Childbearing, Child-Rearing, Cardiovascular Risk Factors, and Progression of Carotid Intima-Media Thickness
The Cardiovascular Risk in Young Finns Study

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Background and Purpose—Parity is associated with the risk of clinical cardiovascular events and the severity of preclinical atherosclerosis in older subjects. We sought to determine whether childbearing is associated with concurrent changes in cardiovascular risk factors and the progression of carotid intima-media thickness.

Methods—We examined the association between the number of children born during a 6-year period and concurrent changes in cardiovascular risk factors and progression of carotid intima-media thickness in men and women of reproductive age from the Cardiovascular Risk in Young Finns study. Complete data for parity and carotid intima-media thickness were available for 1786 subjects (1005 females, 781 males).

Results—For females, childbirth during the 6-year follow-up was associated with concurrent reductions in high-density lipoprotein cholesterol (Ptrend<0.0001), apolipoprotein A-I (Ptrend<0.0001), and apolipoprotein B (Ptrend=0.01); a redistribution of adiposity to abdominal deposits; and increased progression of carotid intima-media thickness (7.5±3.2 μm/birth [mean±SEM], P=0.02). The association of childbirth with carotid intima-media thickness progression was not greatly modified by adjustment for concurrent changes in cardiovascular risk factors (fully adjusted: P=0.05). This association was significantly stronger in females than males (P_heterogeneity=0.001), who served as a control group exposed to the social and lifestyle influences of child-rearing but not the biological influences of childbearing.

Conclusions—The progression of carotid atherosclerosis over a 6-year period is increased in females who gave birth during the same period, independent of traditional risk factors. Mechanisms that underlie this observation possibly include parity-induced changes in nontraditional risk factors or an acute influence of pregnancy itself. (Stroke. 2010;41:1332-1337.)

Key Words: atherosclerosis ■ intima-media thickness ■ parity ■ sex

The identification of risk factors and risk markers is a major ongoing challenge for the prevention of cardiovascular disease. Parity, the number of times a woman has given birth, is associated with the risk of both incident stroke and coronary heart disease1–3 and severity of preclinical atherosclerosis.4–6 This association appears to be partially modified by changes in lifestyle and socioeconomic status associated with child-rearing2,3 and changes in cardiovascular risk profile that persist indefinitely after the pregnancy, including an increased prevalence of overweight and obesity.2–4 Nonetheless, the association between parity and cardiovascular disease in females appears to remain, albeit weakened, after adjustment for lifestyle and cardiovascular risk factors.1–6

The possibility that pregnancy may drive a rapid progression of atherosclerosis is one potential explanation for the association of parity with cardiovascular disease. This may be driven by perigestational factors such as acute elevations in lipids, insulin resistance, oxidative stress, and inflammation or may be related to the changes in sex steroids or hemodilution.7,8

To study whether pregnancy is associated with the progression of atherosclerosis, we examined the association between the number of children born during a 6-year period and the concurrent progression of carotid intima-media thickness (cIMT) in women of a reproductive age from the Cardiovascular Risk in Young Finns study. We also studied males from the same cohort as a control group exposed to child-rearing...
but not childbearing, allowing us to differentiate the effects of changes in risk behaviors and lifestyle factors that accompany child-rearing from the biological influences of childbearing.\textsuperscript{9}

Additionally, we took the opportunity to describe the changes in cardiovascular risk factors that associate with childbirth, because these may also influence the rate of cIMT progression in both the short and long term.

As such, this study provides evidence of whether childbearing increases the severity of atherosclerosis independent of concurrent changes in traditional cardiovascular risk factors.

Materials and Methods

Population

The Cardiovascular Risk in Young Finns Study is an ongoing epidemiological study of atherosclerosis risk factors from childhood to adulthood. In 1980, children and adolescents aged 3 to 18 years were invited to participate (n=3596). The study was carried out in all 5 Finnish university cities with medical schools (Helsinki, Kuopio, Oulu, Tampere, Turku) and their rural surroundings with subjects chosen randomly from the national population register from these areas. Details of the study design have been presented elsewhere.\textsuperscript{10}

The 21-year and 27-year follow-up visits were undertaken in 2001 and 2007 (n=2265 and n=2197, respectively). Participants who had missing cIMT data from 2001 or 2007 were excluded from this analysis. Complete data for both parity and cIMT were available for 1796 subjects. Ten subjects with decreases in the number of children during the follow-up were excluded, resulting in 1786 participants included in these analyses.

The study was approved by local ethics committees, and subjects gave written informed consent.

Carotid Intima-Media Thickness

Ultrasound studies to measure cIMT were performed as previously reported.\textsuperscript{11,12} Briefly, high-resolution ultrasound images were obtained of the left common carotid artery in longitudinal section, and cIMT was measured in a segment of the posterior wall of the artery approximately 1 cm proximal to the bifurcation by a single observer blinded to subjects’ clinical characteristics. The mean of at least 4 measures (mean cIMT) and the maximum single measure (maximum cIMT) were used in these analyses. This technique has previously been demonstrated to have a high degree of reproducibility in our laboratory.\textsuperscript{11}

Assessment of Socioeconomic, Lifestyle, and Cardiovascular Risk Factors

Height, weight, and waist circumference were measured and body mass index (BMI) calculated. Blood pressure was measured using a random zero sphygmomanometer; the average of 3 measurements was used in the analysis. Venous blood samples were drawn after an overnight fast with serum samples stored at \(-70^\circ\text{C}\) until analysis. Serum lipids were measured in duplicate using standard enzymatic methods, low-density lipoprotein cholesterol (LDL-C) concentration was calculated,\textsuperscript{13} apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) were analyzed immunoturbidimetrically (Orion Diagnostics), high-sensitive C-reactive protein (hsCRP) was analyzed by latex turbidimetric immunomassay (Wako Chemicals), glucose concentrations were measured enzymatically (Olympus), and serum insulin was measured by microparticle enzyme immunoassay (Abbott Diagnostics).\textsuperscript{14} Insulin resistance was calculated using the homeostasis model assessment.\textsuperscript{15}

A self-administered questionnaire was used to determine the number of children, employment and marital status, medical history (including use of oral contraception), and smoking status. Employment status was categorized as manual, lower-grade nonmanual, and higher-grade nonmanual. Smoking status was dichotomized as those who smoke on a daily basis and those who do not smoke or smoke less frequently than daily.

Statistical Analyses

Differences between groups in cardiovascular risk factors (entered as the dependent variable in separate models) were determined by multivariable analysis of covariance for continuous variables and logistic regression for dichotomous variables. The association between parity and the progression of cIMT was examined using multivariable linear regression; results are presented as unstandardized \(\beta\)-coefficient (SE). Statistical analyses were performed using SPSS software (Version 17.0; SPSS, Chicago, Ill). Statistical significance was inferred at \(P<0.05\).

Results

Participant characteristics for the baseline visit (2001) are displayed in Table 1 stratified by sex and number of children born from 2001 to 2007. The average number of children born during the 6-year follow-up was 0.45 (SD 0.75) and 0.51 (SD 0.77) for females and males, respectively.

Parity and Cardiovascular Risk Factors During 6-Year Follow-Up

The associations between the number of children born during the 6-year follow-up period and concurrent changes in cardiovascular risk factors are shown in Table 2.

For females, increasing parity during the follow-up period was associated with reductions in high-density lipoprotein cholesterol (HDL-C), apoA-I, and apoB. Furthermore, concurrent childbirth was directly associated with increases in the LDL:HDL ratio (\(P_{\text{trend}}=0.02\), adjusted as per Table 2). There was some evidence for a direct association between childbirth and increasing waist circumference among females despite a weak, non-statistically significant inverse association with the change in BMI. We further explored these contrasting associations by examining the association between the number of children born and changes in waist circumference adjusted for the change in BMI. Childbirth was highly significant in this model (\(P_{\text{trend}}<0.0001\)), suggesting a redistribution of adipose tissue depots to a phenotype characterized by abdominal adiposity.

The inverse association between the number of children born and concurrent change in apoA-I during the 6-year follow-up period was also seen for males, although this was weaker than for females.

Use of an interaction term (“number of children born”\*sex) indicated that statistically significant sex differences were present for the association between the number of children born and concurrent changes in LDL-C, HDL-C, apoB, and apoA-I (LDL-C: \(P_{\text{heterogeneity}}=0.01\); HDL-C: \(P_{\text{heterogeneity}}=0.0004\); apoB: \(P_{\text{heterogeneity}}=0.05\); apoA-I: \(P_{\text{heterogeneity}}=0.001\); \(P_{\text{heterogeneity}}>0.10\) for all other comparisons; adjusted as per Table 2).

Parity and cIMT: Cross-Sectional Analyses in 2001

In cross-sectional analyses of the 2001 visit, there was a weak, nonstatistically significant direct association in females between the number of children and cIMT (no children: 0.567 mm; 1 child: 0.569 mm; 2 children: 0.575 mm; \(\geq3\) children: 0.577 mm; \(P_{\text{trend}}=0.22\), adjusted for age, marital status, and employment status). For males, there was no evidence for a linear trend between increasing number of children and cIMT (no children: 0.587 mm; 1 child: 0.608 mm; 2 children: 0.588 mm; \(\geq3\) children: 0.587 mm; \(P_{\text{trend}}=0.87\), adjusted for age, marital status, and employment status).
Table 1. Baseline Participant Characteristics Stratified by Sex and No. of Children Born During the Subsequent 6-Year Period (2001 to 2007)

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Children Born:</td>
<td>1 Child Born:</td>
<td>≥2 Children Born:</td>
<td>0 Children Born:</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>32.9 (0.2)</td>
<td>30.4 (0.3)</td>
<td>28.3 (0.3)</td>
<td>32.9 (0.2)</td>
</tr>
<tr>
<td><strong>Smoking, %</strong></td>
<td>19.5</td>
<td>13.5</td>
<td>15.6</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>24.4 (0.2)</td>
<td>24.5 (0.3)</td>
<td>24.0 (0.4)</td>
<td>25.7 (0.2)</td>
</tr>
<tr>
<td><strong>Waist, cm</strong></td>
<td>79.0 (0.4)</td>
<td>78.9 (0.8)</td>
<td>78.7 (1.1)</td>
<td>88.9 (0.5)</td>
</tr>
<tr>
<td><strong>SBP, mm Hg</strong></td>
<td>112.5 (0.5)</td>
<td>112.5 (0.8)</td>
<td>109.4 (1.2)</td>
<td>120.9 (0.6)</td>
</tr>
<tr>
<td><strong>DBP, mm Hg</strong></td>
<td>68.9 (0.4)</td>
<td>68.5 (0.7)</td>
<td>66.1 (1.0)</td>
<td>73.1 (0.5)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>1.39 (0.01)</td>
<td>1.44 (0.02)</td>
<td>1.45 (0.03)</td>
<td>1.14 (0.01)</td>
</tr>
<tr>
<td><strong>SBP indicates systolic blood pressure; DBP, diastolic blood pressure.</strong></td>
<td></td>
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</tbody>
</table>

Table 2. No. of Children Born and Concurrent Changes in Cardiovascular Risk Factors From 2001 to 2007 Stratified by Sex

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Children Born:</td>
<td>1 Child Born:</td>
<td>≥2 Children Born:</td>
<td>0 Children Born:</td>
</tr>
<tr>
<td><strong>HDL-C, mmol/L</strong></td>
<td>0.08 (0.01)</td>
<td>0.01 (0.02)</td>
<td>0.01 (0.02)</td>
<td>0.08 (0.01)</td>
</tr>
<tr>
<td><strong>LDL-C, mmol/L</strong></td>
<td>24.4 (0.2)</td>
<td>24.5 (0.3)</td>
<td>24.0 (0.4)</td>
<td>25.7 (0.2)</td>
</tr>
<tr>
<td><strong>DBP, mm Hg</strong></td>
<td>79.0 (0.4)</td>
<td>78.9 (0.8)</td>
<td>78.7 (1.1)</td>
<td>88.9 (0.5)</td>
</tr>
<tr>
<td><strong>SBP, mm Hg</strong></td>
<td>112.5 (0.5)</td>
<td>112.5 (0.8)</td>
<td>109.4 (1.2)</td>
<td>120.9 (0.6)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>1.39 (0.01)</td>
<td>1.44 (0.02)</td>
<td>1.45 (0.03)</td>
<td>1.14 (0.01)</td>
</tr>
<tr>
<td><strong>SBP indicates systolic blood pressure; DBP, diastolic blood pressure.</strong></td>
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</table>

Parity and cIMT: Changes During 6-Year Follow-Up
From 2001 to 2007, mean cIMT increased by an average of 6.7 μm/year (SD 13.2) and maximum cIMT by 5.7 μm/year (SD 14.2) for females, whereas in males, the mean cIMT increased by 8.9 μm/year (SD 14.9) and maximum cIMT by 7.5 μm/year (SD 16.1).

The number of children in 2001 was not associated with the progression of cIMT during the subsequent 6-year period in either females or males (females: β [SE]=0.4 [2.2], P=0.85; males: β [SE]=3.7 [3.0], P=0.22; for mean cIMT adjusted for age, IMT at baseline, employment status, and marital status).

Among females, the number of children born from 2001 to 2007 was directly associated with cIMT progression during the same period such that mean cIMT increased by 7.5±3.2 μm per child born and maximum cIMT by 5.7±1.6 μm per child born.
Table 3. No. of Children Born and Concurrent Change in cIMT From 2001 to 2007 Adjusted for Cardiovascular Risk Factors and Stratified by Sex

<table>
<thead>
<tr>
<th>Model</th>
<th>No. of children born</th>
<th>0 children born</th>
<th>1 child born</th>
<th>2+ children born</th>
<th>Linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females: Model 1</td>
<td>7.5 (3.2)</td>
<td>0.0 (referent)</td>
<td>11.3 (5.6)</td>
<td>12.9 (7.7)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>8.3 (3.4)</td>
<td>0.04</td>
<td>11.4 (6.1)</td>
<td>14.6 (8.3)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0 (referent)</td>
<td>0.0 (referent)</td>
<td>0.0 (referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0 (referent)</td>
<td>9.9 (6.2)</td>
<td>11.0 (8.4)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>6.4 (3.3)</td>
<td>0.08</td>
<td>7.1 (4.2)</td>
<td>10.1 (5.7)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.13</td>
<td>6.0 (4.5)</td>
<td>9.2 (8.4)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>0 children born</td>
<td>0.0 (referent)</td>
<td>0.0 (referent)</td>
<td>0.0 (referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 children born</td>
<td>0.0 (referent)</td>
<td>7.2 (7.4)</td>
<td>17.4 (9.7)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>0 children born</td>
<td>0.33</td>
<td>6.7 (8.1)</td>
<td>16.7 (10.6)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>0 children born</td>
<td>0.06</td>
<td>6.5 (4.6)</td>
<td>18.2 (9.9)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>0 children born</td>
<td>0.04</td>
<td>6.0 (4.5)</td>
<td>16.8 (10.8)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are regression coefficients for change in cIMT (expressed in micrometers).

Model 1: Adjusted for age, no. of children at baseline, cIMT at baseline, employment status, marital status, and baseline cardiovascular risk factors (BMI, LDL-C, HDL-C, triglycerides [natural logarithm transformed], glucose [natural logarithm transformed], systolic blood pressure, hsCRP [natural logarithm transformed], smoking status). Females: n=958; males: n=756.

Model 2: Adjusted as per model 1, with additional adjustment for change in risk factors (BMI, LDL-C, HDL-C, triglycerides, glucose, systolic blood pressure, hsCRP, smoking status) from 2001 to 2007. Females: n=958; males: n=728.

Discussion

We found that the number of times a woman gives birth during a 6-year period is directly associated with the concurrent progression of cIMT. The increase in cIMT per child born was 7 μm, which is similar in magnitude to the observed increase in cIMT per year for females in this cohort. The magnitude of this observed annual increase in cIMT is consistent with studies demonstrating that older subjects at risk of stroke have markedly greater cIMT (often ≥1 mm) than that observed among the relatively young participants in this study.

Childbirth also modified cardiovascular risk factors, most notably a redistribution of body fat to a phenotype characterized by increased abdominal adiposity and marked reductions in HDL-C and apoA-I. However, the association between childbirth and concurrent changes in cIMT was independent of traditional cardiovascular risk factors.

Childbirth and Cardiovascular Risk Profile

Our findings are consistent with previous studies that have reported associations of parity with higher BMI, higher prevalence of obesity, abdominal obesity, reduced HDL-C, and raised triglycerides. The majority of these studies have been limited to cross-sectional assessment of parity; however, there is some evidence from longitudinal studies showing similar parity-associated concurrent reduc-
tions in HDL-C and increases in adiposity. However, none of these longitudinal studies have assessed concurrent progression of cIMT or other measures of atherosclerosis nor included males in their analyses, which allows for differentiation between the roles of child-rearing and childbearing. To our knowledge, our study is the first to report on the associations between parity and concurrent changes in apoB and apoA-I. It is likely that the long-term changes in the cardiovascular risk profile, in particular the reduction in HDL-C, will associate with continued gradual increases in atherosclerosis over time, consistent with previously reported associations in older subjects.

Childbirth and cIMT Progression: Other Potential Mechanisms

In addition to these long-term changes in risk profile, it is possible that part of the association of childbirth with augmented cIMT progression is due to the direct result of the biological burden of childbearing (Figure 2). Atherosclerosis is a gradual process, the progression of which is influenced by the severity of risk factors and the duration of exposure. It is plausible that childbearing is accompanied by an increased rate of progression of atherosclerosis during the perigestational period, which is strongly supported by the relatively short time period between cIMT measurements. Potential mechanisms underlying a direct biological effect of pregnancy on atherosclerosis may include the transient hemodilution of pregnancy or increases of lipids, insulin resistance, oxidative stress, sex steroids, and inflammation during pregnancy. In contrast, endothelial function is improved and asymmetrical dimethylarginine decreased during pregnancy, both of which would be expected to slow the progression of atherosclerosis.

Childbearing or Child-Rearing: Insights Derived From Males

We included males in this study as a control group exposed to the changes in risk behavior and social and lifestyle influences of raising a child, but not the physical influences of pregnancy. In men, there was an inverse association between the number of children born and the concurrent change in cIMT in direct contrast to the direct association in women. As such, our results suggest that having children has short-term atheroprotective benefits for males, putatively through social and lifestyle factors. If these benefits carry true for females, this would indicate that the magnitude of the detrimental influences of childbearing is greater than otherwise indicated by the study of females alone. Indeed, there was strong evidence for heterogeneity between the sexes for the association of the number of children born during the follow-up period and the concurrent progression of cIMT, which in theory reflects the strength of the association between childbearing and cIMT progression after accounting for the influences of child-rearing. Nonetheless, we cannot preclude a role for other socioeconomic or lifestyle factors that were unaccounted for in our analyses or which differ between males and females. To our knowledge, the mechanisms of the putative short-term vascular benefits conferred by parity in males have not previously been investigated and warrant being addressed in future studies.

Implications for Risk Prediction and Prevention Strategies

This research highlights the influence of childbearing on the progression of atherosclerosis and thus the potential importance of parity as a cardiovascular risk factor for females. Evidence is required from studies that specifically address the usefulness of parity in risk prediction algorithms, especially given that the association with cIMT progression was independent of traditional risk factors and also whether treatment of high-risk patients identified using such equations that incorporate parity is effective in reducing event rates for cardiovascular disease.

Investigation of prevention strategies implemented during or soon after pregnancy may also be warranted. These could target either the proposed effect of childbearing on cardiovascular health, the mechanisms of which remain unknown, or the parity-associated changes in cardiovascular risk factors. Perhaps the easiest of these to identify and target would be pregnancy-associated changes in adiposity, the prevention of which may have subsequent flow-through effects on lipids and vascular health.

Study Limitations

The limitations of the cohort itself have been discussed elsewhere in detail. Serial measures of cIMT and cardiovascular risk factors directly before, during, and directly after pregnancy.
and lactation would provide greater insight on the dynamic influence of childbearing on cardiovascular risk factors and atherosclerosis. The study of the male partners of the female participants in this cohort would perhaps have provided a more suitable control group than the males used in this study, who were randomly selected from the population register in 1980. Furthermore, we were unable to include in our analysis other factors that potentially underlie the observed association between childbirth and cIMT progression, including complications of pregnancy such as pre-eclampsia and gestational diabetes and psychological factors such as depression and anxiety.

**Summary**

Our findings indicate that cIMT progression over a 6-year period is augmented in females who gave birth during the same period, thus providing evidence that childbearing can have a rapid influence on the progression of atherosclerosis. This is only partially mediated by changes in cardiovascular risk factors suggesting that some proportion of the association is due to unidentified mechanisms, possibly including a short-term influence of pregnancy itself.

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**Disclosures**

None.

**References**


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**Childbearing and Progression of Carotid IMT**

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