Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort

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Lancet 2020; 396: 1644–52

Published Online November 10, 2020 https://doi.org/10.1016/S0140-6736(20)32233-9

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Summary

Background Findings of historical studies suggest that elevated LDL cholesterol is not associated with increased risk of myocardial infarction and atherosclerotic cardiovascular disease in patients older than 70 years. We aimed to test this hypothesis in a contemporary population of individuals aged 70–100 years.

Methods We included in our analysis individuals (aged 20–100 years) from the Copenhagen General Population Study (CGPS) who did not have atherosclerotic cardiovascular disease or diabetes at baseline and who were not taking statins. Standard hospital assays were used to measure LDL cholesterol. We calculated hazard ratios (HRs) and absolute event rates for myocardial infarction and atherosclerotic cardiovascular disease, and we estimated the number needed to treat (NNT) in 5 years to prevent one event.

Findings Between Nov 25, 2003, and Feb 17, 2015, 91131 individuals were enrolled in CGPS. During mean 7·7 (SD 3·2) years of follow-up (to Dec 7, 2018), 1515 individuals had a first myocardial infarction and 3389 had atherosclerotic cardiovascular disease. Risk of myocardial infarction per 1·0 mmol/L increase in LDL cholesterol was augmented for the overall population (HR 1·34, 95% CI 1·27–1·41) and was amplified for all age groups, particularly those aged 70–100 years. Risk of atherosclerotic cardiovascular disease was also raised per 1·0 mmol/L increase in LDL cholesterol overall (HR 1·16, 95% CI 1·12–1·21) and in all age groups, particularly those aged 70–100 years. Risk of myocardial infarction was also increased with a 5·0 mmol/L or higher LDL cholesterol (ie, possible familial hypercholesterolaemia) versus less than 3·0 mmol/L in individuals aged 80–100 years (HR 2·99, 95% CI 1·71–5·23) and in those aged 70–79 years (1·82, 1·20–2·77). Myocardial infarction and atherosclerotic cardiovascular disease events per 1000 person-years for every 1·0 mmol/L increase in LDL cholesterol were highest in individuals aged 70–100 years, with number of events lower with younger age. The NNT in 5 years to prevent one myocardial infarction or atherosclerotic cardiovascular disease event if all people were given a moderate-intensity statin was lowest for individuals aged 70–100 years, with the NNT increasing with younger age.

Interpretation In a contemporary primary prevention cohort, people aged 70–100 years with elevated LDL cholesterol had the highest absolute risk of myocardial infarction and atherosclerotic cardiovascular disease and the lowest estimated NNT in 5 years to prevent one event. Our data are important for preventive strategies aimed at reducing the burden of myocardial infarction and atherosclerotic cardiovascular disease in the growing population aged 70–100 years.

Funding None.

Introduction

Atherosclerosis starts early in life and develops slowly over decades before suddenly giving rise to clinical disease (eg, myocardial infarction and atherosclerotic cardiovascular disease) later in life. The role of LDL cholesterol as a central driving force for this process is based on evidence ranging from experimental evidence in animal studies to epidemiological associations in cohort studies, unbiased genetic evidence from both monogenic and polygenic human disorders, and randomised trial evidence of LDL cholesterol reduction.[1] For this reason, LDL cholesterol remains the primary treatment target in all major guidelines for both primary and secondary prevention.[2,3]

Despite the causal role of LDL cholesterol in development of atherosclerosis, previous studies have indicated that the association of elevated total cholesterol with myocardial infarction and ischaemic heart disease varies greatly with age, with the association being much stronger in younger than older individuals.[4–8] In most people, LDL cholesterol is the main fraction of total cholesterol. In many studies, the association of increased cholesterol with clinical events even disappeared in individuals older than 70 years.[6,7,9,10] However, most previous studies were done in historical cohorts enrolling patients up to four and five decades ago, when prevention and treatment of atherosclerotic cardiovascular disease

Research in context

Evidence before this study

LDL cholesterol is accepted as a causal risk factor for development of myocardial infarction and atherosclerotic cardiovascular disease. In individuals aged 40–75 years, elevated LDL cholesterol constitutes a main treatment target for prevention of atherosclerotic cardiovascular disease in all international guidelines. However, the role of LDL cholesterol in myocardial infarction and atherosclerotic cardiovascular disease in individuals older than 70 years is controversial. Previous studies based primarily on historical cohorts enrolling patients decades ago have either found no or little association of elevated LDL cholesterol with increased risk of myocardial infarction in individuals older than 70 years. Further, no randomised controlled trial of LDL-lowering therapy has specifically included patients older than 70 years. Therefore, guidelines have generally not recommended measurement or management of LDL cholesterol with statins in individuals older than 75 years. As the proportion of individuals older than 70 years is increasing fast worldwide, with an expected large detrimental effect on atherosclerotic cardiovascular disease burden in the population, it is important to understand if controlling elevated LDL cholesterol in people aged 70–100 years has the potential to counteract this development.

Added value of this study

We provide the most comprehensive analysis of the association of elevated LDL cholesterol with myocardial infarction and atherosclerotic cardiovascular disease risk in a contemporary primary prevention cohort of individuals aged 70–100 years. The Copenhagen General Population Study (CGPS) provides a unique opportunity to reliably investigate these associations. In 2003–15, 13 779 individuals aged 70–100 years and 77 352 aged 20–69 years were enrolled in CGPS. At baseline, all individuals did not have atherosclerotic cardiovascular disease or diabetes and were not using statins.

Implications of all the available evidence

By contrast with previous historical studies, our data show that LDL cholesterol is an important risk factor for myocardial infarction and atherosclerotic cardiovascular disease in a contemporary primary prevention cohort of individuals aged 70–100 years. For individuals with elevated LDL cholesterol, the relative risk of myocardial infarction was raised similarly in people aged 70–100 years and 50–69 years. Furthermore, a 1·0 mmol/L increase in LDL cholesterol was associated with a several fold greater absolute risk for myocardial infarction in individuals aged 70–100 years than in those aged 20–69 years. By lowering LDL cholesterol in healthy individuals aged 70–100 years, the potential for preventing myocardial infarctions and atherosclerotic cardiovascular disease is huge, and at a substantially lower number needed to treat when compared with those aged 20–69 years. Previous randomised trials of statin therapy have never selectively enrolled patients aged 70–100 years; however, findings of meta-analyses show that no upper age limit exists at which LDL-lowering therapy ceases to prevent myocardial infarction and atherosclerotic cardiovascular disease. Our data should guide decision making about whether older individuals will benefit from statin therapy. With the demographic changes seen worldwide with aging populations, our data point at a huge potential for reducing the population burden of atherosclerotic cardiovascular disease in countries with aging populations.

and other chronic diseases differed from contemporary practice. Since then, life expectancy has increased substantially, at least partly due to improved health among older individuals.[11] Further, age-standardised myocardial infarction event rates have fallen more in younger than in older people, yielding a higher proportion of myocardial infarction and atherosclerotic cardiovascular disease events occurring in individuals older than 70 years.[12] Together, these changes over time could have altered the importance of elevated LDL cholesterol on development of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years in contemporary populations, due to increased life expectancies and fewer comorbidities with increasing age, creating an evidence gap. As the proportion and number of individuals older than 70 years is increasing fast worldwide, understanding the association of elevated LDL cholesterol with risk of myocardial infarction and atherosclerotic cardiovascular disease in people older than 70 years in the current era is important for appropriate management and patient–doctor discussions on preventive interventions.[13] We, therefore, aimed to test the hypothesis that elevated LDL cholesterol is associated with increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years.

Methods

Participants

Data for our study were obtained from individuals enrolled in the Copenhagen General Population Study (CGPS), a large and contemporary general population cohort study of the Danish general population. Participants for CGPS were randomly selected through the Danish Civil Registration system to reflect the Danish general population aged 20–100 years. All individuals aged 40–100 years were invited along with a random selection of 25% of individuals aged 20–39 years in selected parts of Copenhagen. CGPS covers all regions of Copenhagen, including surrounding countryside and both high-income and low-income areas. For this study, we included individuals from a white European ethnic background of Danish descent (to ensure homogeneity in the population with respect to factors such as genetics)

who were enrolled consecutively in 2003–15. We excluded individuals with pre-existing atherosclerotic cardiovascular disease (defined as known previous ischaemic heart disease or stroke), diabetes, or statin use at baseline. (According to European guidelines, most patients with atherosclerotic cardiovascular disease and diabetes are given statins.[2])

The study was approved by Herlev and Gentofte Hospital and by the Danish ethics committee for the Capital Region covering Copenhagen. Written informed consent was obtained from all individuals.

Procedures

The baseline examination included a questionnaire, physical examination, and non-fasting blood sampling for biochemical measurements. Current smoking status and statin therapy were self-reported. Blood pressure was measured using an automated digital blood pressure monitor (Kivex, Hellerup, Denmark) after 5 min of rest with the individual in the sitting position. LDL cholesterol in mmol/L was calculated using the Friedewald equation (total cholesterol − HDL cholesterol − triglycerides / 2·2) when triglycerides were less than 4·0 mmol/L; otherwise LDL cholesterol was measured directly. Total cholesterol, HDL cholesterol, triglycerides, and direct LDL cholesterol were measured using standard hospital assays (Roche Cobas, Mannheim, Germany; Konelab, Helsinki, Finland). Similar tests for biomarkers were used for the duration of the study; all tests underwent daily internal control for impression and monthly external control for accuracy.

We chose to study myocardial infarction because this hard endpoint is very well registered in Danish national health registries.[14,15] However, we also show results for all atherosclerotic cardiovascular disease events. Myocardial infarction and atherosclerotic cardiovascular disease events were identified by linkage to the national Danish Patient Registry, which covers all public and private Danish hospitals (inpatients from 1977 and outpatients from 1995), and to the national Danish Causes of Death Registry (from 1997). Myocardial infarction was non-fatal or fatal using International Classification of Diseases, 10th revision (ICD-10) codes I21–I22, which are estimated to be more than 99% correct.[14] Atherosclerotic cardiovascular disease was myocardial infarction (ICD-10 codes I21–I22), fatal coronary heart disease (I20–I25), and non-fatal or fatal ischaemic stroke. Possible stroke events (among hospitalised patients) were identified with ICD-10 codes I60, I61, I63, I64, and G45, and then individually validated using the WHO definition of stroke (ie, an acute disturbance of focal or global cerebral function with symptoms lasting >24 h or leading to death, with presumably no other reasons than of vascular origin).[16] Fatal coronary heart disease not from myocardial infarction has not been validated.

All individuals in Denmark are assigned a personal identification number at birth or immigration with which they can be traced in the national registries. Therefore, follow-up was without loss. We followed up all individuals from baseline examination to occurrence of a first myocardial infarction or atherosclerotic cardiovascular disease event, emigration (n=412), death, or to Dec 7, 2018, whichever occurred first. From recruitment in Nov 25, 2003, to Feb 17, 2015, and up to Dec 7, 2018, the quality of endpoint data was probably similar, as Denmark used ICD-10 coding throughout.

Statistical analysis

We used Stata version 13.1 SE for analyses. Baseline characteristics are presented as number and proportion

	All individuals (n=91 131)	Aged 80–100 years (n=3188)	Aged 70–79 years (n=10 591)	Aged 60–69 years (n=21 808)	Aged 50–59 years (n=24 205)	Aged 20–49 years (n=31 339)
Age, years	56 (47–65)	83 (81–86)	73 (72–76)	64 (62–67)	54 (52–57)	44 (40–47)
Women	51 690 (57%)	1775 (56%)	5840 (55%)	12 422 (57%)	13 641 (56%)	18 012 (57%)
Men	39 441 (43%)	1413 (44%)	4751 (45%)	9386 (43%)	10 564 (44%)	13 327 (43%)
Systolic blood pressure, mm Hg	139 (125–153)	155 (140–170)	150 (137–165)	145 (131–160)	138 (125–152)	130 (120–141)
Diastolic blood pressure, mm Hg	84 (76–91)	82 (75–90)	85 (77–92)	85 (79–93)	85 (78–92)	80 (75–88)
Total cholesterol, mmol/L	5·6 (5·0–6·4)	5·8 (5·1–6·5)	5·9 (5·3–6·6)	6·0 (5·3–6·6)	5·8 (5·2–6·5)	5·2 (4·6–5·8)
HDL cholesterol, mmol/L	1·6 (1·3–2·0)	1·7 (1·4–2·1)	1·7 (1·3–2·1)	1·7 (1·3–2·1)	1·6 (1·3–2·0)	1·5 (1·2–1·8)
LDL cholesterol, mmol/L	3·3 (2·7–3·9)	3·3 (2·8–3·9)	3·4 (2·9–4·0)	3·5 (2·9–4·1)	3·4 (2·8–4·0)	3·0 (2·4–3·6)
Current smokers	15 680 (17%)	390 (12%)	1466 (14%)	1699 (17%)	4778 (20%)	5347 (17%)
Hypertension	46 684 (51%)	2646 (83%)	7989 (75%)	14 086 (65%)	12 141 (50%)	9822 (31%)
First myocardial infarction	1515	166	393	409	337	210
Myocardial infarction events per 1000 person-years	2·2	8·5	5·2	2·5	1·8	0·8
ASCVD events	3389	494	957	951	631	356
ASCVD events per 1000 person-years	4·7	25·3	12·6	5·7	3·2	1·3

Data are n (%), median (IQR), or n. ASCVD=atherosclerotic cardiovascular disease.

Table 1: **Baseline characteristics in the overall population and stratified by age groups in the Copenhagen General Population Study**

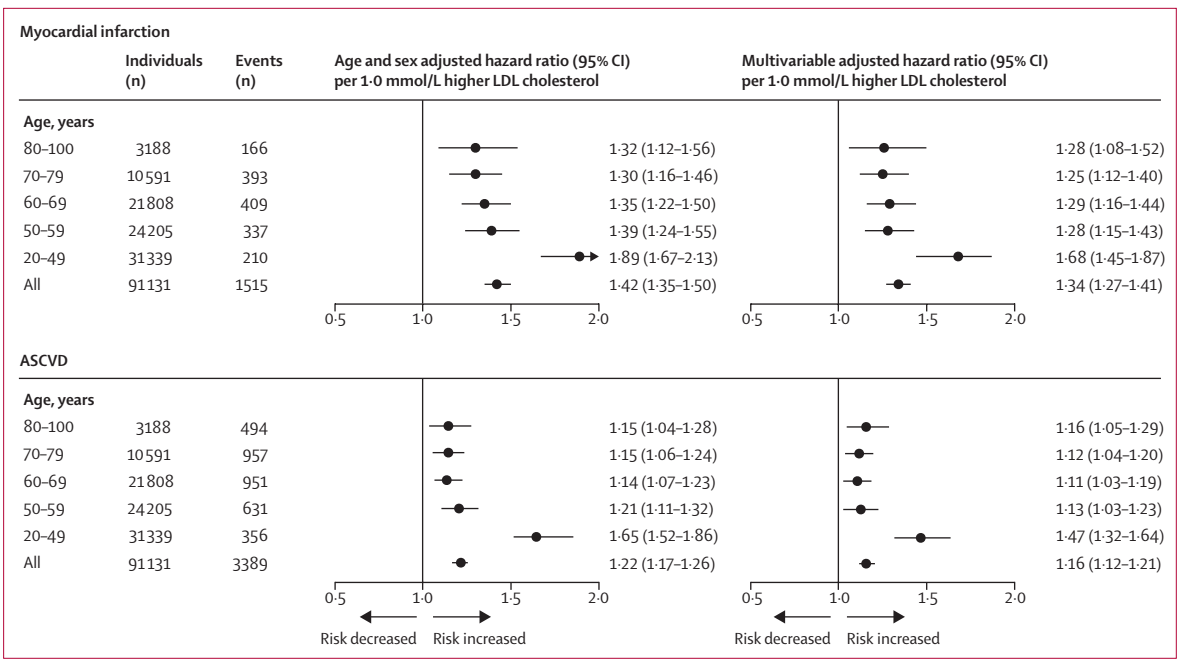


Figure 1: **Association of 1·0 mmol/L higher LDL cholesterol with development of myocardial infarction and ASCVD, stratified by age groups in the Copenhagen General Population Study**

Multivariable analyses were adjusted for age, sex, smoking status, HDL cholesterol, body-mass index, hypertension, and estimated glomerular filtration rate. ASCVD=atherosclerotic cardiovascular disease.

for categorical variables and as median (IQR) for continuous variables.

Cox proportional hazard models assessed the relation between elevated LDL cholesterol and risk of myocardial infarction and atherosclerotic cardiovascular disease. Hazard ratios (HRs) were first adjusted for age (continuously) and sex, then in multivariable analyses additionally for smoking status, HDL cholesterol (continuously), body-mass index (continuously), hypertension, and estimated glomerular filtration rate (continuously). These covariates were 99·6% complete and missing data were inserted with multiple imputation. Results were similar with and without imputed covariates. We tested the Cox proportional hazard assumption visually for covariates using Shoenfeld residuals and found no violations. In sensitivity analyses, we used Fine-Gray subdistribution HRs to allow for death and emigration as competing events.

The crude myocardial infarction event rate per 1000 person-years was calculated in individuals stratified by age groups (20–49, 50–59, 60–69, 70–79, and 80–100 years) and amounts of LDL cholesterol (<2·0, 2·0–2·9, 3·0–3·9, 4·0–4·9, and ≥5·0 mmol/L).

We estimated the number needed to treat (NNT) in 5 years to prevent one event with moderate-intensity statin therapy, as done previously.[17] For these calculations, we assumed 30% and 22% relative risk reduction of myocardial infarction and atherosclerotic cardiovascular disease, respectively, per 1·0 mmol/L reduction in LDL cholesterol in individuals free of atherosclerotic cardiovascular disease, as observed in the Cholesterol Trialist Collaboration meta-analyses.[18] Moderate-intensity statin therapy was expected to reduce LDL cholesterol by about 30%.[19] For these analyses, we first assessed the total number of events in 5 years by age groups, using Kaplan-Meier analysis.

	All individuals (n)	Individuals with LDL cholesterol ≥5·0 mmol/L (n [%])	Hazard ratio (95% CI) for LDL cholesterol ≥5·0 mmol/L *vs* <3·0 mmol/L	
			Age and sex adjusted	Multivariable adjusted*
Myocardial infarction				
Aged 80–100 years	3188	216 (7%)	2·83 (1·64–4·88)	2·99 (1·71–5·23)
Aged 70–79 years	10591	727 (7%)	2·08 (1·39–3·11)	1·82 (1·20–2·77)
Aged 60–69 years	21808	1891 (9%)	2·59 (1·79–3·77)	2·47 (1·67–3·65)
Aged 50–59 years	24205	1884 (8%)	2·34 (1·60–3·45)	2·08 (1·39–3·11)
Aged 20–49 years	31339	1338 (4%)	6·97 (4·30–11·3)	5·34 (3·13–9·15)
ASCVD				
Aged 80–100 years	3188	216 (7%)	1·75 (1·20–2·53)	1·90 (1·27–2·83)
Aged 70–79 years	10591	727 (7%)	1·36 (1·01–1·83)	1·25 (0·92–1·71)
Aged 60–69 years	21808	1891 (9%)	1·45 (1·11–1·90)	1·31 (0·98–1·75)
Aged 50–59 years	24205	1884 (8%)	1·88 (1·40–2·52)	1·65 (1·21–2·26)
Aged 20–49 years	31339	1338 (4%)	4·23 (2·78–6·41)	3·20 (2·04–5·03)

ASCVD=atherosclerotic cardiovascular disease. *Adjusted for age, sex, smoking status, HDL cholesterol, hypertension, body-mass index, and estimated glomerular filtration rate.

Table 2: **Association of LDL cholesterol ≥5·0 mmol/L *vs* <3·0 mmol/L with development of myocardial infarction and ASCVD, stratified by age groups in the Copenhagen General Population Study**

The potential for overall event reduction in 5 years was then estimated as the number of events theoretically reduced by assigning moderate-intensity statin therapy, divided by the total number of events among all individuals in each age group. The NNT in 5 years was estimated as the reciprocal of the absolute risk differences in 5-year event rate (eg, 100/2 events prevented = 50 for NNT in 5 years).

Role of the funding source

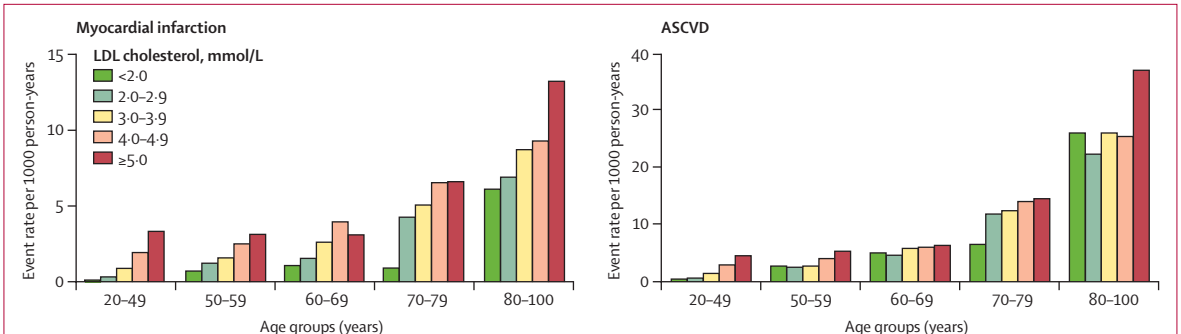
No direct funding was received for this study. The funder of CGPS had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MBM and BGN had full access to all data in the study and were responsible for the decision to submit for publication. Data were verified independently (Langsted A, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark).

Results

Between Nov 25, 2003, and Feb 17, 2015, 91131 individuals aged 20–100 years were enrolled in CGPS who, at baseline, did not have atherosclerotic cardiovascular disease or diabetes and were not using statins. Baseline characteristics in the overall population and by age group are shown in table 1. 3188 (3%) individuals were aged 80–100 years, 10591 (12%) were aged 70–79 years, 21808 (24%) were aged 60–69 years, 24205 (27%) were aged 50–59 years, and 31339 (34%) were aged 20–49 years. During mean follow-up of 7·7 (SD 3·2) years (to Dec 7, 2018), 1515 individuals had a first myocardial infarction and 3389 had atherosclerotic cardiovascular disease.

LDL cholesterol was associated with development of myocardial infarction and atherosclerotic cardiovascular disease in the overall population and in all age groups separately (figure 1). Risk of myocardial infarction per 1·0 mmol/L increase in LDL cholesterol was augmented for the overall population (HR 1·34, 95% CI 1·27–1·41) and was amplified in all age groups, particularly in those aged 70–100 years. Risk of atherosclerotic cardiovascular disease was also raised per 1·0 mmol/L increase in LDL cholesterol overall (HR 1·16, 95% CI 1·12–1·21) and in all age groups.

An amount of LDL cholesterol of 5·0 mmol/L or higher (suggestive of a diagnosis of familial hypercholesterolaemia) was recorded in 216 individuals aged 80–100 years (7% of people in this age group), 727 (7%) aged 70–79 years, 1891 (9%) aged 60–69 years, 1884 (8%) aged 50–59 years, and in 1338 (4%) aged 20–49 years (table 2). 5·0 mmol/L or higher LDL cholesterol versus less than 3·0 mmol/L was associated with higher risk of myocardial infarction (HR 2·99, 95% CI 1·71–5·23) and atherosclerotic cardiovascular disease (1·90, 1·27–2·83)



Event rate per 1000 person-years					
Age, years	LDL cholesterol, mmol/L				
	<2·0	2·0–2·9	3·0–3·9	4·0–4·9	≥5·0
80–100	6·1	6·9	8·7	9·3	13·2
70–79	1·0	4·2	5·1	6·5	6·6
60–69	1·1	1·6	2·6	3·9	3·1
50–59	0·7	1·2	1·6	2·5	3·1
20–49	0·1	0·3	0·9	1·9	3·3
Number of individuals/events					
80–100	132/5	925/38	1342/72	573/30	216/21
70–79	309/2	2722/81	4621/167	2212/108	727/35
60–69	596/5	5053/59	9440/186	4828/110	1891/49
50–59	885/5	6397/62	10200/128	4839/99	1884/43
20–49	2670/3	12650/34	11020/81	3661/56	1338/36

Event rate per 1000 person-years					
Age, years	LDL cholesterol, mmol/L				
	<2·0	2·0–2·9	3·0–3·9	4·0–4·9	≥5·0
80–100	26·1	22·4	26·1	25·5	37·1
70–79	6·6	11·9	12·5	14·1	14·6
60–69	5·1	4·7	5·9	6·1	6·4
50–59	2·8	2·6	2·8	4·1	5·4
20–49	0·5	0·7	1·5	3·0	4·6
Number of individuals/events					
80–100	132/22	925/128	1342/210	573/87	216/47
70–79	309/17	2722/230	4621/411	2212/230	727/69
60–69	596/25	5053/180	9440/427	4828/223	1891/96
50–59	885/20	6397/139	10200/231	4839/170	1884/71
20–49	2670/13	12650/78	11020/135	3661/88	1338/42

Figure 2: **Event rate per 1000 person-years for myocardial infarction and ASCVD according to baseline levels of LDL cholesterol and age in the Copenhagen General Population Study**
ASCVD=atherosclerotic cardiovascular disease.

in individuals aged 80–100 years, and in other age groups (table 2).

Myocardial infarction and atherosclerotic cardiovascular disease event rates increased with both higher LDL cholesterol levels and older age (figure 2). The highest event rates were recorded in individuals aged 80–100 years with LDL cholesterol of 5·0 mmol/L or higher, for both myocardial infarction (13·2 events per 1000 person-years) and atherosclerotic cardiovascular disease (37·1 events per 1000 person-years; figure 2). In individuals with LDL cholesterol of 5·0 mmol/L or higher, the myocardial infarction event rate was nearly four times higher in people aged 80–100 years than in those aged 20–69 years (multivariable adjusted hazard ratio 3·7, 95% CI 1·6–8·8).

Myocardial infarction events per 1000 person-years for every 1·0 mmol/L increase in LDL cholesterol were 2·5 for individuals aged 80–100 years, 1·3 for those aged 70–79 years, 0·7 for those aged 60–69 years, 0·5 for those aged 50–59 years, and 0·6 for those aged 20–49 years (figure 3). Atherosclerotic cardiovascular disease events per 1000 person-years for every 1·0 mmol/L increase in LDL cholesterol were 4·0 for individuals aged 80–100 years, 1·5 for those aged 70–79 years, 0·7 for those aged 60–69 years, 0·5 for those aged 50–59 years, and 0·6 for those aged 20–49 years (figure 3).

To estimate the potential effect of lowering LDL cholesterol in the five different age groups, we calculated the NNT in 5 years to prevent one event using moderate-intensity statin therapy, assuming a 30% relative risk reduction for myocardial infarction and a 22% relative risk reduction for atherosclerotic cardiovascular disease events per 1·0 mmol/L LDL cholesterol-lowering. The NNT in 5 years to prevent one myocardial infarction was 80 for individuals aged 80–100 years, 145 for those aged 70–79 years, 261 for those aged 60–69 years, 439 for those aged 50–59 years, and 1107 for those aged 20–49 years. NNT in 5 years to prevent one atherosclerotic cardiovascular disease event were 42 for individuals aged 80–100 years, 88 for those aged 70–79 years, 164 for those aged 60–69 years, 345 for those aged 50–59 years, and 769 for those aged 20–49 years (figure 4). Similar results were found when analyses were restricted to individuals who fulfilled either European or US criteria for statin therapy used in those aged 40–75 years but applied to all age groups (figure 4).

In sensitivity analyses, we reanalysed the association of a 1·0 mmol/L increase in LDL cholesterol and 5·0 mmol/L or greater versus less than 3·0 mmol/L LDL cholesterol with risk of myocardial infarction and atherosclerotic cardiovascular disease, using death and emigration as competing events. Associations were similar to those in the main analyses (appendix pp 1–3), with elevated LDL cholesterol associated with increased risk of myocardial infarction and atherosclerotic cardiovascular disease across all ages, including in people aged 70–100 years.

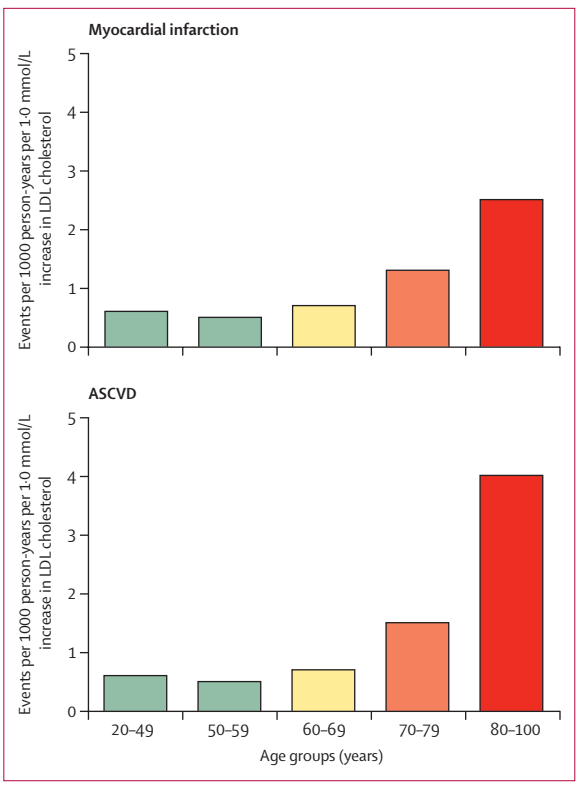


Figure 3: **Myocardial infarction and ASCVD event rates per 1·0 mmol/L increase in LDL cholesterol levels, by age groups in the Copenhagen General Population Study**

Analyses are based on the linear association of LDL cholesterol with risk of myocardial infarction and ASCVD in the different age groups. ASCVD=atherosclerotic cardiovascular disease.

Discussion

Our findings in a contemporary primary prevention cohort showed that raised LDL cholesterol was associated with greatly increased absolute risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years compared with people aged 20–69 years. Individuals aged 70–100 years had the lowest estimated NNT in 5 years to prevent one event. These robust findings are novel. Findings of historical studies suggested that elevated LDL cholesterol levels were not associated with increased risk for myocardial infarction in individuals older than 70 years.[4–7,9] This idea was probably based on the misconception of survival of the fittest, and that people who have not had a vascular event before age 70 years are healthier and have a subsequent reduced risk for atherosclerotic cardiovascular disease. Rather, in view of the consistent risks for myocardial infarction and atherosclerotic cardiovascular disease extending well above age 70 years to much older age groups reported here, the issue has previously most likely been one of insufficient evidence in populations with increasing life expectancy.

See Online for appendix

Based on a contemporary primary prevention cohort of 91131 individuals of white European ethnic origin,

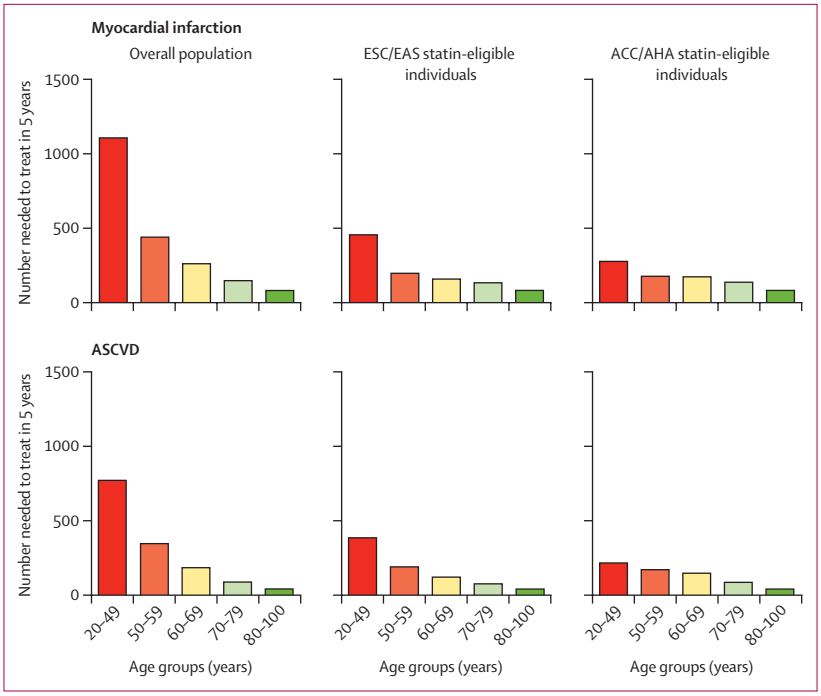


Figure 4: **Estimated number needed to treat for 5 years to prevent one myocardial infarction and one atherosclerotic cardiovascular disease event with moderate-intensity statin therapy**
Analyses assume 30% and 22% relative risk reduction per 1·0 mmol/L lowering of LDL cholesterol. (Left panels) In the overall population, if moderate-intensity statins were given to all individuals. (Middle panels) Among individuals who are eligible for statins, according to ESC/EAS guidelines for people aged 40–75 years, but applied to all ages—ie, according to estimated risk (10-year fatal ASCVD risk ≥5% using the European Systematic Coronary Risk, baseline LDL cholesterol ≥4·9 mmol/L, or both). (Right panels) Among individuals who are eligible for statins according to ACC/AHA guidelines for people aged 40–75 years, but applied to all ages—ie, according to estimated risk (10-year ASCVD risk ≥7·5% using the US Pooled Cohort Equation), baseline LDL cholesterol ≥4·9 mmol/L, or both. ASCVD=atherosclerotic cardiovascular disease. ESC=European Society of Cardiology. EAS=European Atherosclerosis Society. ACC=American College of Cardiology. AHA=American Heart Association.

we provide updated insights into the association of elevated LDL cholesterol with development of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years, an age group for whom the predictive value of elevated LDL cholesterol has been controversial.[6,7,9,10] Indeed, guidelines in Canada, Europe, the UK, and the USA primarily advise on cholesterol-lowering with statins in those aged 40–75 years. Besides the highest absolute risk and lowest NNT in 5 years in individuals aged 70–100 years, we also show that the relative risk of myocardial infarction in those with elevated versus lower LDL cholesterol was similar in individuals aged 70–100 years and 50–69 years, whereas in those aged 20–49 years the relative risk was the highest.

Previous studies have suggested that the association of elevated total and LDL cholesterol levels with increased risk of myocardial infarction and atherosclerotic cardiovascular disease decreases substantially with increasing age.[4–8] For example, in the Prospective Studies Collaboration meta-analyses of 61 prospective cohort studies enrolling patients from the 1950s to 1980s,[5] a 1·0 mmol/L higher total cholesterol was associated with greater mortality from ischaemic heart disease, by 55% in people younger than 50 years, 42% at age 50–59 years, 28% at age 60–69 years, 18% at age 70–79 years, and by 15% at in people older than 80 years. In other studies, the association between elevated cholesterol and risk of ischaemic heart disease even disappeared in individuals older than 70 years.[4,6,7,9] For example, Gränsbo and colleagues[7] reported from the Malmö Preventive Project (enrolling participants in 1974–92) that raised total cholesterol was only associated with increased risk of myocardial infarction in individuals younger than 70 years.[7] Likewise, Iversen and colleagues[6] reported from the Copenhagen City Heart Study (enrolling participants in 1981–83) that the association of high plasma cholesterol with risk of ischaemic heart disease declined successively with increasing age. In people aged 70–80 years, only total cholesterol higher than 8·0 mmol/L was associated with increased risk, and in people older than 80 years, no association with risk was found. By contrast, in our contemporary cohort, the absolute risk of myocardial infarction increased much more with higher LDL cholesterol levels in individuals aged 70–100 years than in those aged 20–69 years.

Most previous studies investigating the association of elevated cholesterol with risk of ischaemic heart disease were based on cohorts enrolling patients decades ago, when prevention and treatment of atherosclerotic cardiovascular disease and other chronic diseases were very different from contemporary practice. Since then, life expectancy has increased in many high-income countries, accompanied by a larger proportion of the population being older than 65 years.[11] Life expectancy is now more than age 80 years in most high-income countries, and many people who reach age 80 years will also survive until age 90 years.[11,20] Besides increased life expectancy, evidence suggests that older individuals have become healthier, with compression of morbidity—ie, a shorter time of life is lived with disabling comorbidity due to postponement of disease onset.[21,22] These favourable changes could account for why elevated LDL cholesterol is associated with increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years in contemporary, but not in historic, populations.

Although we observed that the relative risk of myocardial infarction and atherosclerotic cardiovascular disease for elevated LDL was highest among people aged 20–49 years, in accordance with previous results,[23] the corresponding absolute risk was much higher in individuals aged 70–100 years. For example, in people with LDL cholesterol 5·0 mmol/L or higher, the absolute event rate was four times higher in those aged 80–100 years than in those aged 20–69 years. Individuals aged 70–100 years are, therefore, likely to gain a substantially greater 5-year benefit from LDL cholesterol-lowering than are younger people. The general belief that amounts of cholesterol are much less important

for risk of myocardial infarction and atherosclerotic cardiovascular disease in older than in younger individuals is probably one of the reasons why statin prescriptions decline in people without known atherosclerotic cardiovascular disease who are older than 70 years.[24,25] Further, since no direct clinical trial evidence shows statin efficacy in individuals older than 75 years, nearly all primary prevention guidelines from Canada, Europe, and the USA do not provide strong statin recommendations in this age group, with the only exception being UK National Institute of Health and Care Excellence guidelines, with a strong recommendation for statins until age 84 years.[2] It is, however, important to note that the proportion of myocardial infarctions occurring among individuals older than 70 years has increased in the past 20–30 years.[20] Thus, focus on prevention of myocardial infarction and atherosclerotic cardiovascular disease events in people older than 70 years is of growing importance in modern preventive cardiology. Although no randomised controlled trial of statin therapy in primary prevention has specifically enrolled participants older than 75 years, available randomised controlled trial evidence has not indicated an upper age threshold beyond which statin therapy does not reduce risk. For example, subgroup analyses from the MEGA trial (entry age 40–70 years),[26] CARDS (entry age 40–75 years),[27] JUPITER (entry age ≥50 years for men and ≥60 years for women),[28] and the HOPE-3 trial (entry age ≥55 years for men and ≥65 years for women)[29] have shown that statin therapy reduces atherosclerotic cardiovascular disease risk in individuals older than 65 years at enrolment, with relative risk reductions similar to those seen in younger people. Further, age-stratified outcome data from JUPITER and the HOPE-3 trial showed that rosuvastatin reduced the risk of atherosclerotic cardiovascular disease by 26% in participants older than 70 years.[29] Finally, an updated meta-analysis from the Cholesterol Treatment Trialists' Collaboration showed that statin therapy reduces the risk for atherosclerotic cardiovascular disease irrespective of age, including in people older than 75 years.[30] Taken together, these data suggest that statin therapy in selected individuals older than 75 years with high cholesterol could be appropriate after careful patient–doctor discussions, considering potential benefits, harms, and LDL cholesterol levels.

A potential limitation of our study is that we only included individuals of white European origin, thus, our results might not necessarily apply to other ethnic groups. However, we are not aware of data to suggest that our results should not apply to people of most ethnic backgrounds living in high-income countries with similar life-expectancies and standards for prevention and treatment of atherosclerotic cardiovascular disease as in Denmark. Nevertheless, generalisability to low-income countries could be limited. Second, our estimates for NNT in 5 years to prevent one myocardial infarction and atherosclerotic cardiovascular disease event are based on modelling analyses with assumptions about efficacy of LDL cholesterol-lowering. However, the underlying event rates in different age groups and LDL cholesterol levels are actual data from CGPS, meaning that estimates for NNT in 5 years probably are reliable. Third, if individuals with known atherosclerotic cardiovascular disease or diabetes and statin use at baseline were also included, these people would probably have increased absolute risks even further in those aged 70–100 years.

A strength of our study is that we included 3188 individuals aged 80–100 years, in whom 166 myocardial infarctions and 494 atherosclerotic cardiovascular disease events arose. A second strength is that our data originate from a large and contemporary cohort with not one individual lost to follow-up. Third, we excluded patients with atherosclerotic cardiovascular disease, diabetes, or statin use at baseline to assess relations in a primary prevention setting in which the role of lipid-lowering is less well defined. A final strength is that, besides atherosclerotic cardiovascular disease, we assessed the association of LDL cholesterol with myocardial infarction, which is a hard and reliable endpoint with high sensitivity and specificity in the Danish registries.[15]

In conclusion, in a contemporary primary prevention cohort of individuals free from known atherosclerotic cardiovascular disease, diabetes, and statin use at baseline, higher LDL cholesterol was associated with greatly increased absolute risk of myocardial infarction in people aged 70–100 years. These individuals had the lowest estimated number needed to treat to prevent one event. This finding supports the idea of cumulative burden of LDL cholesterol over a person's lifetime and progressive increase in risk for myocardial infarction and atherosclerotic cardiovascular disease with age. Thus, high LDL cholesterol in apparently healthy people older than 70 years is not a benign finding because it is associated with a substantially higher risk of developing myocardial infarction and atherosclerotic cardiovascular disease.

These data are of importance for primary prevention strategies and guidelines aimed at managing and reducing atherosclerotic cardiovascular disease in the growing older population. However, efficacy and safety of statin therapy in individuals aged 70–100 years needs to be tested directly in randomised trials. Specifically, statin-associated adverse events might increase with aging due to impaired statin metabolism from age-related declines in renal and hepatic function and higher numbers of concomitant drugs with potential drug–drug interactions. Finally, in older populations, competing risks exist that make prescribing decisions more complex. However, even when we allowed for competing risk of death from other causes, our results were similar. In other words, our results suggest that statin therapy in people aged 70–100 years with elevated LDL cholesterol will help many older people live additional years free of myocardial infarction and

atherosclerotic cardiovascular disease before the end of life.

Contributors

MBM analysed the data and drafted the report. BGN supervised the process and critically reviewed the report. MBM and BGN designed the study and independently directly accessed and verified the data reported.

Declaration of interests

We declare no competing interests.

Data sharing

The Danish data protection agency does not allow open access. However, on reasonable request, additional analyses can be done after contacting the corresponding author.

Acknowledgments

We thank Anne Langsted (Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark) for independent verification of data; and participants and staff of CGPS for their invaluable contributions. The work reported here received no direct funding. CGPS was funded by Herlev and Gentofte Hospital. MBM received funding from the Lundbeck Foundation.

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