

Original Article

Lipid and lipoprotein reference values from 133,450 Dutch Lifelines participants: Age- and gender-specific baseline lipid values and percentiles

Jan W. Balder, BSc, Jeroen K. de Vries, MD, Ilja M. Nolte, PhD,
Peter J. Lansberg, MD, PhD, Jan A. Kuivenhoven, PhD^{*,1},
Pieter W. Kamphuisen, MD, PhD¹

Department of Pediatrics, Section Molecular Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Drs Balder, Lansberg, and Kuivenhoven); Department of Vascular Medicine, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Drs Balder, Vries, and Kamphuisen); Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Dr Nolte); and Department of Internal Medicine, Tergooi, Hilversum, the Netherlands (Dr Kamphuisen)

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BACKGROUND: Lipids and lipoproteins are recognized as the most important modifiable risk factors for cardiovascular disease. Although reference values for the major lipoproteins, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides, have been collected in numerous studies and cohorts, complete contemporary percentile-based reference values are underreported.

OBJECTIVE: We set out to provide such reference lipid data using a large contemporary population-based cohort study.

STUDY DESIGN AND SETTING: Lifelines is a cross-sectional population-based Dutch cohort study. We analyzed 133,540 adult fasting participants without cardiovascular disease and without lipid-lowering drug use. Lipid levels were directly measured and selected percentiles of all lipid parameters were calculated. Friedewald LDL-C estimation was calculated as well.

RESULTS: From 20 till 49 years of age, men were found to exhibit a steep 64% increase of LDL-C (median +54 mg/dL), while triglyceride levels increased almost two-fold. In women, LDL-C levels did not change from 18 till 35 years, followed by a steep 42% increase till 59 years (median +42 mg/dL). In contrast to men, triglycerides were stable in ageing women. Overall, Friedewald LDL-C levels are lower compared with the direct measurement, especially with increasing triglyceride levels.

CONCLUSIONS: This observational study highlights striking gender- and age-related differences in plasma lipid profiles. The given reference ranges of plasma lipids can assist in early identification of individuals with hypocholesterolemia and hypercholesterolemia, especially familial hypercholesterolemia. These reference ranges are available for physicians and patients at www.my-cholesterol.care/.

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¹ These authors contributed equally to this to this work.

* Corresponding author. Department of Pediatrics, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, the Netherlands.

E-mail address: j.a.kuivenhoven@umcg.nl

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Introduction

Healthcare in the 21st century is challenged by an increasing number of people experiencing noncommunicable chronic diseases. Cardiovascular disease (CVD) affects most men beyond the age of 55 years and women beyond 65 years of age.¹ Consequently, CVD is generally regarded an ageing disorder. However, it has long been known that fatty streaks and subsequent plaque formation already starts at a very young age, and the pace of progression is related to plasma low-density lipoprotein cholesterol (LDL-C) levels concentration.² To curtail this threat, early prevention seems the preferred approach to curb this exponential increase in avoidable chronic diseases.^{3,4} From this perspective, the early identification of modifiable risk factors, especially dyslipidemia, is key to effective prevention and management of CVD.^{2,5}

Cohort studies can provide insight in what is needed to promote “healthy ageing” and find solutions for early identification and intervention of individuals at increased CVD risk. The Lifelines cohort study, initiated in 2006, is the largest ongoing prospective observational European population study to date.⁶ Study participants, 152,180 adult inhabitants of the northern part of the Netherlands, were recruited by their primary care physicians, through family members or by registering at the Lifelines Website (www.lifelines.nl). The total duration of follow-up will be 30 years, the first 5-year follow-up visit is in process, the next 10-year follow-up visit is being planned. Data consist of self-reported/validated questionnaires, routine clinical biochemistry, physical examination, biobanking of biomaterials including blood, urine, and feces and genome-wide genotyping. Thereby, the Lifelines study can provide insight into the prevalence and incidence of multifactorial diseases and their risk factors, including lipids. Based on the concepts of modifiers and the three-generation design, this study may provide better understanding of the causes and prognosis of dyslipidemia over a lifetime. This may ultimately result in optimal tailored treatment of, for example, hypercholesterolemia, overriding standard preventive strategies.

Identifying dyslipidemia requires knowledge of the normal distribution of blood lipids in the population. Reference values for total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides have been collected in numerous studies and cohorts. However, contemporary and comprehensive percentile-based reference values are surprisingly missing. Apart from the broad variation of these values in different geographical regions,⁷ there are also time-dependent changes reflecting modifications in age, lifestyle, and pharmaceutical interventions.^{8,9}

This article aims to provide baseline information and facilitate future research, by providing age- and gender-based reference values for lipid levels. These lipid reference values are indispensable for comparison with populations from different regions or different genetic

background, as well as monitoring prospective changes. Importantly, they can also serve the early identification of individuals with, for example, familial hypercholesterolemia, a common but underdiagnosed and undertreated genetic disease.²

Methods

Participants

Lifelines is a large population-based prospective cohort study conducted in the north of the Netherlands. Participants of almost exclusively Caucasian descent were included between 2006 and 2013. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen, and all participants provided written informed consent. The design and rationale of the study are described elsewhere.⁶ In short, general practitioners asked their patients, between the age of 25 and 50 years, if they were willing to participate. After a positive response, family members from all ages (partner, parents, parents-in-law, and children) were also invited to participate. In addition, individuals aged ≥ 18 years could become a participant through self-registration. These individuals were also asked to invite family members.

At baseline, all participants filled out questionnaires and underwent a comprehensive physical examination. The questionnaires covered health topics, psychosocial parameters, information on lifestyle, and medication use (including lipid-lowering drugs). Physical examination included anthropometry, blood pressure measurement, pulmonary function tests, echocardiogram, and a neuropsychiatric interview. Fasting blood was drawn from all participants for clinical chemistry measurements including plasma lipids.

Exclusion criteria

The data of children (aged < 18 years) have not yet been released and could therefore not be included. Participants with a history of CVD at baseline, defined as myocardial infarction, coronary surgery (balloon angioplasty or bypass surgery) or stroke, were excluded. Transient ischemic attack and peripheral vascular disease could not be accounted for because these clinical features could not be adequately scored with the questionnaires used. In addition, participants reporting lipid-lowering drug use (ie, statins, fibrates, or ezetimibe) at baseline, and those with nonfasting blood tests at baseline were excluded from this analysis.

Cholesterol measurements

Venous blood samples were collected following a standard protocol, after an overnight fast. Plasma from heparinized tubes was used for clinical chemistry. Lipid measurements were performed using Roche Modular P automated analyzer (Mannheim, Germany). Total

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