Only a fraction of patients with ischaemic diseases or diabetes are treated to recommended target values for plasma lipids

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ABSTRACT

INTRODUCTION: We tested the hypothesis that individuals in the general population with and without ischaemic cardiovascular disease, or with diabetes, are treated to recommended target values for plasma lipids.

MATERIAL AND METHODS: We used the Copenhagen General Population Study in which 69,354 individuals were examined cross-sectionally from 2004 through 2010. Among this population, 1,521 had previously had myocardial infarction, 2,372 other ischaemic heart disease, 542 ischaemic stroke, 2,086 claudicatio intermittens and 2,155 had diabetes.

RESULTS: The fraction of participants using lipid-lowering therapy among those with myocardial infarction was 70%, other ischaemic heart disease 44%, ischaemic stroke 60%, claudicatio intermittens 33%, diabetes 48%, and for those without ischaemic cardiovascular disease 8%. Among those with myocardial infarction with and without lipid lowering therapy, 41% and 84%, respectively, had not reached a total cholesterol < 4.5 mmol/l, 30% and 79%, respectively, had not reached a low-density lipoprotein cholesterol < 2.5 mmol/l, and 46% and 48%, respectively, had not reached triglycerides < 1.7 mmol/l. In those with other ischaemic cardiovascular disease, with diabetes or without ischaemic cardiovascular disease, a similar or larger fraction of individuals did not reach guideline lipid targets.

CONCLUSION: Large fractions of individuals with ischaemic cardiovascular disease or diabetes are not treated with lipid-lowering therapy. Even among many of those treated, plasma total cholesterol, low-density lipoprotein cholesterol and triglycerides are not treated to guideline targets.

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TRIAL REGISTRATION: not relevant.

The lipid target values for treatment of individuals without ischaemic cardiovascular disease or diabetes are plasma total cholesterol < 5 mmol/l (< 190 mg/dl), low-density lipoprotein (LDL) cholesterol < 3 mmol/l (< 115 mg/dl) and plasma triglycerides < 1.7 mmol/l (< 150 mg/dl) [1, 2]. Target values for patients with cardiovascular disease or diabetes are even lower at a plasma total cholesterol < 4.5 mmol/l (< 175 mg/dl) with an option of < 4 mmol/l (< 155 mg/dl) if feasible, LDL cholesterol < 2.5 mmol/l (< 100 mg/dl) with an option of < 2 mmol/l (< 80 mg/dl) if feasible, and plasma triglycerides < 1.7 mmol/l (< 150 mg/dl) [1, 2]. The most recent guidelines even recommend that for patients with a very high cardiovascular risk such as those with cardiovascular disease or diabetes, the treatment target for LDL cholesterol should be < 1.8 mmol/l (< 70 mg/dl) or a ≥ 50% reduction from baseline LDL cholesterol [3]. The guidelines do not recommend values for high-density lipoprotein cholesterol above a certain lower limit due to lack of evidence [1-3]. The same is true for lipoprotein(a), although a desirable level has recently been suggested [4].

Statins or other lipid-lowering therapy should be prescribed to most patients with ischaemic cardiovascular disease or diabetes as well as to those who are at a high risk of ischaemic cardiovascular disease [1-6]. Although the use of lipid-lowering therapy has increased from year 2000 through 2004 [7], a discordance between guideline recommendations and drug therapy practice apparently still exists [7-9]. Despite this knowledge, it is presently unknown whether the use of lipid-lowering therapy according to guidelines has improved since 2004 in individuals with ischaemic cardiovascular disease and diabetes in the general population, and whether treatment with lipid-lowering therapy is sufficiently effective to bring lipid levels to the target values prescribed by existing guidelines.

We tested the hypothesis that individuals in the general population with and without ischaemic cardiovascular disease, or with diabetes, are treated to recommended target values for plasma lipids; ischaemic cardiovascular disease was defined as myocardial infarction, other ischaemic heart disease, ischaemic stroke and/or claudicatio intermittens.

MATERIAL AND METHODS

Participants

The Copenhagen General Population Study is an ongoing study which was initiated in late 2003 [10, 11].

Participants were recruited randomly from the general population of Copenhagen, Denmark, using the national Danish Civil Registration System. All participants

ORIGINAL ARTICLE

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were white and of Danish descent. Of those invited, 45% attended. Thus, a total of 69,354 individuals were examined in the 2004-2010-period, all of whom provided information on use of lipid-lowering medication as well as lipid levels at examination. The study was approved by Herlev Hospital and by a Danish Ethical Committee (H-KF-01-144/01). The study complies with the Declaration of Helsinki, and written informed consent was obtained from all participants.

The examination included a self-administered questionnaire on lifestyle, medical history and use of medication. An examiner checked the questionnaire on the day of attendance and performed a physical examination, including measurement of blood pressure, height and weight. Body mass index was calculated as weight divided by height squared (kg/m^2). Hypertension was defined as use of antihypertensive medication, a systolic blood pressure > 140 mmHg, and/or a diastolic blood pressure > 90 mmHg. Nonfasting blood samples [12] were drawn for measurement of plasma levels of total cholesterol, LDL cholesterol, triglycerides and glucose; lipid levels only changed modestly in response to normal food intake in the Copenhagen General Population Study [13, 14].

Use of lipid-lowering therapy was a confirmative answer to the question: "Do you, on a daily basis, take medication for elevated cholesterol?" In Denmark from 2004 through 2010, the most commonly used lipid-lowering medication was 40 mg of simvastatin daily.

Ischaemic cardiovascular disease and diabetes

Diagnoses of myocardial infarction (World Health Organization International Classification of Diseases, 8th and 10th revisions (ICD-8/ICD-10) codes 410 and I21 to I22) were gathered from the national Danish Patient Registry. Other ischaemic heart disease was any ischaemic heart disease minus myocardial infarction (ICD-8 411-414 and ICD-10 I20, I23-I25). Ischaemic stroke was ICD-8 433-434 and ICD-10 I63. Claudicatio intermittens was based on an affirmative answer to all of the following consecutive questions: "Does it hurt in one or both legs when you start walking or when you have been walking for a while?", "If yes – must you rest when you have been walking for a while?", and "If yes – does the pain disappear when you stop walking?".

Diabetes mellitus was self-reported diabetes, use of antidiabetic medication and/or a nonfasting plasma glucose > 11 mmol/l; the group with ischaemic cardiovascular disease or the entire group without ischaemic cardiovascular disease both included individuals with diabetes; however, individuals with ischaemic cardiovascular disease were excluded from the group with diabetes alone.

Lipids

Fresh blood samples were analyzed by the Department of Clinical Biochemistry, Herlev Hospital. Standard assays were used with a Konelab autoanalyser (Helsinki, Finland). Plasma total cholesterol, LDL cholesterol, triglycerides and glucose were measured; LDL cholesterol was calculated using the Friedewald equation if triglycerides were < 4 mmol/l (< 354 mg/dl), but measured with a direct assay at higher triglyceride levels.

Statistical analyses

Data were analyzed using Stata 11.2. Stratification by year of examination was pre-planned. Stratification by age was also pre-planned in individuals < 50 years, 50-59 years, 60-69 years, 70-79 years, and ≥ 80 years.

We tested for differences in the fraction of individ-

TABLE 1

Fractions of individuals with and without ischaemic cardiovascular disease or with diabetes using lipid-lowering therapy.

		With ischaemic cardiovascular disease, %				Without ischaemic cardiovascular disease, %	
	Total population, n (%)	myocardial infarction (n = 1,521)	other ischaemic heart disease (n = 2,372)	ischaemic stroke (n = 542)	claudicatio intermittens (n = 2,086)	diabetes (n = 2,155)	all (n = 65,022)
All	69,354 (100)	70	44	60	33	48	8
Gender							
Men	30,903 (45)	73	52	64	40	46	8
Women	38,451 (55)	63	35	54	27	50	7
p-value		0.001	< 0.001	0.01	< 0.001	0.02	0.03
Age, years							
< 50	21,650 (31)	46	14	43	10	28	1
50-59	17,581 (25)	65	36	63	21	44	6
60-69	17,185 (25)	77	46	61	35	54	12
70-79	9,678 (14)	75	56	63	41	52	16
≥ 80	3,260 (5)	59	41	54	35	38	13
p-value		< 0.001	< 0.001	0.3	< 0.001	< 0.001	< 0.001

uals using lipid-lowering therapy across sex and age groups by logistic regression and a Wald test. Use of lipid-lowering therapy was included in the logistic regression model as a dependent variable, while sex and age groups were independent variables; age was included as a categorical variable according to the pre-planned stratification. The distribution of plasma levels of total cholesterol, LDL cholesterol and triglycerides were estimated using a Gaussian kernel function with a smoothing function. Fractions of individuals above guideline lipid targets were compared using a Pearson's χ^2-test. We tested for trends across 2004 through 2010, e.g. the fraction of individuals using lipid-lowering therapy or the fraction of individuals with lipid levels above guideline targets were tested by a Wilcoxon extension of a Kruskal-Wallis test.

Trial registration: not relevant.

RESULTS

Among 69,354 participants, 1,521 (2.2%) had previously had myocardial infarction, 2,372 (3.4%) other ischaemic heart disease, 542 (0.8%) ischaemic stroke, 2,086 (3.0%) claudicatio intermittens and 2,155 (3.1%) had diabetes (**Table 1**). Some individuals had more than one ischaemic cardiovascular disease and/or diabetes.

Use of lipid-lowering therapy

The fraction of participants using lipid-lowering therapy was 70% for those with myocardial infarction, 44% for other ischemic heart disease, 60% for ischemic stroke, 33% for claudicatio intermittens, 48% for diabetes, and 8% for those without ischaemic cardiovascular disease (Table 1).

Men were more often than women on lipid-lowering therapy in all four subgroups of ischaemic cardiovascular disease, but not among those with diabetes or among those without ischaemic cardiovascular disease (Table 1). The use of lipid-lowering therapy increased in all subgroups of ischaemic cardiovascular disease up to the age 80 years, although this trend did not reach statistical significance in participants with ischaemic stroke. Use of lipid-lowering therapy also increased with age up to 80 years in those with diabetes and in those without ischaemic cardiovascular disease.

From 2004 through 2010, use of lipid-lowering therapy increased among participants in all four subgroups of ischaemic cardiovascular disease, in those with diabetes and in those without ischaemic cardiovascular disease (**Figure 1**).

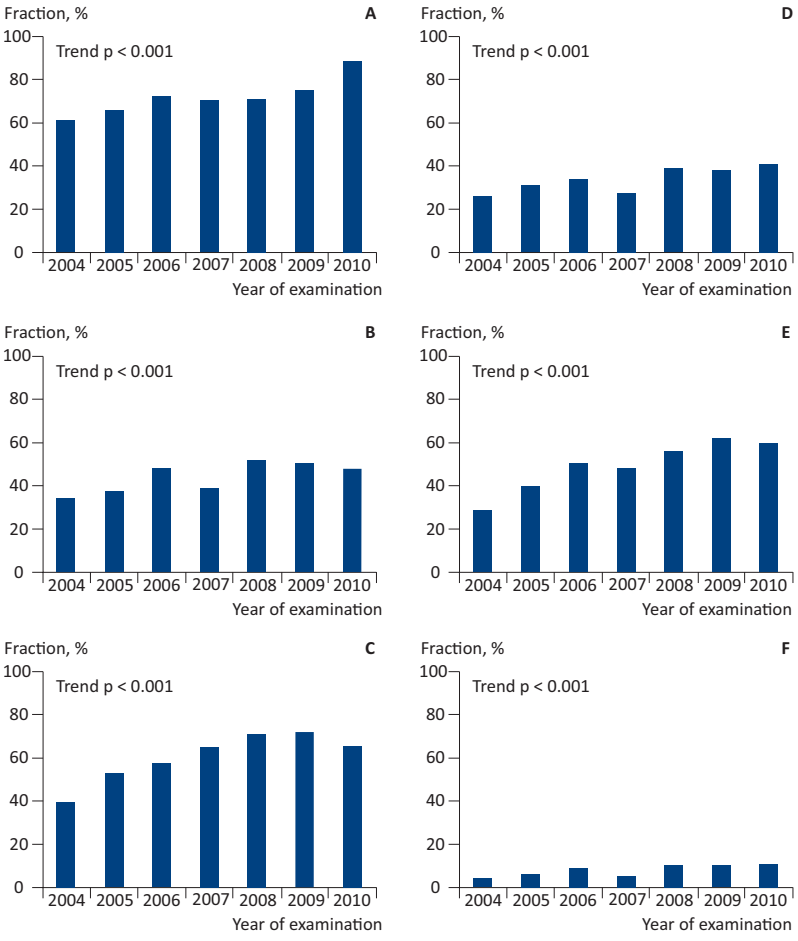
Treatment according to guideline lipid targets

Among those with myocardial infarction with and without lipid-lowering therapy, 41% and 84%, respectively, had not reached a total cholesterol of < 4.5 mmol/l; 30% and 79%, respectively, had not reached an LDL cholesterol of < 2.5 mmol/l, while 46% and 48%, respectively, had not reached triglycerides < 1.7 mmol/l (**Figure 2**). In general, 30-50% of the participants with a prior history of ischaemic cardiovascular disease who were receiving lipid-lowering therapy still had a plasma total cholesterol > 4.5 mmol/l and an LDL cholesterol > 2.5 mmol/l (**Table 2**); among those not receiving lipid-lowering therapy, this was true for 80-90%. For plasma triglycerides, the fractions among those with ischaemic cardiovascular disease not reaching triglycerides < 1.7 mmol/l were 40-50%. This was true in both those with and without lipid-lowering therapy.

In diabetics with and without lipid-lowering therapy, 44% and 79%, respectively, had not reached a total cholesterol < 4.5 mmol/l, 27% and 71%, respectively,

FIGURE 1

Fractions of individuals on lipid-lowering therapy in 2004 through 2010 in participants with a prior history of myocardial infarction (**A**), other ischaemic heart disease (**B**), ischaemic stroke (**C**), claudicatio intermittens (**D**), diabetes (E) and in participants without ischaemic cardiovascular disease (F). Based on 69,354 individuals from the Copenhagen General Population Study. Trend p-values by Wilcoxon extension of a Kruskal-Wallis test.

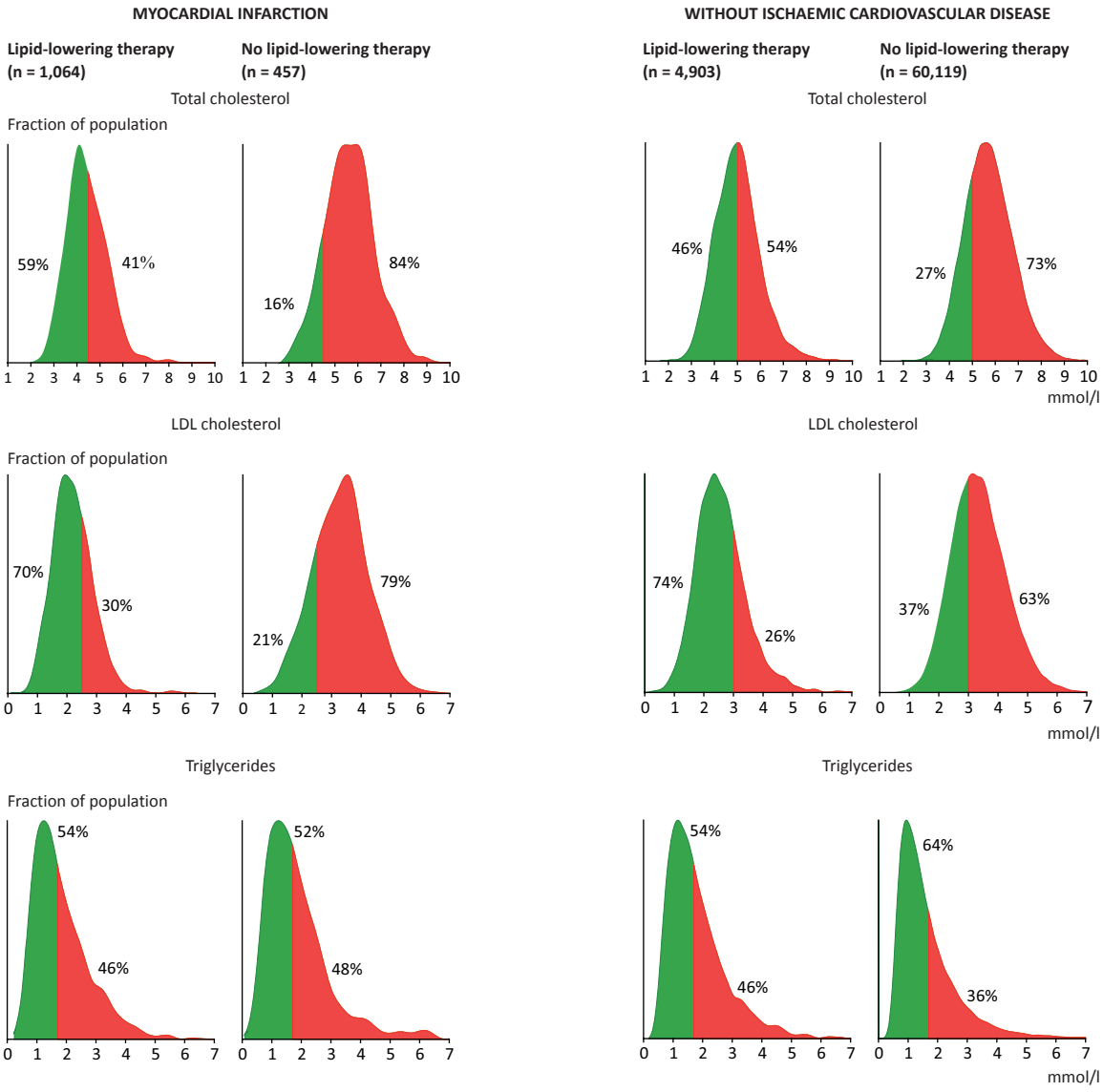


had not reached LDL cholesterol < 2.5 mmol/l, and 54% and 54%, respectively, had not reached triglycerides < 1.7 mmol/l (Table 2).

In smokers and in those with hypertension or obesity, but without ischaemic cardiovascular disease, 45% of the participants who were receiving lipid-lowering therapy did not reach a plasma total cholesterol < 5 mmol/l, while roughly 25% did not reach an LDL cholesterol < 3 mmol/l (Table 2); for those not receiving lipid-lowering therapy, this was true for roughly 80% for total cholesterol and for roughly 70% for LDL cholesterol. For plasma triglycerides in these groups, those with lipid-lowering therapy had higher triglyceride levels than those who did not, and the fraction not reaching triglycerides < 1.7 mmol/l reached 63% in obese individuals receiving lipid-lowering therapy.

From 2004 through 2010, the fraction of participants on lipid-lowering therapy who were not treated according to guideline targets for total cholesterol decreased slightly, both for participants with a prior history of myocardial infarction and for those without ischaemic cardiovascular disease (**Figure 3**). However, the fraction of participants on lipid-lowering therapy, but not treated according to guideline targets for LDL cholesterol was similar from 2004 through 2010 in both groups or decreased only slightly. Finally, the fraction of participants on lipid-lowering therapy who were not treated according to guideline targets for plasma triglycerides declined

FIGURE 2



Distribution of plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides in individuals with a prior history of myocardial infarction and in individuals without ischaemic cardiovascular disease. The green area illustrates the fraction of individuals (also shown as percentages) with values at target according to guidelines, while the red area illustrates the fraction of individuals (also shown as percentages) not reaching target values. The percentage of individuals not reaching target values (red fraction) is in Table 2 also shown for other groups than those shown in this figure. Based on 69,354 individuals from the Copenhagen General Population Study.

slightly from 2004 through 2010, both for participants with a prior history of myocardial infarction and for participants without ischaemic cardiovascular disease.

DISCUSSION

The present data do not provide explanations as to why large factions of individuals with and without ischaemic cardiovascular disease, or with diabetes, do not receive lipid-lowering therapy, or do not have lipids treated to target values according to guidelines. However, medical doctors at hospitals and in general practice as well as the patients themselves all have part in the decision on whether to take lipid-lowering therapy or not, and in the decision on which type of lipid-lowering therapy to use. During hospitalisation, individuals with ischaemic cardiovascular disease and/or diabetes simply may not be prescribed lipid-lowering therapy. Also, if seen in general practice, doctors may not prescribe lipid-lowering therapy or may even decide to stop lipid lowering-therapy although such drugs were prescribed by hospitals. Finally, patient compliance may be poor either because of real or perceived side effects, or because of a wish not to take medications in general. Importantly, in Denmark it is unlikely that lipid-lowering therapy in general is not taken due to the cost, as the least expensive simvastatin 40 mg costs less than 0.2 Euro daily. However, part of the explanation as to why many patients on lipid-lowering therapy did not reach lipid targets may, indeed, be the cost as the more potent statins atorvastatin and rosuvastatin were 10-30 fold more expensive than simvastatin in Denmark in the period from 2004 through 2010; because atorvastatin lost its patent in Denmark May 2012 and in many other countries soon, the cost as an explanation for not reaching lipid targets may disappear in the near future. Other potential explanations as to why individuals treated with lipid-lowering therapy still have lipid values above guideline targets include 1) a low starting dose which has not been adjusted according to lipid levels, 2) side effects of lipid-lowering therapy that may require a lower dose than needed to reach guideline targets, 3) lack of patient compliance resulting in omission or partial omission of lipid-lowering therapy in the dose and frequency prescribed and last, but not least, 4) doctors' lack of knowledge of current guidelines [15].

Another interesting observation was that although a larger fraction of individuals with lipid-lowering therapy than without such therapy reached guideline targets for total and LDL cholesterol, this was not the case for triglycerides. This may suggest that many doctors simply do not focus on reducing triglycerides, as suggested in a recent European consensus statement [2]. Alternatively, it is possible that patients receiving lipid-lowering therapy become more relaxed with their lifestyle which may partly offset the triglyceride-reducing effect of lipid-lowering therapy. Such a scenario could also help explain the higher triglyceride levels in smokers and in those with hypertension or obesity among those with versus those without lipid lowering therapy. However, it is possibly more likely that smokers and those with hypertension or obesity will initially have much higher triglyceride levels when given lipid lowering therapy by their doctors than those not receiving lipid-lowering therapy.

None of the previous studies [7-9, 16-18] examined individuals in the general population as was the case in the present study. Previous studies have all examined

TABLE 2

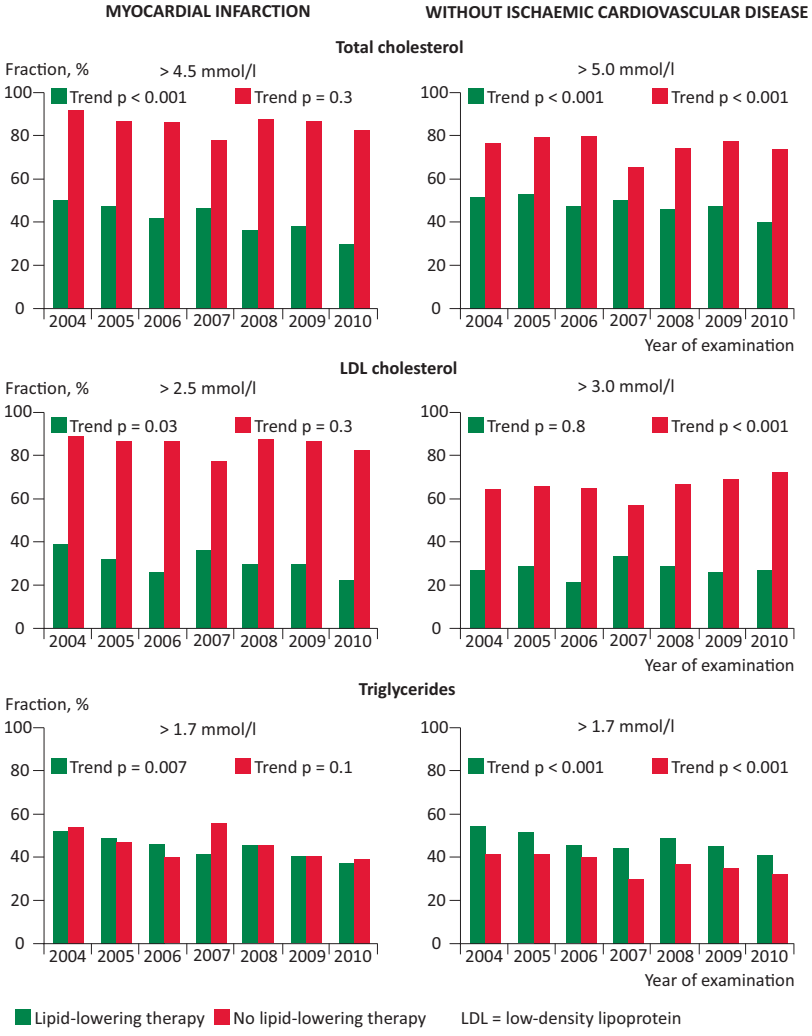
Fractions in % of individuals above guideline targets for plasma levels of total cholesterol, low-density lipoprotein cholesterol and triglycerides, with or without lipid-lowering therapy. Based on individuals from the Copenhagen General Population Study from 2004-2010. Fractions of individuals above guideline targets in those with versus without lipid-lowering therapy were compared using a Pearson's χ^2-test.

	Total cholesterol						LDL cholesterol						Triglycerides		
	lipids > 4.5 mmol/l			lipids > 5.0 mmol/l			lipids > 2.5 mmol/l			lipids > 3.0 mmol/l			lipids > 1.7 mmol/l		
	with	without	p-value	with	without	p-value	with	without	p-value	with	without	p-value	with	without	p-value
With ischaemic cardiovascular disease															
Myocardial infarction	41	84	< 0.001	–	–		30	79	< 0.001	–	–		46	48	0.5
Other ischaemic heart disease	49	89	< 0.001	–	–		33	84	< 0.001	–	–		45	43	0.2
Ischaemic stroke	51	84	< 0.001	–	–		34	76	< 0.001	–	–		42	42	0.9
Claudicatio intermittens	52	89	< 0.001	–	–		38	85	< 0.001	–	–		55	50	0.03
Without ischaemic cardiovascular disease															
Diabetes mellitus	44	79	< 0.001	–	–		27	71	< 0.001	–	–		54	54	1.0
Smoking	–	–		45	74	< 0.001	–	–		25	64	< 0.001	47	36	< 0.001
Hypertension	–	–		45	80	< 0.001				25	69	< 0.001	47	43	< 0.001
Obesity: BMI > 30 kg/m^2	–	–		45	80	< 0.001	–	–		27	73	< 0.001	63	58	0.003

BMI = body mass index; LDL = low density lipoprotein.

FIGURE 3

Fractions of individuals with levels of plasma total cholesterol, low-density lipoprotein cholesterol, and triglycerides above guideline targets in 2004 through 2010 in participants with a prior history of myocardial infarction and in participants without ischaemic cardiovascular disease. Based on 69,354 individuals from the Copenhagen General Population Study. Trend p-values by Wilcoxon extension of a Kruskal-Wallis test.



patients at hospitals or patients being followed as outpatients, and they are thus prone to recall and selection bias, which is less likely in the present study examining a large random fraction of the general population.

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