Atherosclerosis 274 (2018) 191–198

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Non-LDL dyslipidemia is prevalent in the young and determined by lifestyle factors and age: The LifeLines cohort

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ARTICLE INFO

Article history:
Received 28 January 2018
Received in revised form
28 April 2018
Accepted 10 May 2018

Keywords:
Cardiovascular risk management
Cohort study
Dyslipidemia
Lifestyle
Non-LDL cholesterol
Population study
Obesity

ABSTRACT

Background and aims: Non-LDL dyslipidemia (NLD) confers cardiovascular risk, and prevalence rates appear to be high in elderly populations. Small cohorts have identified several lifestyle, anthropometric, and medical factors associated with NLD. We aimed to assess sex- and age-specific prevalence of NLD in a contemporary population cohort (n = 167 729), and to identify independent determinants of NLD, focusing on lifestyle, anthropometric, and medical factors.

Methods: The prevalence of NLD was assessed per 10-year age intervals in adults without cardiovascular disease not using lipid-modifying drugs from the Dutch LifeLines cohort. NLD was defined as low HDL-cholesterol or high triglycerides or high remnant cholesterol as per guideline cut-off values. Multivariable regression was used to identify factors independently associated with NLD. Determinants included age, smoking, alcohol use, physical activity, diet, BMI, diabetes mellitus (DM), chronic kidney disease, and in women, menopausal state and oral contraceptive use.

Results: NLD occurred in 15–19% of women and 13–30% of men in this cohort, with the highest prevalence of 30% in 35–55 year old men. In most age groups, the prevalence in women was lower than in men. Obesity (both sexes: Odds ratio (OR) 5.3, 95% confidence interval (95%CI) 5.0–5.7), current smoking (men: OR 1.8, 95%CI 1.7–1.9; women OR 2.2, 95%CI 2.1–2.3), and DM (men: OR 2.2, 95%CI 1.8–2.6; women: OR 2.7, 95%CI 2.3–3.1) were strongly associated with NLD.

Conclusions: NLD already occurs frequently at an early age. Modifiable lifestyle choices, obesity, and DM were strong determinants of NLD. Public health efforts could substantially contribute to decrease NLD.

1. Introduction

Development of atherosclerotic cardiovascular disease (ASCVD) is strongly determined by modifiable risk factors such as dyslipidemia [1]. Besides elevated total cholesterol (Tc) and low-density lipoprotein cholesterol (LDLc), non-LDL dyslipidemia, including low levels of high-density lipoprotein cholesterol (HDLc), elevated triglycerides (TG), or high remnant cholesterol (Rc), is associated with increased risk of developing ASCVD [2–5]. Current guidelines provide ample recommendations for LDLc-lowering therapy in appropriate subgroups, whereas treatment of non-LDL dyslipidemia is more controversial [5]. Reported prevalence rates of individual components of non-LDL dyslipidemia range between 22% and 74% in various –often small and elderly– cohorts [6,7], but little is known about the prevalence rate in general population.

Many adverse lifestyle factors are growingly prevalent in young adults, increasing the burden of non-LDL dyslipidemia and adding to the development of ASCVD [8,9]. Early recognition and treatment of non-LDL dyslipidemia and its determining factors could contribute to the reduction of ASCVD. It is crucial to ascertain the prevalence of non-LDL dyslipidemia and its determining factors in young and healthy people [9].

Elevated LDLc has a stronger genetic component compared to

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https://doi.org/10.1016/j.atherosclerosis.2018.05.016
0021-9150/

non-LDL dyslipidemia, whereas lifestyle choices and anthropometric and medical factors are more strongly associated with non-LDL dyslipidemia compared to LDLc [10]. Factors have been identified as potentially associated with non-LDL dyslipidemia, including age, sex, obesity, smoking, alcohol use, physical activity, dietary factors, menopausal state and oral contraceptive use for women, and medical conditions like diabetes mellitus (DM) and chronic kidney disease (CKD) [4,11–23]. Most of these studies, however, have studied the association between single factors or a small subset of these factors and individual components of non-LDL dyslipidemia. Little is known about the interplay of lifestyle, anthropometric, and medical factors together on non-LDL dyslipidemia in the general population.

Our aim is to describe sex- and age-specific prevalence rates of non-LDL dyslipidemia in a large, contemporary population cohort without known ASCVD, and identify determinants of non-LDL dyslipidemia. We hypothesize that lifestyle, anthropometric, and medical factors are independently associated with non-LDL dyslipidemia.

2. Materials and methods

2.1. Participants and data collection

We included adult participants from the LifeLines cohort, a large, prospective, population-based cohort study with a 3-generational design, examining health and health-related behaviors in a representative sample of 167,729 persons from the North Netherlands. Individuals aged 25–50 years were invited to participate. On inclusion, the participant's partner, parents, and children were also invited to participate. Following this design, young adults were oversampled. Recruitment lasted from 2006 to 2013. Detailed information has been published previously [24]. All participants provided written informed consent.

For our study, adult participants with known ASCVD, missing lipid levels, or use of drugs that are known to alter serum lipid levels were excluded (Supplementary Fig. 1). Data were collected through questionnaires on: demographics; health status (European Community Respiratory Health Survey (ECRHS II)); diet (Food Frequency Questionnaire (FFQ), specifically developed for LifeLines); and physical activity (Short Questionnaire to Assess Health-Enhancing (SQUASH)) [24]. Height, weight, and blood pressure were measured at baseline visit. All prescribed and over-the-counter medication was brought to the study center and classified according to the Anatomical Therapeutic Chemical (ATC) classification system by a study nurse. Blood and urine were sampled for routine chemistry panels. Tc, LDLc, and HDLc were measured with a direct assay, TG using an enzymatic colorimetric test, and creatinine using an IDMS-traceable enzymatic method (all on Roche, Modular P, Mannheim, Germany). HbA1c was measured using a turbidimetric assay (Roche Diagnostics Nederland BV, Almere, The Netherlands).

2.2. Primary outcome: definition of non-LDL dyslipidemia and its constituents

We defined non-LDL dyslipidemia as a composite of low HDLc (<1.0 mmol/l for men or <1.2 mmol/l for women), high TG (fasting TG > 1.70 mmol/l), or high Rc (calculated by subtracting LDLc and HDLc from Tc; defined as Rc > 0.7 mmol/l) [4,5]. Non-fasting TG measurements were excluded from analysis. These cut-off points aid clinical decisions to initiate treatment, and we consider non-LDL dyslipidemia clinically relevant when any of the components exceeds the aforementioned cut-off levels [5].

2.3. Determinants

Age, alcohol use, smoking, physical activity, dietary intake of fruit, vegeTables, fish, and meat, BMI, DM, CKD, and for women, oral contraceptive use and menopausal state were considered as potential determinants of non-LDL dyslipidemia. Alcohol use was self-reported and classified as abstainers, light drinkers, moderate drinkers, or heavy drinkers (0, ≤1, >1–2, and >2 drinks/day, respectively). Smoking was self-reported; non-smokers have never smoked; former smokers stopped smoking for at least a year; and current smokers reported smoking in the previous month and smoking for at least a year. Physical activity, self-reported using SQUASH, was classified as sufficient (moderate activity ≥30 min/day, ≥5 days/week), sedentary (no days/week with ≥30 min of moderate physical activity) or insufficient (the remainder). Intake of fruit, fish, meat (all in servings/week), and vegeTables (serving spoons/week) was self-reported using an FFQ and modeled as continuous variables.

BMI was classified as normal, overweight, and obese (<25, ≥25-<30, and ≥30 kg/m^2, respectively).

DM was defined as self-reported, using glucose-lowering drugs, or HbA1c ≥ 6.5%. CKD was defined as eGFR <60 ml/min (CKD-epi) [25]. In women, use of oral contraception or hormone replacement therapy was self-reported in the month before the baseline visit. Menopausal state was defined as self-reported, or when the menstrual cycle was absent and the last menstruation was >1 year before the baseline visit, or when this information was missing and age was ≥63 years (three standard deviations above the mean age of menopause in The Netherlands) [26].

2.4. Statistical analysis

The dataset was stratified by sex, and all analyses were done for men and women separately. Baseline characteristics were presented as mean (±standard deviation, SD) for normally distributed continuous variables, median (25–75th percentile) for skewed variables, or proportions (n, %) for categorical variables. Proportions of non-LDL-dyslipidemia were calculated per 10-year age interval. Multiple imputations using the iterative Markov chain Monte Carlo method was performed for missing data on smoking, alcohol use, dietary intake, physical activity, and menopause (maximum 10% missing data). Ten imputed datasets were created, and the pooled results were used for further analysis.

Independent associations between non-LDL dyslipidemia and lifestyle, anthropometric, and medical covariates were explored with multivariable logistic regression, stratified by sex. Associations with p-value <0.05 in univariate analyses were included in multivariable analysis. Strength of associations is reported with odds ratios and 95% confidence intervals (OR, 95% CI). Four regression models were created. The first model included age in 10-year intervals as determinant of non-LDL dyslipidemia. Consecutively, lifestyle factors (smoking, alcohol use, physical activity and dietary factors), BMI, and medical factors (DM, CKD and for women menopausal state and oral contraceptive use) were added. All possible sequences were analyzed. Receiver operating curves (ROC) were created for each model, and the increase in area under the curve (AUC) was used to assess the additional value of each subsequent step. Differences in AUC were assessed according to Hanley and McNeil [27]. Sensitivity analyses were performed in the non-imputed database.

We used SPSS version 22 (IBM, Armonk, New York, USA). Two-tailed p-values <0.05 were considered statistically significant.

3. Results

A total of 133,721 adult participants met the inclusion criteria