment (the product of fasting glucose and insulin concentrations in mmol/l divided by 22.5).[25] Body composition variables included BMI (kg/m²) at baseline and assessed via recall

of weight at age 25, abdominal circumference, and visceral fat (estimated with CT scans between fourth and fifth lumbar vertebrae).[26] Inflammatory markers considered were IL-6 and CRP (measured in duplicate from overnight fasting serum by an enzyme-linked immunosorbent assay kit from R&D Systems [Minneapolis, MN]).

Statistical analysis

Characteristics of women were evaluated according to parity group using chi square tests or ANOVA. Visceral fat, pulse wave velocity, HOMA, triglycerides and inflammatory markers were log-transformed prior to analysis to achieve normality; results are presented as geometric means. Logistic regression was used to determine the association between CVD status and parity with and without a history of pregnancy complications. Nulliparous women were the referent group. The models were adjusted *a priori* for age and race; other covariates were considered confounders if they changed the beta coefficient associated with parity status by more than 10%. Covariates considered included low socioeconomic status, young maternal age, smoking status, HDL cholesterol, total cholesterol, use of statins, hypertension, diabetes, glucose, insulin resistance, pulse wave velocity, and inflammatory markers

Results

Of the 540 women studied, 89 (16.5%) reported no births, and 321 parous women (59.4%) reported no history of pregnancy complications of interest in this study. A total of 130 parous women (24.1%) reported at least one pregnancy complicated by preeclampsia or hypertension (n=32), term low birth weight (n=68), preterm birth (n=64), or stillbirth (n=9). There were 35 women who reported two or more affected births.

Parous women with no perinatal complications were younger and, as expected, were more likely to be married compared to nulliparous women (Table 1). They also tended to have lower rates of lifetime smoking and were less likely to be obese compared to nulliparous women although there appeared to be a u-shaped relation between obesity and parity. Vascular stiffness and rates of hypertension decreased modestly as parity increased among this group. Total cholesterol and LDL cholesterol also tended to decrease with increasing parity. Statin use, however, increased 3 to 4 fold as parity increased among women with no perinatal complications.

Many of these trends were similar among women with at least one perinatal complication. In contrast to the findings in women with uncomplicated births, rates of the metabolic syndrome tended to increase as parity increased among this group. HDL cholesterol decreased and triglycerides increased as parity increased, trends that were not significant among women without perinatal complications.

Parous women with and without pregnancy complications had rates of CVD 2.81 and 2.05 times higher than that of nulliparous women, adjusted for age, race and lifetime smoking status (Table 2). After additional adjustment for statin use and HDL cholesterol, parous women without perinatal complications were twice as likely to have CVD (OR 1.95, 95% CI 1.03,3.68) compared to nulliparous women. Parous women with at least one complicated pregnancy had a 2.67-fold increased risk of CVD (95% CI 1.34, 5.33).

When evaluated according to number of births, nulliparous women had the lowest prevalence of CVD (Table 3). Women with 1–2 births had a 2.30-fold (95% CI 1.22,4.34) increased prevalence of CVD, adjusted for age, race, and smoking. This was attenuated to 2.19 (95% CI 1.13, 4.23) after adjustment for statins and HDL, and further attenuated to 2.02 (95% CI 1.04–3.95) when adjusted for perinatal complications. Compared to the nulliparous group, women with 5 or more births had a 2.88-fold (95% CI 1.34, 6.18) higher risk of CVD that was attenuated

to 2.27 (95% CI 1.00,5.15) after accounting for perinatal complications and other covariates. Adjustment for statins and HDL accounted for 10% of the elevated risk in this group, and adjustment for pregnancy complications accounted for 13% of the remaining excess risk.

When analysis was limited to women with no perinatal complications (n=381), estimates associated with parity were similar to those from models that were adjusted for complications. In addition, when perinatal complications were modeled as one vs. ≥2 affected births, estimates associated with parity were similar. Although confidence intervals were wide, there was an association between parity with complications and prevalent (OR 2.40; 95% CI 1.19,4.82) as well as incident CVD (OR 8.1; 95% CI 1.0, 65.0).

Discussion

Our results indicate that almost a quarter of the older women in our study reported a previous experience of at least pregnancy complicated by the conditions of interest. Parous women with no pregnancy complications were twice as likely to have CVD compared to nulliparous women, and those with at least one complicated pregnancy had rates of CVD almost three times higher. High rates of statin use, lower HDL, and pregnancy complications accounted for some but not all of this excess CVD prevalence among parous women.

Parous women in our study with and without pregnancy complications had high percentages of statin therapy compared to nulliparous women, suggesting that dyslipidemia is an important factor relating parity to CVD prevalence. Our results are consistent with the evidence that increased parity is associated with reduced concentrations of HDL cholesterol.[1, 2, 27, 28] In our data, however, this trend was only significant in women with perinatal complications, raising the possibility that an atherogenic phenotype may emerge or be exacerbated in the presence of pregnancy complications. Alternatively, lipid differences may antedate the first pregnancy, thus perhaps affecting fertility as well as the likelihood of complications. A recent study relating greater intake of high fat dairy foods to lower risk of anovulatory infertility supports this possibility.[29] Prospective studies that are designed to evaluate these factors across the life course are needed to explore these possibilities.

We considered that women with five or more live births may be less likely to have poor pregnancy outcomes, as subfertility, preeclampsia, low birth weight and preterm delivery tend to aggregate.[30–32] Our results, however, indicated that this is not the case. The presence of perinatal complications increased as parity increased such that 40% of women with 5 or more births reported perinatal complications. However, presence of an affected pregnancy accounted for only 13% of the relationship between high parity and CVD. To our knowledge, there are no previous reports of the lifetime prevalence of adverse pregnancy events across a woman's reproductive history, nor are there studies of how these cumulative exposures may be related to chronic disease risk. We could not evaluate the temporal relation between pregnancy complications, subsequent pregnancy risks, and CVD risk and future longitudinal studies are needed to discern these relationships.

Our finding that nulliparous women had the lowest risk of CVD is consistent with some[2–5] but not all studies.[1, 6, 7] Hannaford, et al reported that nulliparous women had a higher prevalence of hypertension later in adulthood compared to women with normotensive births. [6] Indeed, nulliparous women in our study were older, tended to be more obese, and had evidence of vascular stiffness and hypertension compared to parous women without perinatal complications. However, they also were much less likely to report statin therapy suggesting a less atherogenic lipid profile. Our results suggest that a variety of biologic and environmental factors across a woman's life, including her reproductive history, combine in complex ways to affect her lifelong risk for survival to age 80 free of CVD. Our results also suggest the possibility of a u-shaped relationship between parity and CVD, such that women with 1–2

births had a higher prevalence compared to women with 3–4 births. Women with 5 or more births had highest CVD prevalence. We had limited power to study this possibility directly, although this warrants further study in larger cohorts.

While we accounted for a variety of biologic and socio-economic factors that may confound the relationship between parity and CVD, we cannot rule out the possibility that unmeasured factors could explain our findings. For example, that the majority of nulliparous women in our study were married raises the possibility that infertility, which itself is a heterogenous phenomenon, confounded our results. However, evidence is conflicting regarding the relationship between characteristics associated with subfertility and CVD status,[33, 34] and therefore this may not be an important confounder.

Our results should be considered in light of several limitations. Our sample size was modest and this limited the precision of our estimates and precluded investigation of what might be meaningful interactions between parity and pregnancy complications. Because pregnancy data were collected via recall, our exposure variables are subject to misclassification. Mothers have, however, been found to reliably recall certain pregnancy characteristics many years post partum and we confirmed the validity and reliability of the recall in our study population.[18] Recall has been reported as most precise for first births and small babies[18, 19] which represent the majority of births with perinatal complications included in our study. Nonetheless, assuming the presence of misclassification, it is unlikely that women would systematically over or under report preterm or infant birth weight based on cardiovascular disease status so the impact of recall bias would likely be that our observed associations were attenuated. While it is possible that women may report hypertensive complications of pregnancy differentially based on presence of hypertension in older adulthood, the fact that hypertension was highly prevalent at study baseline (63%) but cases of hypertension during pregnancy were quite small (3.3%) makes it unlikely that this was reported with bias. In addition, nulliparous women were those with no pregnancies lasting more than 6 months, and therefore pregnancy losses < 6 months could have occurred and these may be related to CVD risk. We were unable to study this possibility. Community dwelling, well-functioning women who survive to late old age with reasonable cognitive function are healthier than the general population, and our study should be replicated among a younger cohort of women to determine the direction of this survivor bias. We would expect, however, that survival bias would lead to an underestimation of the true effect of reproductive factors on maternal health as excess CVD mortality following pregnancy complications has been detected among relatively young women.[13–15, 35] In addition, women in our study had their births prior to systematic screening for gestational diabetes, and therefore we could not assess the relation between this pregnancy complication and CVD risk. We also were limited to body composition assessed in old age, and it could be that body size earlier in life is more relevant to future CVD risk. We did assess BMI at age 25 based on recall of weight, but this factor did not change our results.

There are several strengths to our study. We were able to examine extensive physical and biologic variables associated with cardiovascular disease and parity. The prevalence of pregnancy complications as well as cardiovascular disease among Black women are about twice that of White women, and ours is the first study to our knowledge to examine parity and CVD risk in a racially diverse cohort. Interestingly, our results indicated that the rate of CVD related to parity was similar in Black and White women, although we cannot rule out the possibility that Black women at highest risk of CVD may not be part of our study because of death or disability. We also were able to evaluate the cumulative effect of reproductive exposures across a woman's life.

Our results suggest even after accounting for pregnancy complications, parous women had increased prevalence of CVD at age 80 compared to nulliparous women. These findings held

even after accounting for the fact that nulliparous women were older, tended to be heavier, smoked more, and had evidence of vascular stiffness. In contrast, parous women without perinatal complications had high percentages of statin therapy. Among women with perinatal complications, this trend was accompanied by lower HDL and higher triglyceride concentrations among women with five or more births. Our results indicate that dyslipidemia and pregnancy complications account for some but not all of the excess CVD prevalence among older, parous women.

Acknowledgements

Abbreviations

CVD

Cardiovascular disease

HDL

high density lipoproteins

CRP

C-reactive protein

IL-6

interleukin-6

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Table 1

Maternal characteristics according to parity status, evaluated by presence of at least one pregnancy complication (mean [SD] or percent)

	Nulliparous 0 births (n=89)	No complicated births (n=321)				≥1 complicated birth (n=130)			
		1–2 births (n=151)	3–4 births (n=132)	≥5 births (n=38)	p trend*	1–2 births (n=43)	3–4 births (n=62)	≥5 births (n=25)	p trend*
Maternal characteristics									
Maternal age at baseline (years)	74.3 (2.7)	73.5 (2.9)	72.6 (2.7)	73.4 (2.9)	0.01	72.7 (2.4)	72.9 (2.7)	73.0 (2.9)	0.08
Married (%)	65.1	99.2	99.1	97.1	<0.01	97.5	98.0	100.0	<0.01
Black race (%)	51.7	41.7	37.1	55.3	0.45	55.8	50.0	44.0	0.55
< High school education (%)	15.7	16.6	10.6	34.2	0.31	11.6	11.3	16.0	0.69
Low SES (%)	20.2	13.9	9.1	31.6	0.97	14.3	17.7	4.4	0.16
Ever smoked (%)	52.8	47.7	33.3	44.7	0.02	60.5	45.2	40.0	0.18
Body composition									
BMI at age 25 (kg/m²)	22.6 (3.9)	22.0 (3.0)	21.9 (2.6)	22.0 (2.6)	0.27	21.7 (2.2)	21.9 (3.1)	21.9 (2.2)	0.67
BMI at study baseline (kg/m²)	29.4 (5.9)	28.4 (5.0)	27.6 (5.4)	29.0 (6.0)	0.47	27.1 (4.7)	29.2 (6.6)	28.3 (4.2)	0.93
Obese at baseline (BMI ≥30 kg/m²)	44.9	30.5	23.5	39.5	0.04	26.6	35.5	36.0	0.26
Vascular									
Waist circumference (cm)	98.1 (14.8)	95.9 (13.1)	94.7 (13.6)	95.9 (15.9)	0.32	94.0 (13.5)	99.9 (14.8)	98.3 (23.3)	0.42
Visceral fat (cm.)	109.9 (64)	114.1 (63)	113.3 (56.9)	108.4 (51.5)	0.73	99.7 (45.9)	120.3 (57.4)	110.3 (78.2)	0.44
Systolic BP (mmHg.)	140.4 (18.7)	137.8 (19.7)	136.5 (21.8)	137.9 (19.3)	0.43	140.4 (23.0)	138.4 (22.4)	142.7 (21.3)	0.81
Diastolic BP (mmHg)	74.6 (10.4)	71.9 (10.6)	71.9 (9.7)	73.2 (9.3)	0.48	73.9 (11.8)	71.8 (8.8)	73.8 (9.9)	0.45
Pulse wave velocity (cm/sec)	854 (490)	788 (446)	721 (322)	780 (385)	0.09	693 (222)	796 (444)	906 (718)	0.25
Hypertension (%)	69.7	63.6	59.9	57.9	0.11	67.4	59.7	76	0.74
Metabolic									
Diabetes (%)	13.6	6.6	7.6	21.6	0.65	7.0	6.6	16.0	0.61
Metabolic syndrome (%)	35.6	42.7	35.9	39.5	0.96	39.5	38.7	64.0	0.05
Insulin resistance (HOMA)†	1.67 (1.16)	1.73 (1.4)	1.42 (1.8)	1.57 (1.6)	0.23	1.63 (1.2)	1.91 (2.6)	1.61 (1.2)	0.85
Cholesterol (mg/dl)	225.1 (43.4)	225.0 (38.4)	214.6 (37.9)	213.4 (36.0)	0.04	220.7 (36.2)	214.9 (43.0)	215.7 (36.9)	0.23
HDL-C (mg/dl)	64.8 (18.7)	58.7 (17.1)	62.2 (18.2)	59.3 (12.3)	0.29	63.9 (18.2)	62.6 (19.2)	53.0 (13.1)	<0.01
LDL-C (mg/dl)	134.3 (36.9)	137.0 (35.0)	125.3 (34.7)	125.6 (32.9)	0.04	130.5 (37.6)	124.2 (38.6)	124.1 (30.1)	0.16
Triglycerides (mg/dl)	118.5 (57.8)	144.2 (70.1)	135.9 (68.1)	142.3 (75.5)	0.55	131.0 (61.5)	140.2 (63.9)	195.6 (128.8)	<0.01
Statin use (%)	6.8	19.9	18.2	27.0	0.01	20.9	19.4	24.0	0.01
Inflammatory									
IL-6 (pg/ml)	1.80 (1.64)	1.83 (2.3)	1.81 (1.6)	2.05 (2.4)	0.39	1.83 (1.9)	1.81 (1.6)	2.05 (1.4)	0.39
CRP (pg/ml)	1.77 (5.67)	1.89 (6.7)	2.01 (2.9)	2.14 (2.4)	0.18	2.54 (4.6)	2.16 (3.8)	1.54 (4.1)	0.31

*
Trend evaluated separately according to presence of ≥1 adverse outcome, with nulliparous women (parity=0) as the baseline for each group

†
Non-diabetics

Table 2

Prevalence of cardiovascular disease, according to parity status and presence of ≥1 pregnancy complication (preeclampsia, low birth weight, preterm birth or stillbirth)

	CVD (%)	Crude OR	Adjusted for age and race OR (95% CI)	Adjusted for age, race, and smoking OR (95% CI)	Adjusted for age, race, smoking, statins, and HDL OR (95% CI)
Nulliparous (n=89)	18	1.0	1.0	1.0	1.0
Parous, no pregnancy complications (n=321)	27.7	1.75	1.95 (1.06–3.58)	2.05 (1.11,3.77)	1.95 (1.03,3.68)
Parous, ≥1 pregnancy complication (n=130)	36.2	2.58	2.74 (1.41,5.32)	2.81 (1.45,5.48)	2.67 (1.34,5.33)

Table 3

Presence of cardiovascular disease, according to parity group and presence of ≥1 pregnancy complication (preeclampsia, low birth weight, preterm birth, or stillbirth)

Parity	N	CVD (%)	≥1 pregnancy complication (%)	Model 1: Adjusted for age, race and smoking OR (95% CI)	Model 2: Additional adjustment for statins and HDL OR (95% CI)	Model 3: Additional Adjustment for ≥1 adverse outcome OR (95% CI)[*]	% change [†]
0	89	18.8		1.0	1.0	1.0	
1–2	194	31.4	22.2	2.30 (1.22,4.34)	2.19 (1.13,4.23)	2.02 (1.04,3.95)	8%
3–4	194	28.6	32.0	2.00 (1.04,3.84)	1.95 (0.99,3.84)	1.74 (0.86,3.49)	11%
≥5	63	36.5	39.7	2.88 (1.34,6.18)	2.60 (1.17,5.76)	2.27 (1.00,5.15)	13%

[*] Adjusted for age, race, presence of ≥1 adverse outcome, statin use, smoking, HDL cholesterol

[†] Percent change in odds ratio, Model 2 compared to Model 3