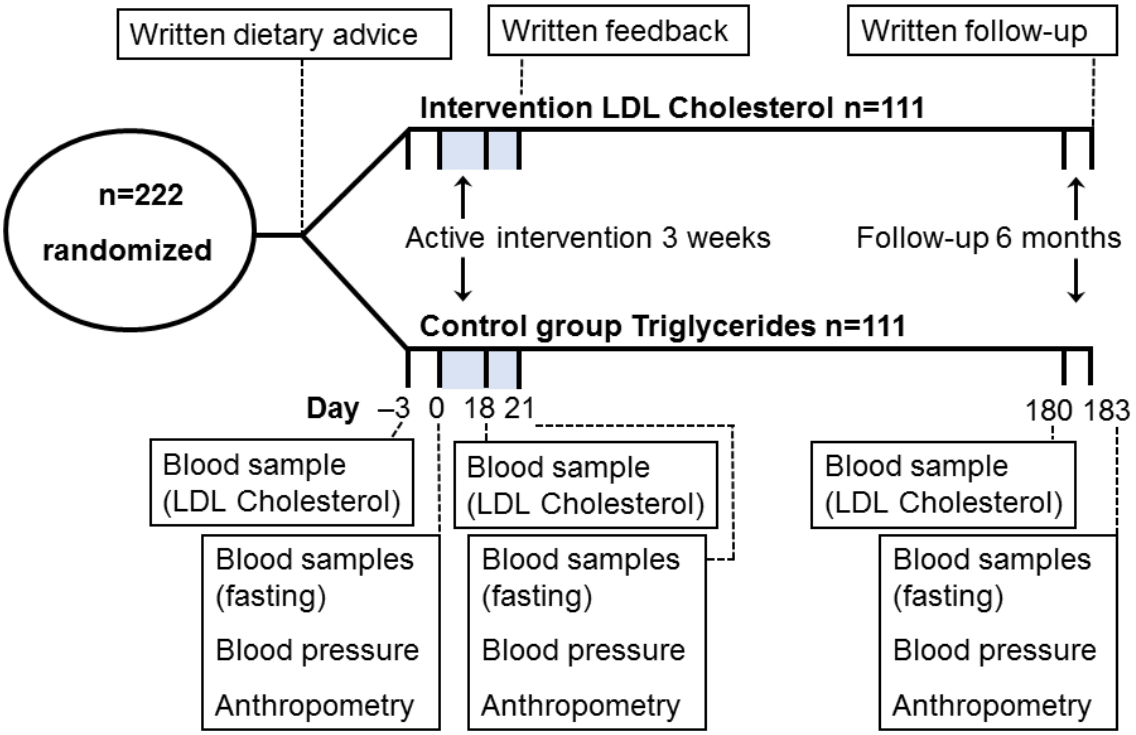
Figure 1. **MYDICLIN study**



Effectiveness of Written Dietary Advice on Lipoproteins - a Pragmatic Randomized Controlled Trial (MYDICLIN)

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Background

Dietary factors are the most important determinants of health in Sweden[1], and cardiovascular disease is still the leading cause of death in the Western world. Dietary advice is offered less in Swedish primary health care compared with e.g. the USA[2], and the attitude towards preventive healthcare varies greatly among Swedish GPs[3], despite many patients in primary care having an elevated cardiovascular risk. The Swedish National Board of Health and Welfare recommends that care providers offer "Kvalificerat rådgivande samtal", an extensive and theory-based counselling, to all patients with unhealthy eating habits (approximately 20-25% of the Swedish population), especially to patients with elevated cardiovascular risk[4]. Such interventions however demand resources not readily available in clinical practice, and require time, theoretical knowledge in nutrition, and skills in communication e.g. Motivational Interviewing or Cognitive Behavioral Therapy.

Previous studies of lifestyle interventions in primary care have demonstrated only modest effects on LDL cholesterol (0.07-0.16 mmol/L) after 6-12 months, with greater effects after more intense interventions[5,6]. However, no clear advantage has been demonstrated for dietary counseling by a dietitian compared with self-help resources[7]. Written dietary advice provide the advantage of being simple, objective and reproducible, without being costly or time-consuming. Detailed advice regarding foods that affect blood lipoproteins could also provide individually tailored, person-centered care; in which the patient becomes responsible for the dietary changes he/she wants to pursue. The advice could also contain elements of motivational strategies, in order to increase long-term compliance. Another opportunity is providing personal feedback after three weeks´ intervention, as most dietary effects on lipoproteins reach a new steady state after 13-14 days[8], and three weeks is often considered the least time required for attaining new habits (although more recent research indicates it often takes longer[9]). Personal feedback has provided little or no effect on lipoproteins in previous studies [10], but as genetic factors[11] and previous dietary habits induces individual differences in responsiveness to dietary changes[12], this could still be relevant in order to increase long-term compliance, especially for those individuals who get a clear beneficial response.

If such written advice would prove effective not only in the short term, it should be a cost-effective compared with other alternatives and possible to reproduce and implement in Swedish and international primary care. The food choices that lower LDL cholesterol accord well with Swedish[13] and international[14,15] guidelines for prevention and care of the major non-communicable diseases, e.g., cardiovascular disease, overweight and obesity, diabetes and cancer[16]. Thus, the present study could make available a novel tool in clinical practice, increase access to effective lifestyle counseling and improve patients´ diet, even beside effects on blood lipoproteins.

Purpose

The main purpose is to investigate whether written dietary advice with individual written feedback can affect blood lipoproteins in the short-term (3 weeks) and medium-term (6 months).

Specific aims

- What effect does written dietary advice have on LDL cholesterol (primary outcome) and other lipoproteins and risk factors (secondary outcomes) after 3 weeks and 6 months, compared with a control group?
- What proportion of individuals achieve a ≥10% reduction in LDL cholesterol from baseline, after 3 weeks and 6 months?
- In the group of responders (≥10% reduction in LDL cholesterol from baseline), what is the effect after 3 weeks and 6 months?
- Is double sampling of LDL cholesterol required in clinical practice, i.e., how many would be misclassified as responders/non-responders if only one sample was taken at 3 weeks and 6 months?
- How does the intervention´s cost compare with estimated future health care savings, as estimated per mean LDL cholesterol reduction, and per individual reaching ≥10% reduction in LDL cholesterol at 6 months?
- Which food choices are associated with reductions in LDL cholesterol in practice?
- What are the reasons given for wanting to reduce LDL cholesterol? Is there any association between reasons given and effect on LDL cholesterol?

Methods

The study will be carried out at Svärdsjö Primary Health Care Centre, during May 2018 to April 2019, as a pragmatic randomized controlled trial. Participating patients will be recruited by local advertisement at the clinic, in the nearby society, in the local advertisement bulletin and local social media groups. Inclusion criteria are: patients listed at the health care centre, wish to improve blood lipoproteins, ages 18-99 years. Exclusion criteria are: drugs affecting lipid metabolism (statins, ezetemibe, fibrates, PCSK9 inhibitors, neuroleptics, cortisone, amiodarone, estrogen, progesterone, testosterone, cyclosporin, tacrolimus, loop diuretics, protease inhibitors and anti-convulsants, whereas beta-blockers, tiazid-diuretics and SGLT2 inhibitors are accepted at stable use), malignant disease, extreme diet (vegan diet, strict low-carbohydrate diet, other weight-loss diet), disturbed metabolism e.g. untreated hypothyroidism or hyperthyroidism, dementia or inability to understand written Swedish instructions, other participant from same household, employment at the health care centre.

The participants will be block randomized after providing oral and written informed consent to either active intervention or control group (blind to researchers, personnel and participants at study start). If more than one potential participant belong to the same household, only one will be included in the study (by coin toss). All participants will receive an opaque envelope,

provided by an external source that construct the randomization sequence (Uppsala Clinical Research Center). The envelopes contain one double-sided A4 paper containing written dietary advice and some motivational strategies: “It's great that you want to improve your blood lipids! What are your three main reasons that you want to improve your blood lipids? What food choices suit you? How low can you go?” and a table in which participants are instructed to mark each day they have performed specific dietary changes. The intervention group receive detailed information on which food choices that have been demonstrated to beneficially affect LDL cholesterol, in accordance with current dietary recommendations and a recently performed systematic review of the literature (unpublished data). The control group will receive corresponding information, but instead on which food choices are known to reduce fasting triglycerides – advice neutral for LDL cholesterol (and vice versa).

Blood samples will be drawn on days -3, 0 (start of intervention), 18, 21, 180 and 183 (Figure 1). Days -3, 18 and 180, only LDL cholesterol will be analyzed, in order to get double samples three days apart. This reduces the biological variability of LDL cholesterol and thus reduces the required study size, and increases the precision of individual feedback. Days 0, 21 and 183, height (day 0 only), weight, waist circumference and blood pressure will be measured according to local routines and fasting blood samples will be drawn, including LDL cholesterol, total cholesterol, HDL cholesterol, triglycerides, apo B, apo AI, glucose, HbA1c, ALAT, as well as three 4 ml blood samples (whole blood, serum, plasma) to be frozen in -70 ^{o}C for future analyzes. Such analyses are not predetermined but may include genetic analyses, lipoprotein subfractions, lipoprotein(a) or serum PCSK9. At day 0, also TSH will be analyzed, in order to identify any unknown disturbances of thyroid function. If TSH is not between 0.1-8.9 mIU/L, the individual will be excluded from the study.

After day 21, participants will receive a standardized written letter containing results from the lab tests and personalized feedback depending on whether their LDL cholesterol has not improved (≤0%), improved little (0.1-9.9%), or clearly improved (≥10% reduction). The control group will receive a letter similar to intervention group, but with effects on triglycerides replacing LDL cholesterol. The effects on triglycerides in control vs intervention groups will also be analyzed as a secondary outcome. However, LDL cholesterol is the surrogate marker most clinically useful and is considered causally related to atherosclerosis development[8,15,17]. After day 183, all participants will receive another letter containing results from blood samples and the other groups´ dietary advice. Further blood or other analyses will however not be offered as part of the study. In order to compensate for increased expenses, extra health care visits and to minimize loss to follow-up, all participants will receive 500 SEK (~50 €) after the final blood samples are drawn, independently of result on blood lipids or how many dietary changes have been made. Participants that are lost to follow-up at 6 months will however not receive this compensation. The participants will not receive any food items or any other lifestyle advice, in order to make the study environment as similar to clinical practice as possible.

Blood samples will be analyzed at Falu Lasarett using standard routines, during the same day or be kept cool and analyzed the following day, if the sample is drawn in the afternoon. LDL cholesterol is measured in plasma using direct method (P- LDL-Kolesterol SWE05408).

Statistical analyses

Based on previous randomized intervention studies of dietary fat quality and effects on lipoproteins[18-20], at least n=222 participants are required (for alpha = 0.05 and beta = 0.10) to detect an effect in LDL cholesterol of 0.175 mmol/L (~5%), which is an effect slightly exceeding that in most previous studies, parallels within-individual day-to-day variation (at double sampling), and has some clinical significance. This calculation takes into account a 20% loss to follow-up in the intervention group and a contamination effect of 5% in the control group.

The results will be analyzed according to intention-to-treat principle. Missing data at follow-up will be handled by imputing the baseline value. For LDL cholesterol, the mean value of the double analyses at days -3/0, 18/21 and 180/183 will be used. The CV of the biological variation will thus be decreased from 7[21] to 5%[22]. Between-group comparisons for effects on all outcomes will be performed as a generalized linear model (GLM) in SPSS software, adjusted for factors *a priori* considered likely to modify effects (baseline values, BMI, age and sex). As sensitivity analyses, also unadjusted, non-parametric testing (Mann-Whitney U-test) will be performed. $P<0.05$ will be considered as statistically significant.

Ethical considerations

Dietary habits and blood lipoproteins are of major importance for common diseases of high disease burden. Much is already known on the effects of different foods on lipoproteins. However, knowledge is lacking regarding effective strategies to influence patients into healthy food choices. The present study is thus considered of high potential value. Increased knowledge in the area may also increase patient autonomy and access to preventive healthcare, as the method is easy to reproduce and make available. The study design does not jeopardize personal integrity. Sensitive information will be treated in accordance with current regulations (Personuppgiftslagen and its successor, General Data Protection Regulation, taking effect 25 May 2018). The study cost is relatively low considering its size (see below).

Before randomization, all participants will receive oral and written information about the study´s design and purpose, and sign a document of informed consent. No invasive or otherwise risky procedures are includes, besides regular blood sampling. The dietary intervention is not considered as risky, as included food items accord well with current dietary recommendations. The dietary advice also includes a sentence not to exaggerate intakes of any single food item.

Budget

Salary for assistent nurse, 25% employment during one year – 98 565 SEK.

Study expenses (lab tests, biobank, monetary compensation) – 190 048 SEK.

Other costs (randomization, advertisements, publishing etc) – 40 303 SEK.

Total sum: 328 916 SEK.

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