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Epidemiology of low HDL-cholesterol: results of studies and surveys

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Low HDL-cholesterol is a risk factor for adverse cardiovascular outcomes independently of levels of LDL-cholesterol. Surveys in individual countries have revealed a substantial prevalence of low HDL-cholesterol, but the utility of data from these studies is limited by differences in study designs and patient populations. Accordingly, the Pan-European Survey of HDL-cholesterol set out to determine the prevalence of low HDL-cholesterol [$<$1.03 mmol/L (40 mg/dL) in men and $<$1.29 mmol/L (50 mg/dL) in women] in a large ($n = 8545$) population of patients receiving treatment for dyslipidaemia under the care of specialist physicians in 11 European countries. Low HDL-cholesterol was present in 33% of men and 40% of women, with very low HDL-cholesterol present in 14% (both genders combined). Hypertriglyceridaemia was present in 49% of men and 45% of women. Low HDL-cholesterol and hypertriglyceridaemia occurred in 22% of men and 25% of women. Low HDL-cholesterol is common among the European population of patients under treatment for dyslipidaemia and thus contributes importantly to overall cardiovascular risk. Interventions to increase HDL-cholesterol have been shown to inhibit atherosclerosis and to improve cardiovascular prognosis in high-risk study populations. Agents that increase HDL-cholesterol should be used in addition to statins, where necessary, to optimize the lipid profile.

Introduction

Low HDL-cholesterol is a risk factor for adverse cardiovascular outcomes independently of levels of LDL-cholesterol.[1–4] In particular, low HDL-cholesterol is commonly found to coexist with insulin resistance, hypertriglyceridaemia, and a shift in the subclass distribution of LDL towards smaller, denser, and more atherogenic lipoproteins, especially in patients with type 2 diabetes or the metabolic syndrome.[4,5] The simultaneous pharmacological correction of hyperlipidaemia and low HDL-cholesterol, especially with a combination of nicotinic acid with a statin, is increasingly regarded as a rational and evidence-based strategy for improving cardiovascular prognosis beyond that achievable with statins alone.[6]

The generation of accurate data on the prevalence of low HDL-cholesterol is essential if we are to be able to quantify the magnitude of the clinical problem it poses. The purpose of this review is to consider the prevalence of low HDL-cholesterol and the impact of current lipid-modifying treatment on this cardiovascular risk factor. Strong emphasis will be placed on the results of the recently published Pan-European Survey of HDL-cholesterol, a Europe-wide survey of levels of HDL-cholesterol, and other lipid parameters in more than 8500 patients receiving medical care for dyslipidaemia.[7]

Estimates of the prevalence of low HDL-cholesterol from individual countries

Prevalence estimates

Survey evidence collected during the previous decade suggests that a substantial proportion of the dyslipidaemic population has low HDL-cholesterol. *Table 1* provides

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Table 1 Overview of selected large surveys that measured the prevalence of low HDL-cholesterol in different populations

Author	Country	Year	Population	*n*	Diagnostic cut-off (mmol/L)	Prevalence (%)	
						Men	Women
Patel *et al.*[8]	UK	2003	Lipid clinic or general practice	1 736	<1	23.0	8
			Subgroup on lipid-lowering therapy	1 136	<1	25.5	10.1
			Subgroup with CHD	527	<1	23.6	7.6
			Subgroup with diabetes	449	<1	28.5	14.1
Verschuren *et al.*[9]	The Netherlands	1987–92	Urban general population, aged 20–29	>40 000	<0.9	15	4
			Urban general population, aged 50–29	>40 000	<0.9	26	7
Soysal *et al.*[10]	Turkey	2001–02	Urban, aged 30–39	600	NCEP	82	50
Passos *et al.*[13]	Brazil	1997	General population aged 18–59	1 494	NCEP	50 (both genders)	
			General population aged ≥60[6]	818	NCEP	56 (both genders)	
Lorenzo *et al.*[12]	Mexico	1990–92	Low income, urban population	2 282	NCEP	88.6	94.4
		1997–99	Low income, urban population	1 754	NCEP	92.1	96.6
Ford *et al.*[15]	USA	1998–94	US general population (NHANES)	6 436	NCEP	36.2	39.7
		1999–2000	US general population (NHANES)	1 677	NCEP	36.6	43.4
Rubins *et al.*[16]	USA	1991–93	Community-living men with CHD	8 578	<0.9	38	—
Li *et al.*[18]	China	2003	Urban general population	14 963	<0.9	7.7	1.5
Azizi *et al.*[19]	Iran	2000	Urban general population	9 514	<0.9	31	13

NCEP diagnostic criteria of <1.03 mmol/L (men) and <1.29 mmol/L (women). To convert mmol/L to mg/dL, divide by 0.02586.

an overview of large surveys carried out in different regions of the world. An audit of lipid management in a lipid clinic or general practice clinic in the UK showed that roughly one man in four and about one woman in 12 had low HDL-cholesterol, defined as <1.0 mmol/L (39 mg/dL).[8] More than half of this population (65%) was receiving lipid-lowering therapy. This treatment appeared to exert little or no effect on the prevalence of low HDL-cholesterol, which was slightly higher than that measured in the overall population. The higher prevalence of low HDL-cholesterol in diabetic subjects is not surprising, given the close association between low HDL-cholesterol and insulin-resistant states, as described earlier. Data from elsewhere in Europe tell a similar story. For example, very low HDL-cholesterol (<0.9 mmol/L) was observed in about one-quarter of middle-aged Dutch men.[9] The Turkish population is well known for a genetic predisposition towards low HDL-cholesterol,[10] and the majority of the male population and half of the female population of that country were shown to have low HDL-cholesterol, according to the diagnostic criteria from the US National Cholesterol Education Program/Adult Treatment panel III (NCEP/ATPIII).[11]

The prevalence of low HDL-cholesterol appears to be especially high in Latin American subjects, as shown by surveys carried out in Mexico[12] and Brazil[13] (*Table 1*). A further study in Mexico confirmed the healthcare problem posed by low HDL-cholesterol, 46% of men and 29% of women had HDL-cholesterol <0.9 mmol/L.[14] Interestingly, in the study in Mexico shown in *Table 1*, the prevalence of low HDL-cholesterol increased by 2–3% within a period of only 7 years.[12] A large and rapid increase in the prevalence of low HDL-cholesterol was also observed in American women in two cohorts of the US National Health and Nutrition Examination Survey (NHANES), which are representative of the US general population.[15] In the cohort recruited in 1988–94, about one-third of US men and women had low HDL-cholesterol, according to NCEP/ATPIII criteria. By 1999–2000, less than one decade later, the prevalence had increased by 0.4% in men and by 3.7% in women. Further data from the USA, measured in men with prior coronary heart disease screened for inclusion in the Veterans Administration HDL Intervention Trial,[16] revealed a similar prevalence of very low HDL-cholesterol (<0.9 mmol/L) to that measured in the general NHANES population (38% vs. 36%).

The developing world is not being spared the burden of cardiovascular disease associated with insulin resistance and the metabolic syndrome.[17] *Table 1* also shows that HDL-cholesterol <0.9 mmol/L was present in substantial proportions of subjects from China[18] and Iran.[19] These studies, together with other surveys in individual countries, not shown in *Table 1* (reviewed elsewhere),[20] add to the clinical evidence that low HDL-cholesterol is common and likely to present an important source of overall cardiovascular morbidity in the general population and in patients receiving treatment to manage their cardiovascular risk.

Limitations of these surveys

Table 1 also shows that the diagnostic criteria for defining low HDL-cholesterol differ markedly between studies. In addition, some studies used the same cut-off values for men and women. As the level of HDL-cholesterol is generally higher in women than in men, this is likely to underestimate the true prevalence in the overall population. Other important details differed between studies. These include the numbers of subjects and the nature of the survey populations and also the methodology used to measure HDL-cholesterol. With regard to the latter point, measurement of levels of HDL-cholesterol by the two most commonly employed methods (direct measurement or following precipitation from plasma) can provide markedly different results. Indeed, the differences in the level of HDL-cholesterol at baseline in the recent Collaborative Atorvastatin Diabetes Study[21] and the Fenofibrate Intervention and Event Lowering in Diabetes study[22] may result solely from such a difference in methodology.

The Pan-European Survey of HDL-cholesterol was designed to avoid these pitfalls.[7] This was principally achieved by recruiting a large survey population across a number of European countries and assessing low HDL-cholesterol on the basis of the NCEP/ATPIII criteria for men and women. The design and principal results of this major survey are described in the following section.

Pan-European Survey of HDL-cholesterol

Objectives and design

The principal objective of the survey was to obtain a reliable estimate of the prevalence of low HDL according to NCEP ATPIII criteria [$<$1.03 mmol/L ($<$40 mg/dL) in men and $<$1.29 mmol/L ($<$50 mg/dL) in women] in patients receiving treatment for dyslipidaemia across Europe. A secondary objective was to characterize the cardiovascular comorbidity of these patients.

The design of the survey has been published in detail elsewhere.[7,20] Briefly, adult patients (aged $\geq$ 18) with dyslipidaemia were enrolled if they were under the care of a specialist physician experienced in the management of dyslipidaemia and met one of the following inclusion criteria: (i) they had serum cholesterol $\geq$200 mg/dL (5.3 mmol/L)] and/or serum triglycerides $\geq$180 mg/dL (2.0 mmol/L)] despite treatment with diet and exercise for at least 3 months; (ii) they had received treatment with lipid-lowering drugs and diet and exercise for $\geq$3 months; (iii) they had a diagnosis of dyslipidaemia (including dyslipidaemia secondary to diabetes or the metabolic syndrome).

The specialist physicians (mainly cardiologists or endocrinologists) each recruited the first eligible patient seen on each of 3–5 days and recorded patient data on questionnaire. Waist circumference was defined as the smallest horizontal circumference at the waist level. No information that could identify a subject was obtained, and European data protection requirements were respected.

Results

Patients

The final survey database included information on 8545 subjects. *Table 2* shows demographic and disease characteristics of the survey population. Roughly two-thirds of the population were male, and on average, the population was overweight and mean waist circumference in men and women were above the NCEP/ATPIII cut-off values to diagnose abdominal obesity ($>$102 cm in men and $>$88 cm in women).[11] *Figure 1* shows the population stratified for commonly used definitions of overweight and obesity.[23,24] About one-fifth of the population was overweight according to their BMI, and 12% had either severe obesity (BMI 35.0–39.9 kg/m^2) or morbid (very severe) obesity (BMI $>$40 kg/m^2).

Lipid-modifying treatment was received by 6756 patients (79% of the overall population). Most of these

Table 2 Demographic and disease characteristics of the population of the Pan-European Survey of low HDL-cholesterol Mean $\pm$ SD

Demographics	
Male/female (%)	61/38
Mean age (years)	62.2 (11.4)
Mean body-mass index (kg/m^2)	29.0 (5.2)
Mean waist circumference (cm)	
Men	102.6 (13.4)
Women	96.4 (16.0)
Mean BP (mmHg)	138.8 (18.4)/ 80.5 (10.3)
Disease characteristics	
Type 2 diabetes (%)	45.2
Hypertension (%)	72.1
Prior myocardial infarction (%)	24.2
Coronary heart disease (%)	44.7
Peripheral vascular disease (%)	15.9
Other cardiovascular risk factors	
Sedentary[a] (%)	68
Smoker[b] (%)	16
Heavy drinker[c] (%)	7

[a]Participates in sport less than once a week.
[b]At least one cigarette per day.
[c]More than two glasses of wine per day for women and more than three glasses of wine per day for men.

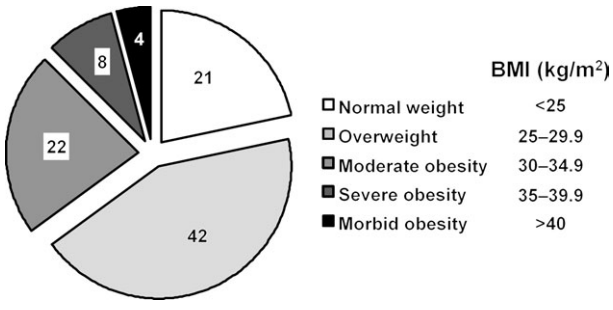

Figure 1 Prevalence (%) of different severities of obesity in the Pan-European Survey of low HDL-cholesterol (excludes 3% of the overall population for whom obesity status was not recorded).

Table 3 Mean (SD) lipid parameters of the population of the Pan-European Survey of low HDL-cholesterol according to whether subjects received lipid-modifying treatment

	Treated	Not treated
Total cholesterol		
mmol/L	5.12 (1.33)	5.87 (1.21)
mg/dL	198 (39)	227 (47)
LDL-cholesterol		
mmol/L	3.04 (1.08)	3.74 (1.08)
mg/dL	118 (42)	145 (42)
HDL-cholesterol		
mmol/L	1.29 (0.41)	1.31 (0.4)
mg/dL	50 (16)	51 (16)
Triglycerides		
mmol/L	2.04 (1.92)	2.17 (1.69)
mg/dL	181 (170)	193 (150)

patients (93%) were receiving pharmacological treatment, usually with a statin (85%). Fibrates were received by 8% of treated patients, and 6% received other treatments. Mean lipid parameters are shown in *Table 3*. On average, mean levels of total and LDL-cholesterol suggested a mild hyperlipidaemia, and mean triglycerides were above the optimal guideline value of 1.7 mmol/L (150 mg/dL).[11] Levels of ApoB-containing lipoproteins (total and LDL-cholesterol) were markedly lower in patients receiving lipid-modifying treatment, although there was little difference between these groups for HDL-cholesterol or triglycerides.

Prevalence of low HDL-cholesterol

Low HDL-cholesterol was found in 33–34% of men and 39–40% of women receiving or not receiving lipid-modifying treatment (*Figure 2*). The overall prevalence of low HDL-cholesterol was 33% in men and 40% in women. As elevated triglycerides often accompany low HDL-cholesterol, this parameter was also measured, and hypertriglyceridaemia was found in 47–57% of men and 44–48% of women. Both lipid abnormalities occurred together in 21–26% of men and 25–27% of women. Lipid-modifying treatment had virtually no influence on the prevalence of low HDL-cholesterol, and little influence on the prevalence of hypertriglyceridaemia. Very low HDL-cholesterol (<0.9 mmol/L) was found in 14% of men or women treated for dyslipidaemia and in 13% of untreated patients.

Figure 3 shows the average adjusted level of HDL-cholesterol and the prevalence of low HDL-cholesterol in individual countries within the survey. These measurements were similar in most countries, although a particularly high prevalence of low HDL-cholesterol was observed in the Netherlands (49%). Such differences are interesting and require further study, but should be interpreted with caution as differences were observed in the proportions of different specialities between countries, which may have influenced the precise nature of the patient population. For example, 95% of French physicians were cardiologists,

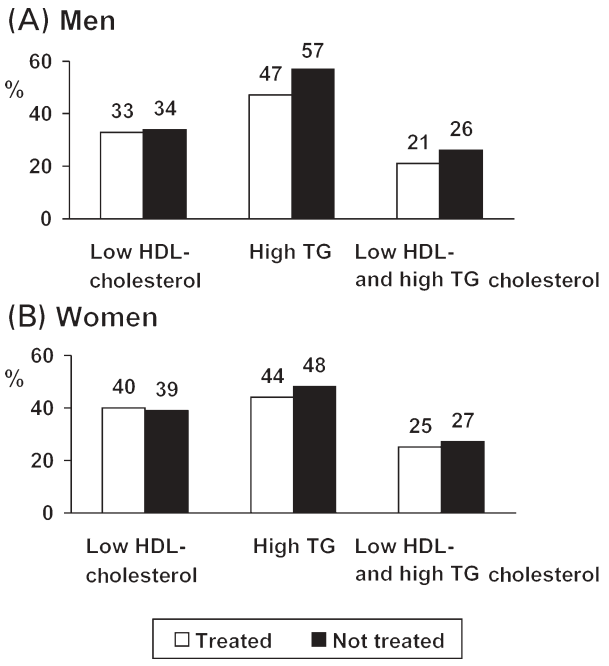

Figure 2 Prevalence of low HDL-cholesterol, hypertriglyceridaemia, or both according to receipt or not of lipid-modifying treatment in the Pan-European Survey of low HDL-cholesterol. Low HDL-cholesterol was defined as <1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women; high triglycerides (TG) was defined as >1.7 mmol/L (150 mg/dL).

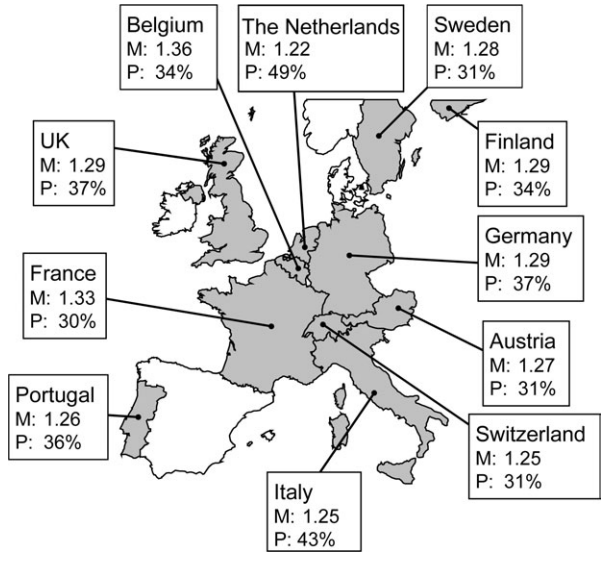

Figure 3 Mean HDL-cholesterol in mmol/L (M) by country and prevalence (P) of low HDL-cholesterol adjusted for eight confounding factors by country; low HDL-cholesterol was defined as <1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women.

compared with 11% in the Netherlands, and 73% of Dutch physicians were internists, compared with none in France. However, an analysis of subjects recruited by physicians of the same speciality (cardiologists) produced results that were very similar to those from the overall

population. Thus, we can be confident that the results of the Pan-European survey as a whole remain valid.

Discussion

The Pan-European Survey of HDL-cholesterol confirms and extends the results of earlier surveys conducted in individual countries and shows that low HDL-cholesterol is a common finding among patients treated for dyslipidaemia. Overall, 33% of men and 40% of women displayed this cardiovascular risk factor. The almost complete lack of effect of lipid-modifying treatment on the prevalence of low HDL-cholesterol and the minor effect of this treatment on the prevalence of hypertriglyceridaemia were striking, although not unexpected. Statins exert little effect on HDL-cholesterol, as shown by a meta-analysis of the results of five long-term randomized trials with these agents that enrolled more than 30 000 patients.[25] In this analysis, the large expected reductions in LDL-cholesterol were observed (average net changes 25–36%), but changes in HDL-cholesterol were only 5–7%, and changes in triglycerides were only 11–17%. Nicotinic acid, in contrast, increased HDL-cholesterol by 15–35%, depending on dose, and produces a useful reduction in triglycerides of 20–50%.[11]

Cardiovascular management guidelines strongly promote control of LDL-cholesterol as the primary approach to lipid management, and statins are the principal means by which this is accomplished in patients insufficiently responsive to lifestyle intervention.[11,26] These guidelines propose an optimal value for HDL-cholesterol [$>$1.03 mmol/L (40 mg/dL) in men and $>$1.29 mmol/L (50 mg/dL) in women], but stop short of identifying this level as a treatment goal that should be addressed independently of other lipid parameters.

In practice, the management of LDL-cholesterol and HDL-cholesterol is not mutually exclusive. Cardiovascular management guidelines strongly promote lifestyle interventions (diet and exercise) for the management of cardiovascular risk, and structured evaluations of exercise regimes have demonstrated modest short-term improvements in the lipid profile, including HDL-cholesterol,[27] and long-term increases in HDL-cholesterol associated with reduced abdominal obesity.[28,] A combination of weight loss and exercise may be important for improving HDL-cholesterol. For example, the NCEP, a study in 21 obese men, showed that exercise alone did not alter the lipid profile to a clinically significant extent, but that HDL-cholesterol increased by 11% when a weight loss programme was added to the exercise regime.[29] A study in 377 subjects with low HDL-cholesterol and hyperlipidaemia, however, did not replicate these findings; diet + exercise improved LDL-cholesterol, but not HDL-cholesterol, in this study.[30] Nevertheless, abdominal obesity promotes the atherogenic low HDL-cholesterol/high triglyceride/small, dense LDL phenotype,[31] and obesity may account for a substantial proportion of the prevalence of low HDL-cholesterol. All patients should be encouraged to diet, to exercise, and to lose weight.

Where lifestyle intervention plus a statin is insufficiently effective, appropriate combination therapy with a statin and nicotinic acid or a fibrate can achieve simultaneous control of LDL-cholesterol and HDL-cholesterol. It should be noted in this regard that a combination of a statin and nicotinic acid delivered cardiovascular event rate reductions of up to 90% in the high-risk population of the HDL Atherosclerosis Treatment Study[32] and that a statin combined with prolonged-release nicotinic acid (Niaspan®) induced regression of atherosclerosis during up to 2 years of treatment in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 and 3 studies.[33,34] The high prevalence of low HDL-cholesterol, described earlier, adds urgency to these therapeutic considerations.

Conclusions

Low HDL-cholesterol is an independent risk factor for cardiovascular disease and is present in about one-third of patients receiving treatment for dyslipidaemia in Europe. There is no doubt that low HDL-cholesterol is an important contributor to global cardiovascular risk in many patients. Physicians should be aware of the high possibility of low HDL-cholesterol, especially in patients with type 2 diabetes or the metabolic syndrome, and appropriate combination regimens, for example, with a statin and nicotinic acid, should be employed where necessary to optimize the lipid profile.

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