Hyperlipidemia in Early Adulthood Increases Long-Term Risk of Coronary Heart Disease

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Background—Many young adults with moderate hyperlipidemia do not meet statin treatment criteria under the new American Heart Association/American College of Cardiology cholesterol guidelines because they focus on 10-year cardiovascular risk. We evaluated the association between years of exposure to hypercholesterolemia in early adulthood and future coronary heart disease (CHD) risk.

Methods and Results—We examined Framingham Offspring Cohort data to identify adults without incident cardiovascular disease to 55 years of age (n=1478), and explored the association between duration of moderate hyperlipidemia (non–high-density lipoprotein cholesterol≥160 mg/dL) in early adulthood and subsequent CHD. At median 15-year follow-up, CHD rates were significantly elevated among adults with prolonged hyperlipidemia exposure by 55 years of age: 4.4% for those with no exposure, 8.1% for those with 1 to 10 years of exposure, and 16.5% for those with 11 to 20 years of exposure (P<0.001); this association persisted after adjustment for other cardiac risk factors including non–high-density lipoprotein cholesterol at 55 years of age (hazard ratio, 1.39; 95% confidence interval, 1.05–1.85 per decade of hyperlipidemia). Overall, 85% of young adults with prolonged hyperlipidemia would not have been recommended for statin therapy at 40 years of age under current national guidelines. However, among those not considered statin therapy candidates at 55 years of age, there remained a significant association between cumulative exposure to hyperlipidemia in young adulthood and subsequent CHD risk (adjusted hazard ratio, 1.67; 95% confidence interval, 1.06–2.64).

Conclusions—Cumulative exposure to hyperlipidemia in young adulthood increases the subsequent risk of CHD in a dose-dependent fashion. Adults with prolonged exposure to even moderate elevations in non–high-density lipoprotein cholesterol have elevated risk for future CHD and may benefit from more aggressive primary prevention. 

Key Words: coronary disease ■ hyperlipidemias ■ risk

Hyperlipidemia is a potent risk factor for atherosclerosis and coronary heart disease (CHD) and is present in a substantial proportion of young adults. According to data from the National Health and Nutrition Examination Survey, 11.7% of adults aged 20 to 39 and 41.2% of adults aged 40 to 64 had elevated low-density lipoprotein cholesterol (LDL-C) levels, but only 10.6% of adults aged 20 to 39 and 47.7% of adults age 40 to 64 with hyperlipidemia were receiving treatment.1 The newly released American Heart Association/American College of Cardiology guidelines for the treatment of blood cholesterol for the prevention of cardiovascular disease (CVD) recommend statin therapy for all adults with prevalent CVD, LDL-C ≥190 mg/dL, diabetes mellitus, or 10-year risk of atherosclerotic CVD ≥7.5%, as assessed by the new Pooled Cohort Equations.2 Although CVD events such as myocardial infarction present suddenly, the advanced extensive complex intramural lesions that lead to plaque rupture develop over decades. Because the natural history of atherosclerosis is prolonged, the risk of clinical events rises exponentially late in life. As a result, the new cholesterol guidelines led to a high number of older adults aged ≥60 years to be recommended for statin therapy, with relatively fewer younger adults meeting statin recommendation thresholds.1

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Studies on adults with familial hypercholesterolemia have shown that CVD risk is increased early among those with very high LDL-C levels.3 Similarly, adults with extremely low LDL-C levels conferred by genetic polymorphisms have significantly lower than average risk of CVD.4,5 However, the association between prolonged exposure to mild to
moderately elevated lipid levels in young adulthood on an individual’s subsequent risk of CHD has not been well described. Therefore, we used the Framingham Offspring Study to address the impact of duration of hyperlipidemia in young adulthood (35–55 years of age) and future risk of CHD beyond 55 years of age.

Methods

Study Design and Sample

Our study examined data on 5124 individuals from the Offspring Cohort of the Framingham Heart Study recruited between 1971 and 1975. To identify participants with sufficient observation time to evaluate both the number of years of exposure to hyperlipidemia, and the person’s future risk of CHD, as well, participants were eligible for inclusion in this analysis if: (1) they had attended Offspring Cohort examination 4 (1987–1991), 5 (1991–1995), or 6 (1995–1998); (2) were between 53 and 57 years of age; and (3) were free of CVD or transient ischemic attack, stroke, CHD death, cardiovascular death, heart failure, or any CHD event. Median follow-up was 15 years.

Outcomes and Exposures

The primary factor of interest was the number of years of exposure to hyperlipidemia in the 20 years before the baseline visit at 55 years of age (eg, number of years of elevated non–high-density lipoprotein cholesterol [HDL-C] between 35 and 55 years of age). Consistent with the lipid measures used in the newest Pooled Cohort Equations, hyperlipidemia in our primary analysis was defined based on non-HDL-C, with levels of ≥160 mg/dL considered elevated. This level is equivalent to the 70th percentile of the American population according to the National Health and Nutrition Examination Survey. Because Framingham Offspring examinations occur approximately every 4 years, we interpolated hyperlipidemic status in the years between the examinations. For individuals who developed hyperlipidemia in the time interval between study visits, we assumed that the date of development was midway between the 2 examinations. For individuals with <20 years of data before baseline, we conservatively assumed that the participant was free of hyperlipidemia for the time period without data. For participants with missing data at any follow-up examination, the value from the previous examination was carried forward.

In sensitivity analyses, we also examined previous obesity of non-HDL-C as a continuous variable. Each person’s average non-HDL-C over the preceding 20 years was calculated, weighted by the number of years between examinations. In addition, LDL-C, rather than non-HDL-C was evaluated by using the number of years with LDL-C ≥130 mg/dL. Because the Friedewald equation was used to calculate LDL-C, adults with triglycerides >400 mg/dL at any time were excluded from the LDL-C analysis.

Statistical Analysis

First, by using the number of years of hyperlipidemia by 55 years of age, adults were stratified into 3 groups: (1) those without hyperlipidemia by 55 years of age; (2) those with 1 to 10 years of hyperlipidemia; and (3) those with 11 to 20 years of hyperlipidemia. Kaplan–Meier survival curves were generated to evaluate the risk of CHD over the subsequent years, and the log-rank test was used to test the overall survival experience.

Cox proportional hazards regression models were used to evaluate the relative risk of increasing the number of years with hyperlipidemia on the onset of CHD events by evaluating the association between the number of years of exposure to hyperlipidemia at 55 years if age as a continuous variable between 0 and 20 and future risk of CHD. To determine to what extent the association between duration of hyperlipidemia and CHD risk could be attributed to a worse overall health state associated with hyperlipidemia, multivariable analyses were performed adjusting for the following standard nonlipid risk factors: age, sex, systolic blood pressure, antihypertensive treatment, HDL-C, diabetes mellitus, and smoking. Next, to determine if the cumulative exposure to hyperlipidemia was a marker for prevalent hyperlipidemia at 55 years of age or if the duration of hyperlipidemia was associated with increased CHD risk independent of lipid levels at that age, baseline (55 years of age) non-HDL-C level was also included in the multivariable analysis. The final multivariable model also included adjustment for lipid-lowering therapy at baseline and over the follow-up period in a time-dependent fashion. Hazard ratios for the association between duration of hyperlipidemia and future CHD risk are presented per 10-year increase.

As secondary analyses, we repeated our primary analysis of association between years of exposure to non-HDL-C ≥160 mg/dL in the sub sample of young adults who would not be specifically recommended for statin therapy under the 2013 American Heart Association/American College of Cardiology guidelines. This excluded adults with 10-year CVD risk ≥7.5%, diabetest mellitus with LDL-C 270 mg/dL, or LDL-C ≥190 mg/dL.

Next, we assessed the proportion of adults who would have been recommended for statin therapy at 40 and 50 years of age under the current guidelines based on diabetes mellitus status, LDL-C, and 10-year CVD risk, stratified by years of exposure to hyperlipidemia (0, 1–10, and 11–20 years of hyperlipidemia). We considered both the ≥7.5% and the ≥5% risk thresholds to determine treatment eligibility per the new guidelines. This analysis was performed to determine the extent to which individuals with prolonged hyperlipidemia would have been identified as treatment candidates by the new guidelines during the period of exposure to hyperlipidemia. Because LDL-C was estimated by using Friedewald’s equation and, therefore, unavailable in adults with triglycerides >400 mg/dL, adults with triglycerides >400 mg/dL were considered statin eligible in the analysis that evaluated statin recommendations.

In sensitivity analysis, we investigated the robustness of our results to the choice of lipid parameter and choice of threshold. First, the association between years of exposure to LDL-C ≥130 mg/dL and future CHD was evaluated by using multivariable Cox proportional hazards modeling. Second, to determine whether the results depend on the 160 mg/dL non-HDL-C threshold, the association between the weighted average non-HDL-C over the previous 20 years and future risk of CHD was evaluated by using restricted cubic splines. Inflection points in the graph, rounded to the nearest 5 mg/dL non-HDL-C threshold, the association between years of exposure to non-HDL-C ≥160 mg/dL, non-HDL-C ≥130 mg/dL, and future CHD risk. Cox proportional hazards modeling was performed evaluating the impact of each 10 mg/dL increase in average previous elevation of non-HDL-C and future risk of CHD, adjusting for the same characteristics at baseline as in the primary analysis (age, sex, systolic blood pressure, antihypertensive treatment, diabetes mellitus, smoking, non-HDL-C, HDL-C, and lipid therapy). Finally, to evaluate the impact of including adults on lipid-lowering therapy at baseline, the primary analyses of the association between years of elevation in non-HDL-C and future CHD risk were repeated excluding adults on lipid-lowering therapy at baseline.

The analysis was approved by the Duke University Institutional Review Board. All Framingham Offspring cohort participants gave informed consent for participation. Statistical analysis was performed by using SAS version 9.3.

Results

Study Population

Characteristics of the study sample at baseline are presented in Table 1. A total of 124 individuals in the cohort developed...
CVD before 55 years of age and were not included in our sample. The final sample included 1478 adults free of CVD at baseline with 0 to 20 years of hyperlipidemia. Of these, 512 adults did not have hyperlipidemia, 389 adults had 1 to 10 years of hyperlipidemia, and 577 adults had 11 to 20 years of hyperlipidemia exposure by baseline age. Individuals with hyperlipidemia at baseline were more likely to be diabetic, male, and smokers, and had higher systolic blood pressure, body mass index, total cholesterol levels, and lower HDL-C levels than those without hyperlipidemia. Only 85 patients overall (5.8%) were on lipid-lowering treatment at the baseline visit.

**Years of Hyperlipidemia and Risk of CHD**

During follow-up, 155 individuals developed new-onset CHD, with 136 events by median follow-up of 15 years. Figure 1 presents Kaplan–Meier CHD event rates from baseline up to 15 years of follow-up among patients stratified by the number of years of hyperlipidemia at baseline. A dose-response pattern is seen, with progressively increasing risk of CHD as the number of years of exposure to hyperlipidemia increases (log-rank test \( P<0.0001 \)). At 15 years, adults with 11 to 20 years of hyperlipidemia at baseline had an overall CHD risk of 16.5% (95% confidence interval [CI], 13.5%–19.9%), in comparison with 8.1% (95% CI, 5.5%–11.7%) for adults with 1 to 10 years of hyperlipidemia, and 4.4% (95% CI, 2.9%–6.6%) for those without hyperlipidemia at baseline.

The unadjusted risk of CHD doubled for every 10 years of exposure to hyperlipidemia (Table 2, univariable hazard ratio [HR], 2.0; 95% CI, 1.63–2.45 per decade of hyperlipidemia); this association was attenuated, but remained statistically significant after adjusting for other standard risk factors including sex, age, systolic blood pressure, antihypertensive therapy, smoking status, HDL-C, and diabetes mellitus (adjusted HR, 1.49; 95% CI, 1.20–1.87 per decade of hyperlipidemia). In addition, the association remained statistically significant after also adjusting for non-HDL-C at baseline (adjusted HR, 1.39; 95% CI, 1.05–1.85 per decade of hyperlipidemia), suggesting that previous cumulative exposure to hyperlipidemia is associated with increased risk of CHD later in life, independent of the cholesterol level at 55 years of age. This association also remained significant after adjusting for lipid-lowering therapy use at baseline and follow-up.

**Statin Recommendations Under Current Guidelines**

The number of participants who would be specifically targeted for statin therapy according to the statin benefit groups as identified by the new guidelines was calculated (Table 3). Of 577 adults with 11 to 20 years of hyperlipidemia at the index age of 55, 87 (15.1%) participants would have met criteria for statin therapy at 40 years of age, and 201 (34.8%) would have met criteria at 50 years of age. These numbers were lower among those with 1 to 10 years of hyperlipidemia at 55 years of age: of 389 adults, 7 (1.8%) would have met criteria for statin therapy at 40 years of age and 44 (11.3%) would have met criteria at 50 years of age. When we used the lower risk threshold proposed by the guidelines (10-year CVD risk ≥5%) to identify adults eligible for statin therapy, 25.1% of adults with 11 to 20 years of hyperlipidemia at baseline would have been recommended for statin therapy at 40 years of age, and 51.6% would have been recommended for statin therapy at 50 years of age.

When we restricted our analyses to those adults not recommended for statin therapy at 55 years of age (ie, 10-year CVD risk <7.5%, LDL-C <190 mg/dL, and no diabetes mellitus with LDL-C ≥70 mg/dL; \( n=971 \)), the association between hyperlipidemia and risk of CHD was preserved; adults with both 1 to 10 and 11 to 20 years of hyperlipidemia at baseline had significantly higher rates of CHD than adults without hyperlipidemia (Figure 2, \( P<0.001 \)). In multivariable models adjusting for standard risk factors and non-HDL-C at baseline, each decade of hyperlipidemia at baseline was associated with a 67% increased risk of CHD at follow-up (Table 2; HR, 1.67; 95% CI, 1.06–2.64, \( P=0.03 \)).

**Sensitivity Analyses**

The use of an LDL-C level of ≥130 mg/dL rather than non-HDL-C ≥160 mg/dL as the primary exposure yielded similar

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**Table 1. Characteristics of Participants Stratified by Years of Hyperlipidemia at Baseline**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=1478)</th>
<th>0 y (n=512)</th>
<th>1–10 y (n=389)</th>
<th>11–20 y (n=577)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 (54–56)</td>
<td>55 (54–56)</td>
<td>55.0 (54–56)</td>
<td>56.0 (54–56)</td>
</tr>
<tr>
<td>Female</td>
<td>791 (53.5)</td>
<td>336 (65.6)</td>
<td>241 (62.0)</td>
<td>214 (37.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>281 (19.0)</td>
<td>89 (17.4)</td>
<td>64 (16.5)</td>
<td>128 (22.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>95 (6.4)</td>
<td>19 (3.7)</td>
<td>23 (5.9)</td>
<td>53 (9.2)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.0 (24.2–30.3)</td>
<td>25.4 (23.0–28.6)</td>
<td>26.9 (24.5–30.1)</td>
<td>28.3 (25.4–31.0)</td>
</tr>
<tr>
<td>Treatment for cholesterol</td>
<td>85 (5.8)</td>
<td>3 (0.6)</td>
<td>10 (2.6)</td>
<td>72 (12.5)</td>
</tr>
<tr>
<td>Treatment for BP</td>
<td>282 (19.1)</td>
<td>59 (11.5)</td>
<td>73 (18.8)</td>
<td>150 (26.0)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>127 (115–137)</td>
<td>123 (112–134)</td>
<td>126 (115–136)</td>
<td>130 (119.0–140.0)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>209 (184–233)</td>
<td>182 (166–199)</td>
<td>215 (199–236)</td>
<td>230 (207–253)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48 (40–60)</td>
<td>57 (46–70)</td>
<td>49 (39–60)</td>
<td>43 (37–51)</td>
</tr>
</tbody>
</table>

Binary data are presented as n (%); continuous variables are presented as median (interquartile range). BMI indicates body mass index; BP, blood pressure; and HDL-C, high-density lipoprotein cholesterol.
The results based on average prior non-HDL-C are shown in Figure 3, where they are plotted against future CHD risk approximated by using a restricted cubic spline and a piecewise linear model. The effect of weighted non-HDL-C below 125 mg/dL on CHD was nonsignificant, suggesting that individuals below this cut point all have a similar (lower) risk of CHD. Similarly, the effect of weighted non-HDL-C >195 mg/dL on CHD was nonsignificant, suggesting that individuals above this cut point all have a similar (high) risk of CHD. The association between average weighted non-HDL-C between 125 and 195 mg/dL and CHD was statistically significant. In Cox proportional hazards modeling, every 10 mg/dL increase in average non-HDL-C between 125 and 195 mg/dL over the preceding 20 years was associated with a 33% increase in future CHD risk (HR per 10 mg/dL increase, 1.33; 95% CI, 1.23–1.45; \( P \) <0.001). After adjusting for standard risk factors including baseline non-HDL-C and lipid therapy at baseline and follow-up, this association remained statistically significant (HR, 1.20; 95% CI, 1.08–1.35; \( P \) =0.001).

Table 2. Future Risk of CHD per Decade of Hyperlipidemia Experienced by 55 Years of Age in Univariable and Multivariable Analyses

<table>
<thead>
<tr>
<th>Model</th>
<th>All Adults (n=1514)</th>
<th>Not Recommended for Statin Therapy at Baseline* (n=971)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR per Decade of Hyperlipidemia (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Univariable: duration of hyperlipidemia</td>
<td>2.00 (1.63–2.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors at baseline†</td>
<td>1.49 (1.20–1.87)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors† + non-HDL-C at baseline</td>
<td>1.39 (1.05–1.85)</td>
<td>0.022</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors† + non-HDL-C at baseline + lipid-lowering therapy at baseline and follow-up</td>
<td>1.40 (1.05–1.87)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; and LDL-C, low-density lipoprotein cholesterol.

*10-year predicted CVD risk <7.5%, no diabetes mellitus and LDL-C ≥70 mg/dL, and LDL-C <190 mg/dL.

†Standard risk factors: sex, age, blood pressure, HDL-C, antihypertensive treatment, smoking, and diabetes mellitus.
excluding adults on lipid-lowering therapy at baseline did not result in substantive changes to the results (Table II in the online-only Data Supplement).

**Discussion**

In this analysis of adults free of CVD at 55 years of age in the Framingham Offspring Study, we found that those with the longest previous exposure to moderately elevated non-HDL-C had a nearly 4-fold increased rate of CHD at follow-up. Importantly, not only does prevalent hyperlipidemia increase future risk of CHD, but the length of exposure to hyperlipidemia in the fourth and fifth decades of life affects future CHD risk in a dose-responsive manner, because the association between exposure to hyperlipidemia in young adulthood and future CHD remained highly significant even after the adjustment for non-HDL-C at 55 years of age. This association was preserved in individuals without direct recommendations for statin therapy under the current guidelines. These findings are aligned with the biological understanding of atherosclerosis as a progressive disease attributable to ongoing vessel injury over time—a substantial part of which is caused by elevated cholesterol levels.\(^5\)

### Table 3. Statin Recommendations at 40 and 50 Years of Age for Adults With and Without Hyperlipidemia at 55 Years of Age*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended for Statin Therapy, ASCVD Risk ≥7.5%</th>
<th>Recommended for Statin Therapy, ASCVD Risk ≥5%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 y of Age</td>
<td>50 y of Age</td>
</tr>
<tr>
<td>0 y (n=512), n (%)</td>
<td>3 (0.6)</td>
<td>16 (3.1)</td>
</tr>
<tr>
<td>1–10 y (n=389), n (%)</td>
<td>7 (1.8)</td>
<td>44 (11.3)</td>
</tr>
<tr>
<td>11–20 y (n=577), n (%)</td>
<td>87 (15.1)</td>
<td>201 (34.8)</td>
</tr>
</tbody>
</table>

ACC indicates American College of Cardiology; AHA, American Heart Association; and ASCVD, atherosclerotic cardiovascular disease.

*Based on 2013 AHA/ACC Cholesterol Guidelines. Adults with triglycerides >400 mg/dL considered statin recommended.

**Figure 2.** Time to diagnosis of CHD by number of years of hyperlipidemia at baseline among adults not recommended for statin therapy at baseline.* This figure shows Kaplan–Meier curves of future risk of CHD stratified by years of hyperlipidemia experienced by 55 years of age (age range, 53–57) among adults not recommended for statin therapy at 55 years of age. Log-rank P value <0.0001. *Excludes those recommended for statins: ASCVD risk ≥7.5%, LDL-C ≥190, diabetes mellitus and LDL-C ≥100. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; and LDL-C, low-density lipoprotein cholesterol.
In addition to 10-year risk calculated using the Pooled Cohort Equations, the current American Heart Association/American College of Cardiology cholesterol guideline recommends considering family history, C-reactive protein, coronary artery calcium, ankle brachial index, and lifetime CVD risk when making statin treatment recommendations. Our data suggest that sustained moderate elevation of lipid levels also confers a substantial risk of future events. Given the potent association between the duration of exposure to hyperlipidemia by midadulthood and future CHD risk, clinicians should also consider lifestyle intervention or statin treatment for adults with prolonged previous exposure to hyperlipidemia. Randomized controlled trial evidence support the clinical benefit of statin therapy for primary prevention in adults in this age group, with a number of primary prevention trials demonstrating that statins initiated in midlife significantly reduce future clinical events.\textsuperscript{9–11}

Although the new guidelines identify those patients with a very high lipid level on a single measurement (LDL-C $\geq$ 190 mg/dL) as candidates for statin therapy, they do not further differentiate risk in others based on lipoprotein levels. Under current guidelines, only 1 in 6 adults in this cohort with prolonged duration of exposure to hyperlipidemia would have been directly recommended for statin therapy at 40 years of age, and 1 in 3 would have been directly recommended for statin therapy at 50 years of age. By design, our analysis cannot answer the question whether early statin intervention in those on the hyperlipidemic trajectory would decrease their future CHD risk. When to initiate treatment in adults with moderately elevated non-HDL-C in early adulthood remains unknown. There are no studies evaluating the long-term effectiveness of statin therapy in adults aged 30 to 50 with only moderately elevated lipid levels and without other risk factors. Furthermore, the initiation of statin therapy at younger ages would result in a much longer duration of statin use than has been studied in randomized trials. This lack of knowledge further stresses the need for additional research focused on the safety and efficacy of long-term statin use in early and middle adulthood to reduce CVD later in life. This analysis also highlights the fact that risk prediction models focused on a 10-year horizon may underestimate the contribution of prolonged exposure to chronic disease and the need to continue to evaluate how to best incorporate 30-year or lifetime risk estimates into current prevention guidelines.\textsuperscript{12,13}

\textbf{Limitations and Strengths}

Our analysis has several limitations. First, we only included adults aged 53 to 57 who were free of CVD; therefore, the point estimates cannot be extrapolated outside this age range. Nevertheless, we believe that this analysis demonstrates the long-term impact of hyperlipidemia in young adulthood. Second, our analysis defined hyperlipidemia by using a
non-HDL-C cutoff of ≥160 mg/dL, which is consistent with how the previous Adult Treatment Panel (ATP) III guidelines defined elevated cholesterol: given that the risk of CHD events expands with increasing levels of non-HDL-C, the use of this or any cut point may have falsely dichotomized a continuous relationship. However, the use of a continuous approach that averaged non-HDL-C over the preceding 20 years yielded similar results, showing that the risk associated with exposure to non-HDL-C increased linearly between 125 and 195 mg/dL. Notably, the number of individuals with prior average non-HDL-C <125 mg/dL and >195 mg/dL is low. Therefore, we cannot definitively determine if the relationship between prior average non-HDL-C and future CHD continues at <125 mg/dL or >195 mg/dL. Third, this analysis only considered the duration of hyperlipidemia and not the duration of other risk factors and comorbidities. Although the presence of comorbidities was accounted for at 55 years of age, it is likely that the duration of certain comorbidities, such as diabetes mellitus and hypertension, may also affect future CHD risk in a similar duration-dependent manner, as demonstrated in this hyperlipidemia analysis.14 Next, our study design excluded 124 individuals with premature CVD before 55 years of age; this represented 8% of the initial sample. As a result, some individuals at highest risk, owing to hyperlipidemia at a young age, may have been excluded; these exclusions would have led to an underestimation of the association between the duration of hyperlipidemia and CHD risk.

Notably, our study also had several strengths. First, our analysis is based on the Framingham Heart Study data collected in an era before widespread statin use, allowing us to evaluate the impact of untreated hyperlipidemia. Not only was the overall rate of lipid-lowering therapy in this group low, but the risk associated with increased duration of hyperlipidemia remained significant even after adjusting for lipid-lowering therapy at baseline and follow-up and excluding adults on lipid-lowering therapy at baseline. Second, owing to the length of follow-up, the Framingham Offspring data allow for accurate, longer-term assessment of risk factors, and follow-up of hard cardiovascular end points. Our analysis fully uses the consecutive follow-up, risk factor, and event ascertainment during the course of 35 years (20 years of potential exposure and 15 years of follow-up), which is uniquely available in Framingham. Finally, our study design eliminates the possibility that the association seen between the duration of hyperlipidemia and risk of coronary events is a result of residual confounding by age, because risk was calculated for all participants starting at ≥55 years of age.

Conclusions
We conclude that the exposure to hyperlipidemia in the fourth and fifth decades of life is associated with a substantially increased risk of CHD in a dose-responsive fashion, even among adults otherwise predicted to have a low risk of CVD. Our findings suggest that adults with longstanding moderate elevations in non-HDL-C should be added to those already identified by the current guidelines as candidates for an informed patient-physician discussion about appropriate lipid management strategies to reduce future risk of heart disease.

Acknowledgments
We thank E. Hanley, MS, for her editorial contributions to this manuscript. E. Hanley did not receive compensation for her contributions, apart from her employment at the institution where this study was conducted.

Sources of Funding
This work was supported internally by the Duke Clinical Research Institute in addition to grant U19HS021092 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (contract N01-HC-25195). This article has been reviewed by Framingham Heart Study Investigators for scientific content and consistency of data interpretation with previous Framingham Heart Study publications.

Disclosures
Dr Peterson has received funding for research grants from Eli Lilly and Janssen Pharmaceuticals, and funding for serving as a consultant/participant on advisory board for Merck, Sanofi-Aventis, Janssen Pharmaceuticals, and Boehringer Ingelheim. Dr Pencina has received funding for serving as a consultant for AbbVie. The other authors report no conflicts.

References
Current guidelines for the treatment of blood cholesterol focus on identifying candidates for statin therapy based on 10-year risk for cardiovascular disease. With the exception of those with low-density lipoprotein cholesterol ≥190 mg/dL, most young adults with moderate elevations in lipid levels do not receive a direct recommendation for treatment. In this study, we found that prolonged exposure to moderate elevation in non–high-density lipoprotein cholesterol (≥160 mg/dL) between the ages of 35 and 55 was associated with an increased frequency of future coronary heart disease (CHD) events. Future CHD risk beyond 55 years of age was increased by 39% for every 10 years of elevated non–high-density lipoprotein cholesterol in young adulthood even after adjusting for other risk factors and actual lipid levels at 55 years of age. Thus, not only does a person’s current lipid level influence CHD risk, but also the duration of previous hyperlipidemia exposure. Similar findings were noted when hyperlipidemia was defined based on low-density lipoprotein cholesterol (≥130 mg/dL). Overall, few young adults would have been identified by current guidelines as candidates for statin therapy. However, the association between years of hypercholesterolemia in young adulthood and future CHD risk persisted even among those for whom statin was not recommended. Clinicians should consider adults with longstanding moderate elevations in non–high-density lipoprotein cholesterol at increased risk for CHD, and engage in an informed patient-physician discussion about appropriate lipid management strategies to reduce future risk of heart disease.
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_Circulation_. 2015;131:451-458; originally published online January 26, 2015; doi: 10.1161/CIRCULATIONAHA.114.012477

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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**SUPPLEMENTAL MATERIAL**

**Supplementary Table 1.** Future Risk of CHD Per Decade of Hyperlipidemia (LDL-C $\geq$130 mg/dL) Experienced by Age 55 in Univariable and Multivariable Analyses

<table>
<thead>
<tr>
<th>Model</th>
<th>HR Per Decade of Hyperlipidemia (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable: duration of hyperlipidemia</td>
<td>1.91 (1.53 - 2.38)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors at baseline†</td>
<td>1.50 (1.19 - 1.89)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors† + non-HDL-C at baseline</td>
<td>1.49 (1.11 - 2.01)</td>
<td>0.0090</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors† + non-HDL-C at baseline + lipid lowering therapy at baseline and follow-up</td>
<td>1.49 (1.10 - 2.02)</td>
<td>0.0106</td>
</tr>
</tbody>
</table>

*Excluding adults with triglyceride level $\geq$400 mg/dL at or prior to baseline. Final sample n=1412

†Standard risk factors: sex, age, blood pressure, HDL-C, antihypertensive treatment, smoking, diabetes

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; All other abbreviations can be found in Table 1.
<table>
<thead>
<tr>
<th>Model</th>
<th>HR Per Decade of Hyperlipidemia (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable: duration of hyperlipidemia</td>
<td>2.02 (1.63 - 2.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors at baseline †</td>
<td>1.49 (1.18 - 1.87)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors † + non-HDL-C at baseline</td>
<td>1.38 (1.03 - 1.85)</td>
<td>0.033</td>
</tr>
<tr>
<td>Duration of hyperlipidemia + standard risk factors † + non-HDL-C at baseline + lipid lowering therapy at baseline and follow-up</td>
<td>1.37 (1.02 - 1.86)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

†Standard risk factors: sex, age, blood pressure, HDL-C, antihypertensive treatment, smoking, diabetes
CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; All other abbreviations can be found in Table 1.