Screening and alerting to Cardiovascular disease risk in Norwegian pharmacies

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Summary

Low awareness of CVD risk factor levels is likely to have contributed to the current large number of individuals with hyperlipidemia, type 2 diabetes, and hypertension. We found than a CVD risk factor screening in Norwegian pharmacies resulted in identification of otherwise healthy subjects with hyperlipidemia, impaired glucose tolerance and hypertension. We identified subsamples of healthy obese and unhealthy normal weight, and found that 11% of >20 000 screenees had a total cholesterol (TC) of ≥7 mmol/L that they were unaware of. We also found that low awareness of TC and blood glucose was common, and associated with being female (TC) and being male (blood glucose), and low educational level for both. All of these findings merit further study and development of effective modes of action to identify and reduce risk factors. We demonstrated that pharmacies were accessible and efficient in screening individuals, and that the screened sample resembled the general Norwegian population in terms of geographical distribution, educational level, smoking status and BMI, but with a slight oversampling of older women. This indicates the potential of pharmacies to attract a broad range of the population. Further, a new and important finding was that the Norwegian pharmacies were efficient in retaining participants in an intervention study to reduce CVD risk. However, we did not find that an intervention of alerting subjects with elevated CVD risk to their risk factor levels had an effect in this pharmacy setting. Nevertheless, we observed that the overall CVD risk factor screening resulted in a small reduction in CVD risk and health-related behaviors after two months, and initiation of CVD preventive medication after 1 year, suggesting clear CVD preventive benefits in a pharmacy-based screening.

Since there were no suitable and available food frequency questionnaire (FFQ) that assessed diet and lifestyle in relation to CVD risk, we developed and evaluated the VISA-FFQ. The VISA-FFQ showed acceptable performance in pharmacies and could be a convenient tool for assessing the relationship between diet, lifestyle and risk of CVD.

Data from the VISA-study are likely to yield more novel findings related to the long-term effects of screening and alerting to high CVD risk, and the potential role of pharmacies in CVD prevention in the future.

Acknowledgements

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Oslo, April 2018

Karianne Svendsen

List of scientific papers

Paper I

Karianne Svendsen, David R. Jacobs, Jr., Ida Tonning Røyseth, Kjersti Wilhelmsen Garstad, Marte Gjeitung Byfuglien, Lisa T. Mørch-Reiersen, Linda Granlund, Vibeke H. Telle-Hansen, Kjetil Retterstøl. Pharmacies offer a potential high-yield and convenient arena for total cholesterol and CVD risk screening. *Submitted: European Journal of Public Health.* 2018.

Paper II

Karianne Svendsen, Vibeke Telle-Hansen, Lisa T. Mørch-Reiersen, Kjersti W. Garstad, Kari Thyholt, Linda Granlund, Hege Berg Henriksen, Jon Michael Gran, David R. Jacobs Jr., Kjetil Retterstøl. A randomized controlled trial in Norwegian pharmacies on effects of risk alert and advice in people with elevated cardiovascular risk. *Submitted Preventive Medicine Reports.* 2018

Paper III

Karianne Svendsen, Hege Berg Henriksen, Beate Østengen, David R. Jacobs Jr., Vibeke H. Telle-Hansen, Monica H. Carlsen, Kjetil Retterstøl. Evaluation of a short Food Frequency Questionnaire to assess Cardiovascular Disease-related Diet and Lifestyle factors. Food and Nutrition Research. 2018;62. DOI: https://doi.org/10.29219/fnr.v62.1370

Paper IV

Tove C.N. Rusvik[1], Karianne Svendsen[1], Thomas Olsen, Stine M. Ulven, Kirsten B. Holven, Kjetil Retterstøl, Vibeke H. Telle-Hansen. Fatty acid profile and estimated desaturase activity in metabolically healthy and unhealthy subjects. Manuscript.

[1]Shared first authorship.

Abbreviations

BMI: Body mass index

CARDIA: Coronary Artery Risk Development in Young Adults Study

CVD: Cardiovascular diseases

FAME: Fatty Acids Methyl Ester

FFQ: Food frequency questionnaire

FH: Familial hypercholesterolemia

GP: General practitioner

HbA1c: glycated hemoglobin A1c

HDL-C: High-density lipoprotein cholesterol

HUNT (study): The Nord-Trøndelag Health Study

ICC: Intraclass correlation coefficient

LDL-C: Low density lipoprotein cholesterol

MI: Myocardial infarction

MH: Metabolically healthy

MU: Metabolically unhealthy

NHANES: National health and Nutrition Examination Survey

RHO: Rank order correlations

RTM: Regression towards the mean

SCD-1: stearoyl-CoA desaturase-1

SD: Standard deviation

SFA: Saturated fatty acids

TC: Total cholesterol

T2D: Type 2 diabetes

VISA: Vascular lifestyle-Intervention and Screening in phArmacies

WHO: World Health Organization

Figures

Tables

Table of contents

1 Introduction

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is the largest group of non-communicable disease and comprises all diseases and disorders of the heart and arteries (2, 3). Within CVDs, the largest contributors to deaths are coronary heart diseases (CHD) and cerebrovascular diseases such as stroke. CHDs are caused by occlusion of the coronary arteries that supply blood to the heart muscle, whereas strokes are caused by blockage of the blood flow, or leakage of the blood vessel, to the brain (4). Deaths from CVDs have decreased substantially in high income countries since the 1970s (5-7). Still, CVD is among the main contributors to death worldwide (6).

1.2 Atherosclerosis

Several risk factors have played a role in the decline of CVD (8). The underlying cause of most of the CHD events is the chronic inflammatory process of atherosclerosis (9). Atherosclerosis is a lifelong process in which accumulation of lipids including cholesterol, immune cells, cellular waste and many other substances deposits in the arterial wall (the intima and media (inner and mid- layers)) leading to atherosclerotic lesions (10, 11). The thickness of carotid intima-media is therefore a widely used surrogate marker for atherosclerosis (12). Over time, the atherosclerotic lesions can build up and result in partial or total occlusion of the arterial lumen resulting in restricted blood flow, as illustrated in Figure 1 (9). Eventually, the plaque can rupture, causing blood clot formation, arterial clogging and consequently infarction such as myocardial infarction (MI) if the occlusion occurs in the arteries into the heart (4, 9).

The process of atherosclerosis, typically starting in childhood especially in high income countries (13), can be accelrated by exposure to several well-known risk factors such as hypertension, diabetes and generally an unhealthy lifestyle (14). Low density lipoprotein cholesterol (LDL-C) has been identified as a causal risk factor for atherosclerosis, which again is associated with age, gender, genes and health-related behaviors such as dietary factors

(15-17). Goldstein and Brown have described a dose-response relationship between LDL-C and the atherosclerosis process in the arteries *"The higher the LDL-C, the faster the plaque evolves"* and vice versa (17). Importantly, lipid-lowering medication has demonstrated to induce moderate regression of atherosclerotic lesions (18).

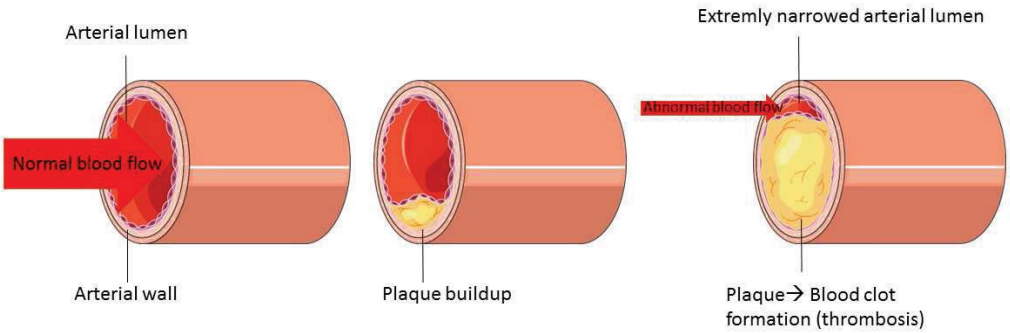


Figure 1. Illustration of development of atherosclerosis, resulting in total blockage of arteries (thrombosis). Based on free images from Servier Medical Art (Creative Commons Attribution License, creativecommons.org/lisences/by 3.0/). Inspired by National Heart, Lung and Blood institute (19).

1.3 Risk factors for CVDs

The large prominent epidemiological studies, the Framingham Heart Study and the Seven Countries Study, were among the first to identify both behavioral and biological factors associated with CHD risk (20, 21). Three major risk factors were identified; high serum total cholesterol (TC), high blood pressure/hypertension and tobacco smoking (20, 21). Improvements in these risk factors have been calculated to account for 69% (men) and 66% (women) of CHD mortality reduction in Finland the previous 10 years (22). By adding physical activity to the calculation, these four risk factors accounted for 66% reduction of total CHD incidence observed in the Tromsø study between 1994 and 2008 (5).

More than 40 years after the Framingham and Seven countries study, high TC, high blood pressure and smoking remain among the most important, modifiable risk factors of CVDs (3). Nevertheless, several modifiable risk factors a have since been identified such as high body mass index (BMI) (3, 23), dyslipidemia (24) and type 2 diabetes (T2D). Notably, elevated blood glucose concentration or imparied glucose tolerance can be markers of CVD risk (25), even among non-diabetic individuals (26). Equally important are the non-modifiable risk

factors age, sex, genetic factors and family history of CVDs (27). Target levels for the modifiable risk factors are presented in Table 1 (28). A combination of small improvements in each of the CVD risk factors is associated with clinically meaningful reductions in CVD events (29, 30). Hence, moderate reductions in several risk factors can be more effective than major reduction in one (31). As a result, the European Society of Cardiology recommend clinicians to use CVD risk scores to guide in prevention and treatment of CVDs. The Systematic COronary Risk Evaluation (SCORE) is a risk chart that calculates risk score based on age, gender, TC, systolic blood pressure and smoking status (28).

Table 1. General target goals for the modifiable CVD risk factors according to European Society of Cardiology guidelines for CVD prevention in Clinical Practice (2016).

Risk factors	**Target level**
LDL-cholesterol	<3.00 mmol/L (low to moderate risk) 2.6 mmol/L (high risk) <1.8 mmol/L (very high risk)
Triglycerides	<1.7 mmol/L[1]
HDL-cholesterol	>1.2 mmol/L (men) [1] >1.0 mmol/L (women)[1]
Blood pressure	<140/90 mmHg
HbA1c (glycated haemoglobin)	≤7% (<53 mmol/mol)
Body mass index	BMI 20–25 kg/m2. and/or Waist circumference <94 cm (men) or <80 cm (women).

[1]No interventions is recommended, but the levels mentioned indicate lower risk.

1.3.1 Asymptomatic CVD risk factors

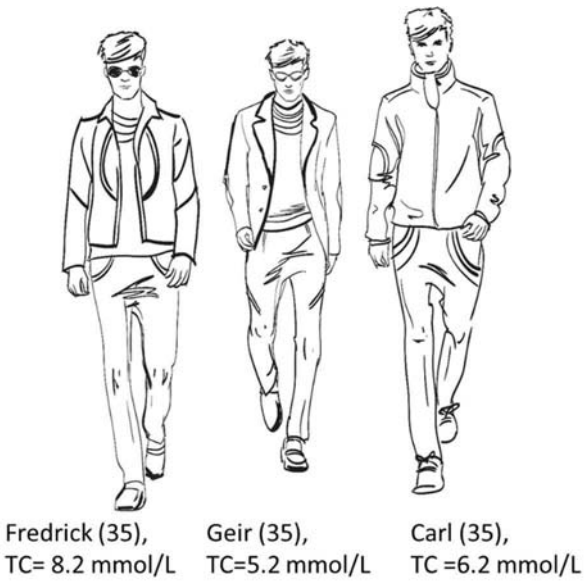


Figure 2. Three apparently similar men with significantly different total cholesterol (TC) concentrations. **Photo:** Colourbox.com.

It is a common misconception that a high TC concentration reveals itself with signs or symptoms (32). Instead, high TC/hyperlipidemia, high blood glucose/T2D, and often high blood pressure/hypertension, rarely reveal, or have easily ignored symptoms (33). Young men are one group that is less likely to have measured their CVD risk factors previously (32, 34). We can therefore assume that these are unaware of their CVD risk factor levels, as risk cannot completely be judged by age, gender, or physical health status, as shown in the simplified Figure 2 (32, 34, 35). Clearly, with low or no awareness of risk factor levels, targeted decisions on how to lower risk are not possible (36). The consequences of low unawareness of high levels of CVD risk factors can be exemplified by the estimation that about 50% of those with T2D are undiagnosed both in Norway and globally (37, 38). Familial hypercholesterolemia (FH) is a hereditary disorder of the lipoprotein metabolism resulting in elevated LDL-C concentration (17). It has been estimated that about 2/3 of those with FH remain undiagnosed in Norway (39), and about 90% globally (40). Both T2D and FH patients have a marked increased risk of premature CVD compared to the general population (41, 42).

1.4 Obesity phenotypes

Overweight (BMI≥ 25 kg/m^2) and obesity (BMI≥ 30 kg/m^2) have had a growing incidence worldwide (43). The World Health Organization (WHO) estimates that 40% of adults worldwide are overweight (44). In contrast to the previously mentioned risk factors, overweight/obesity is a visible, independent risk factor of CVD and T2D (45). The effect of BMI on CVD risk can be mediated through the association of high BMI with elevated TC, hypertension, insulin resistance and generally poor health (46, 47). A Swedish registry study found that physical fitness could partly mitigate the adverse effects of obesity on risk of developing CVDs in young men (48). Nevertheless, BMI as a risk factor is complex, because it does not take into account body mass composition. There are also discussion of whether or not it exists phenotypes of obese individuals with favorable CVD risk factors called metabolically healthy (MH) obese (49). Because of their beneficial metabolic profile, MH obese are at lower risk of developing metabolic disturbances normally associated with obesity (25, 26). Hence, this group of healthy obese might have a lower risk of CVD compared to metabolically unhealthy (MU) obese (50), although this observation does not have general acceptance (51). Notably, there is also a group of normal weight individuals with un-favorable metabolic profile, called metabolically unhealthy (MU) normal weights. These can be treated as MU obese with appropriate lifestyle modification and use of prescription medication when appropriate (52). MH obese and MU normal weight are not easily recognized. Assessing CVD risk factors and stratify subjects according to metabolic phenotypes can therefore potentially help in strategies to treat obesity or obesity-related disorders.

1.5 Health-related behaviors

According to the global burden of disease report, an unhealthy diet contributes to the largest proportion of disability-adjusted life year globally (6). In America, an unhealthy diet is estimated to be associated with about 45% of all deaths from CVD and T2D (53, 54). There is a mutual relationship between health-related behaviors such as diet, lifestyle and smoking cessation and CVD risk factors and CVD risk (14, 55), as illustrated in Figure 3. Nevertheless, a CVD event can result in beneficial changes in health-related behaviors that can protect against recurrence of disease (56), but also by adopting health compromising behaviors that can increase the risk of future disease (57). In high income countries, health comprising behaviors, as defined by Conner & Norman (57), are behaviors that have unbeneficial and sometimes harmful effects on risk of diseases such as CVDs and T2D (58). Comprising behaviors include excess body weight, smoking, alcohol abuse (57, 59), and unhealthy dietary patterns (60) including intake of unprocessed red meats, processed meats, sugar-sweetened beverages and foods high in trans-fatty acids and sodium (58). Health enhancing behaviors (57), include exercise/avoiding a sedentary lifestyle (61) and healthy dietary patterns and foods that comply with nutrient targets (62, 63). For this purpose, several countries have adopted food based dietary guidelines for general disease prevention (64, 65).

Dietary patterns to promote health and lower risk of CVDs have been identified as patterns comprising a variety of fruits, vegetables and whole grains, lean protein foods (meat, fish, poultry, and/or alternatives), nuts, seeds and vegetable oils and reduced fat dairy (62). Furthermore, Micha and colleagues adds to this list an emphasizing on other protein sources such as beans/legumes and intake of yoghurt as having protective effects on risk of CVD and T2D (58). These two recent studies have a slightly different view regarding dairy protein. This can be due to several studies suggesting a neutral or even inverse relationship between dairy fat and cardiovascular outcomes (66, 67), in particular fermented dairy products such as yoghurt and cheese (58, 67). Similar, de Oliveira and colleagues demonstrated that plasma phospholipid 15:0 (pentadecanoic acid), was inversely associated with incident CVD and CHD (68). The saturated fatty acids (SFA) 15:0 and 17:0 (heptadecanoic acid) are specific to ruminant metabolism, and can be considered biomarkers for consumption of milk fat (69, 70). Use of such biomarkers give an objective, and to some extent, more accurate measure

of dietary intake compared to self-reporting of diet (71, 72). However, biomarkers have their own limitations and are affected by metabolism, absorption and genetics that differ among individuals (73).

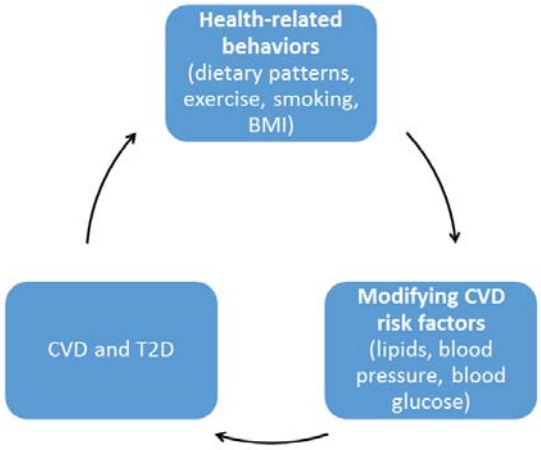


Figure 3. Mutual relationship between risk factors for cardiovascular diseases (CVD).

There are numerous theories and factors that can help explain decision-making towards behavior change, (74) which is defined as; *"efforts to change personal habits to reduce risk of disease"* (75). In intervention studies, features that have been successful in facilitating long-term changes in health-related behavior are often time- and resource consuming and include one-to-one consultations, high intensity interventions and long-term follow-up (25, 76, 77). Social inequality has been associated with the ability to make appropriate decisions to change health-related behaviors in order to stay healthy (78). Already healthy individuals are also more prone to be motivated to maintain health enhancing behavior changes (74).

In regards to risk communication, there are several factors that can affect intention to change behavior, includes risk perception, defined as understanding of own risk (75). Discordance between perceived risk and actual risk, can result in underestimation or overestimation of risk (79). How risk is perceived depends on both subjective understanding, and conveying of the risk message (74). Generally, use of technical language to convey the risk message can increase the possibility of discordance between perceived and actual risk (80), whereas low numeracy can affect how the risk message is conceived (81).

1.5.1 Medication use

Health enhancing behaviors may also include use of medication (82). Several low-cost medications have demonstrated clear reduction of CVD risk (74), such as lipid lowering therapy (statins in majority (83)) and blood pressure lowering medication (84). According to the Norwegian Prescription Database (www.reseptregisteret.no), there were 567 398 unique users of lipid lowering therapy across ages, gender and counties in Norway in 2016. This prevalence corresponds to about 10% of the Norwegian population, and have increased by about 20 000 since 2016 (85).

A recent publication from the Tromsø Study estimated that lipid-lowering medication explained only 21-28% of the decrease in TC observed between 1974 and 2016 in individuals aged ≥ 50 years (86). Whereas data from the Icelandic population suggested that dietary changes and not statin therapy has been the key driver in lowering TC levels on a population level (87).

1.6 The importance of early prevention

To quote Benjamin Franklin: *"An ounce of prevention is worth a pound of cure."*
As such, public health is better served if disease is prevented rather than subsequently treated (88). Prevention of disease before it occurs is called primary prevention, in contrast to secondary prevention, comprising prevention of recurrent disease (89). Premature deaths (occurring before age 65) are highly preventable (2). Therefore, a European Heart Health initiative, the European Charter states that; *"Every child born in the new millennium has the right to live until the age of at least 65 without suffering from avoidable CVD"* (90). Still, in Europe, 700 000 out of four million annual deaths of CVDs occur prematurely (2), comprising about twice as many men as women. In Norway, 844 of 10 936 people died of CVDs before the age of 65 in 2016 according to The Cause of Death Registry (91). Mirroring data from the European population (2), more men than women die prematurely in Norway of which CHD is the main cause of death for both genders (91).

Nevertheless, as stated by Bhatnager and colleagues, *"CVD burden comes not only from deaths, but also from those living with the disease"* (92). Whereas CVD mortality has declined notably during the past years, a worrying tendency towards increased hospital admissions following CVD has been observed in several countries. In USA, the annual number of hospitalizations of MIs increased among women between 2005 and 2012. Although hospitalization of MIs decreased in men, in-hospital mortality increased (93). Similar, Gupta and colleagues reported no reduction in hospitalization rates of acute MI among patients aged <55 years, indicating a potential shift towards the younger population (94). This possible shift towards higher rates of MIs in young adults are also supported by data on adults aged <59 years in a Danish nationwide cohort study (95), in the United Kingdom (92), and in Norway presenting a prominent increase of 11% for hospitalization of a first MI in the age group ≤45 years (96).

Since age is the strongest risk factor for CVDs according to the model for estimating CVD risk in Norway, NORRISK (97), high levels of risk factors in young adults can often be neglected or underestimated due to low total risk of CVDs (28, 98). Nevertheless, early identification, and subsequent treatment of high risk can reduce the burden of premature deaths (99). Parallel with the worrying trends in CVDs in young adults (18-45 years), increasingly unhealthy

health-related behaviors such as poor dietary habits, physical inactivity and obesity have also been observed in the same age group (99). The prevalence of children and adolescence that are overweight or obese has increased from about 16% in 1980 to 23% in 2013 in high-income countries and from about 8 to 13% in the same time interval in low- and middle-income countries (100). The INTERHEART study estimated that the risk factors hyperlipidemia, T2D, hypertension, smoking, abdominal obesity, limited consumption of fruit and vegetables, physical inactivity and psychosocial stressors accounted for 94% of MI in ≤55 years and women ≤65 years (14). However, except for the Coronary Artery Risk Development in Young Adults Study (CARDIA) study including >5000 black and white men and women in the ages 18-30 years (101), there are few prospective studies of CVD risk factors in young adults, due to low incidence of CVDs in the young (99).

The presence of risk factors in adulthood is closely related to atherosclerosis later in life (31, 102, 103), and there is a forecasted future burden of CVD and T2D (100, 104). Therefore, immediate attention to identification and subsequently treatment of high risk factors, starting early in life, can have a potential large public health impact (105, 106).

1.7 Screening

Screening is a search for disease or symptoms of disease in an apparently disease-free population. The aim of screening is to discover disease or risk of disease at an early stage, when the potential for prevention is large (107). The “screen and treat strategy” has been suggested as an approach to identify high CVD risk early and subsequently prevent or treat development of disease (108). The usefulness of screening also depends on the magnitude of the disease it is screening for, and how often screening results cascade into treatment or prevention of disease, and how effective the proposed treatment is (107, 109). Although screenings for CVD risk factors can be useful to identify high risk (110), there are also harms associated with screening, such as the possibility of false positive and false-negative screening results (111). Short term anxiety following screening has also been reported (112).

Various guidelines endorse screening for CVD risk factors in individuals or population groups from the age of 20 (113) or 40 years of age (114). The 2016 European Guidelines on CVD prevention recommends a systematic approach to screening, prioritizing those who potentially have high risk (such as those with family history of premature CVD) (28). To the contrary, the same guidelines discourage opportunistic screening (without a predefined strategy or goal) of individuals aged <40 years of age without presence of CV risk factors (28). In Norway, opportunistic screening is not recommended, but the clinical guidelines for CVD prevention supports systematic approaches to identify high risk individuals and suggest that lipids could be measured from age 40 if not measured previously (115).

Between the 1980s and until the early 2000s, there was a national public screening program for CVD risk factors in Norway called the age-40 program (116). All adults in Norway aged 40-42 years were screened for CVD risk factors within a three-year interval. The program included surveillance, research, education, and prevention of disease through targeted interventions on high-risk individuals (116). Whereas the age-40 program to detect CVD risk was terminated in 1999 due to descending attendance rate and loss of financial support (117, 118), a national public screening program for colorectal cancer for all adults aged 55 years was recently approved by the Directory of Health (107). There also already exist a screening program for mammography in Norway (119).

1.8 Future health care

In the years to come, the number of individuals with CVD may rise due to an aging population and improved survival rates following acute disease (7). The continuously lowering of the threshold for medical treatment of elevated risk factors also imply that more people will need treatment and follow-ups in the years to come (120, 121). In fact, a global health workforce crisis has been predicted with insufficient health manpower to meet the need and demand that comes with an aging population (122). Hence, to limit the burden on the health care system, and also to address key public health issues like health inequalities and overall health improvement, WHO calls for local, novel approaches and convenient ways to deliver health care services (123). In line with this, a recent white paper from Norway emphasizes interdisciplinary collaboration for tomorrow's health care (124). In this regard, the expanded responsibility of pharmacist, nutritionists, nurses and other health care providers in other countries were acknowledged (124).

Policymakers will therefore need high quality evidence about efficient strategies to deliver health care that can help in prevention of CVD and other non-communicable diseases (122). A recommended strategy is to implement community-based studies that enable an understanding of the community, and at the same time generate evidence that can easily be implemented into practice in the health care system (124, 125).

1.8.1 Pharmacies as a platform to provide health care

According to Michael D. Rawlins, the Royal Pharmaceutical Society had already stated in 1988 that the vision of pharmacists in Great Britain was to expand their advisory role in health care, and to treat minor conditions (126). In Great Britain today, the role of pharmacies has indeed been expanded, and the future vision of pharmacies are *"centers to promote health and empower people to take care of their own health"* (127). Similarly, in Canada, use of pharmacists have been identified as the key strategy in helping Canadians to be the healthiest and least hypertensive in the world (128).

Pharmacies are on the frontline of secondary prevention, seeing patients with chronic diseases frequently by preparing and dispensing prescriptions for medications (129). Postgraduate nurses in the United Kingdom and some nurses at diabetes outpatient clinics in Norway can with consent from hospitals, prescribe medication (124). Pharmacies and similar retail-clinics are also highly accesible with long opening hours and affordable drop-in appointments for health services also in the weekends (130). This allows access for people who work a wide range of hours (131). The accessibility of pharmacies gives them a unique position to play a key role in public health initiatives (131). Consequently, pharmacies and similar retail-based clinics offer a growing number of services such as treatment of minor injuries, flu vaccines, measurements of metabolic status, vitamin-D-status, mole scanning and provision of health-related advice and smoking cessation (131-135). Pharmacies can also easily facilitate systematic assessments/screenings and management of CVD risk factor levels, in addition to monitor and enhance adherence to medication use (131, 136-139).

1.9 Knowledge gap

With the termination of the age-40 program, both the population-based surveillance of CVD risk factors, and the routine health check for CVD risk factors in Norway, vanished.
The absence of population-based surveillance of health status in Norway has been recognized through a report made by the Ministry of Health and Care Service, and a pilot study of collecting information on health status through questionnaires was recently launched (140). However, there is no plan for obtaining objective measurements of CVD risk factors (140). During the age-40 program (1985-1999) major differences in CVD risk factors between the 19 counties in Norway were reported (141). For instance, average TC in Finnmark (North-Norway) was 6.2 mmol/L compared to 5.7 mmol/L in Akershus County (East-Norway) (141). Currently in Norway, the regional, longitudinal health surveys, the Nord-Trøndelag health study (the HUNT-study) and the Tromsø study, provide surveillance of CVD risk factors in two counties (142, 143), but we have no information on CVD risk factors from inhabitants living in the 17 other counties in Norway.

The association between socioeconomic status and CVD and knowledge of CVD risk factors, in addition to differences in access to, and utilization of, the health care system, indicate that there might be differences in regards to the population that get their CVD risk factors measured (144-146). Equal opportunity to measure CVD risk factors can have large benefits to lower socioeconomic differences in health in Norway, because once high risk is identified, all people are access to the same prevention and treatment through the national health care system. In countries without government-initiated health checks, CVD risk factor screening in pharmacies has been promoted (34), as such screenings might be able to attract those who are less likely to otherwise have accessed these services (136). In this regard, the effectiveness of screening in pharmacies needs to be considered; Do we reach does who would benefit the most from screening, what are the yields of screening in terms of identification of high risk, and how often do screening results cascade into treatment or prevention of diseases (114).

Waldron *et al.* stated that the awareness of an individual's own risk could encourage the person to take actions to reduce that risk, especially if risk is high (147). Several studies have demonstrated effect of diet- and lifestyle interventions on reducing CVD risk in CVD-free,

high risk patients (76, 148). Little is however known about whether just alerting to high CVD risk (147), in particular in pharmacies, would be effective in reducing risk.

Such evaluation of the effectiveness of screening, and effects of alerting to high CVD risk in Norwegian pharmacies, is in line with the governmental call for high-quality research on health care services that can easily be transferred to practice (124). Research in the area of pharmacies is also sparse and very few high quality randomized controlled trial (RCT)s have been conducted in pharmacies (149, 150).

1.10 The VISA-study

The organizations Boots Norge AS (pharmacy chain), Mills AS (food and brand warehouse), Grete Roede AS (weight loss program), Elixia (fitness center), and the Norwegian Health Association together sponsored cholesterol campaigns with complementary, capillary measurements of TC along with a brief dietary and lifestyle counselling in pharmacies nationwide in Norway in 2011, 2012 and 2014. The overall aim of the campaign was to educate the public about the importance of knowing their TC concentration to prevent CVD.

As the PhD candidate's master project in 2012 (151), research aspects were introduced to the TC campaign with a screening questionnaire. Accordingly, the cholesterol campaign became the Screening effectiveness study, comprising questionnaire data from both 2012 and 2014. The Screening effectiveness study was successful in recruiting participants. This opened up the possibility that studies of more complex design could be implemented in pharmacies. Consequently, the RCT, the Alert/advice intervention study and the Heart age intervention study were initiated in 2014 and 2015, respectively. The Screening effectiveness study, the Alert/advice intervention study and the Heart age intervention study encompasses the Vascular lifestyle-Intervention and Screening in phArmacies (VISA) study described in the current thesis and, in appendix 1, to *paper I.*

Photo: Logo of the cholesterol campaign in 2014.

2 Study aims

The overall aim of this thesis was to study the effectiveness of screening and the effects of alerting to elevated levels of CVD risk factors in a pharmacy setting.

The specific aims were:

- To study the use of pharmacy as a new platform for screening for CVD risk factors in Norway, and the use of pharmacies for conducting intervention studies (*paper I*, *paper II*)
- To study if alerting subjects to their CVD risk factor levels and providing advice could, lead to changes in CVD risk (*paper II*)
- To evaluate the study-specific, newly developed, short-form food frequency questionnaire (FFQ), the VISA-FFQ (*paper III*)
- To describe a sub-population of MH and MU subjects and to study differences in fatty acid profile and the impact of BMI (*paper IV*)

3 Summary of results

Paper I

The aim was to study the effectiveness of screening for TC in Norwegian pharmacies.

The Screening effectiveness sample (n= 21 090) seemed to resemble data from Statistics Norway in regards to geographical distribution, BMI ≥27 kg/h^2, prevalence of smokers and educational level (Table 2). Results from 20 473 participants with present (measured) and previous (self-reported) TC concentrations are presented in Figure 4. The probability that TC and blood pressure had been measure previously increased with age, whereas the probability of not having had glucose measured was 45% in the age group 18-49 years and about the same (47-50%) for the remaining age groups >50 years. Those with high school as highest attained educational level were less likely to have previously measured TC, blood glucose and blood pressure. Women were less likely to have measured TC previously, whereas men were less likely to have measured blood glucose previously.

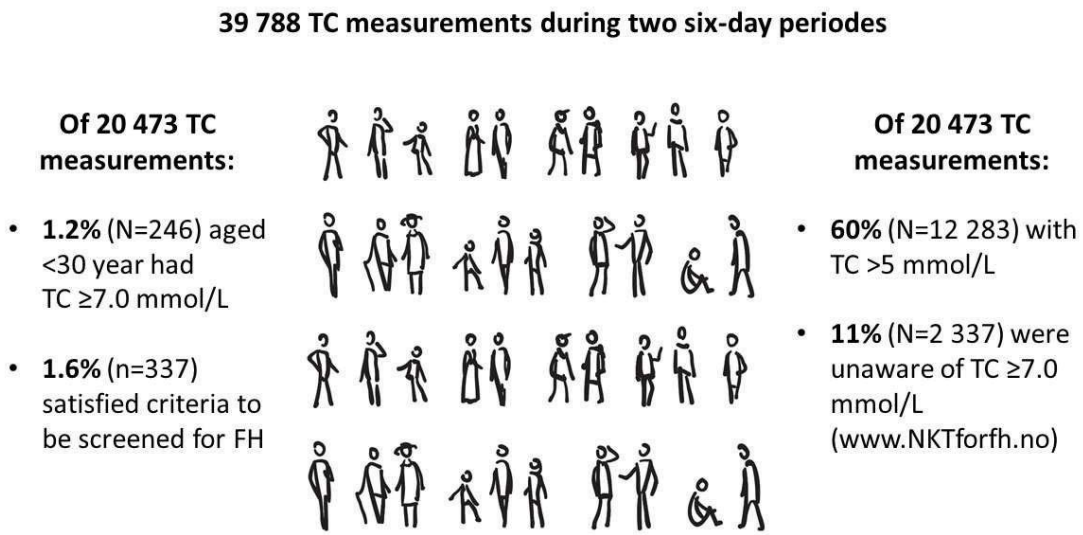


Figure 4. Summary of results from *paper I. Also presented at conference (EuroPrevent)* (1). Illustration by Colourbox.com

Table 2. Background characteristics of participants in the Screening effectiveness study and other comparable reference populations.

	TROMSØ 7 (2015-16) N= 21 083 (152)	HUNT 3 (2006-08) N= 50 666 (153, 154)	Other reference populations (2003-2015)	Total, Screening effectiveness study (2012, 2014) N=21 090[1]	Men, Screening effectiveness study N=6 516	Women, VISA study N=14 285
	Mean±SD % (n/N)	Mean±SD % (n/N)	Mean±SD or %	Mean±SD % (n/N)	Mean±SD % (n/N)	Mean±SD % (n/N)
Women, %	52.5 (11 074/21 083)	54.6 (27 695/50 666)	49.7[6]	68.9		
Age, years	57.3±11.4	53.2±16.1	39.4[7]	54.5±16.0	53.9±16.4	54.8±15.8
Age ≤39 years, %	NA[4]	22.4 (11 399/50 807)	31.9[7*]	19.2 (3 985/20 706)	21.7 (1 401/6 445)	18.2 (2 562/14 066)
TC, mmol/L	5.5±1.1	5.5±1.1	5.6[8]	5.6±1.0	5.4±1.0	5.7±1.1
BMI, kg/m^2	NA	27.2±4.4		25.4 ±4.0	26.3±3.6	25.0±4.1
BMI≥27 kg/m, %	NA	NA	28.0[9]	29.6 (5 953/20 090)	37.4 (2 356/6 292)	26.0 (3 529/13 587)
Highest attained education level:						
Primary school, %	23.2	NA	27.3[10]	15.6 (3 149/20 168)	15.5 (969/6 252)	15.5 (2 125/13 671)
High school %	27.8	NA	41.3[10]	41.3 (8 325/20 168)	40.0 (2 499/6 252)	41.8 (5 720/13 671)
University/college 1-3 years, %	19.4	NA	22.7[10]	25.0 (5 034/20 168)	26.2 (1 639/6 252)	24.5 (33 51/13 671)
University college >3 years, %	29.7	NA	8.7[10]	18.2 (3 660/20 168)	18.3 (1 145/6 252)	18.1 (2 475/13 671)
Inactiv[2], %	NA	NA	17[9]	17.5 (3 629/20 727)	20.7 (1 331/6 421)	16.0 (2 248/14 056)
Smoker[3], %	13.9	12.6[5]	21[11]	19.8 (4 186/21 090)	17.2 (1 118/6 516)	20.9 (2 996/14 285)

VISA, Vascular lifestyle-Intervention and Screening in phArmacies; TC, Total cholesterol; BMI, Body Mass Index. TC in the Screening effectiveness study was measured in pharmacy; all other data were self-reported. [1]VISA study: 289 people with missing gender are included in the total column. [2]Exercise, ≤1 time/week [3] Every day and occasional smoking. [4] Included subjects' ≥40 years. [5]Calculated from number of smokers (not including cigars) References: 6:**(155)**, 7:**(156)** *16-39 years, 8:**(157)**, 9:**(158)**, 10:**(159)**, 11:**(160)**.

Paper II

The aim was to investigate effects of alerting individuals to elevated CVD risk factors accompanied by risk-modifying advice.

The Alert/advice intervention study was an 8-week RCT of which 582 individuals with elevated CVD risk were randomized to either the Alert/advice groups (alerted to measured CVD risk factors and provided risk modifying advice), Advice-only group (no risk alert, but received advice) or Control group (no risk alert nor advice). The formal analysis of change in CVD risk score after 8 weeks between groups was borderline non-significant.
In secondary unadjusted analysis, we observed that the Control group reduced CVD risk score by 14.1% compared to 6.7% reduction in the Alert/advice group (p=0.03) and non-significantly different from the observed 13.7% reduction in the Alert-only group. This pattern of findings persisted even after adding the 48 level pharmacy variable as a random effect variable into the model. We also calculated that in the total, uncontrolled sample of 543 participants, CVD risk score was reduced by 3.2% (-0.17 (95% confidence interval (95%CI): - 0.01 to -0.33) after subtracting risk score reduction that was estimated to be due to regression towards the mean (RTM) (161).

Although there were no significant difference in CVD risk factors nor any health-related behaviors between groups, there were significant differences within groups for TC, LDL-C, HbA1c and blood pressure levels. There was also a trend towards compliance to health-enhancing behaviors assessed with the VISA-FFQ such as reduced intake of foods high in sugar and SFA dairy. Participants were also invited to a follow-up visit after 52 weeks and despite no active intervention, participants had reduced their CVD risk score, blood pressure levels and had made some non-significantly. We also observed small, beneficial changes in health-related behaviors, but less exercise. Furthermore, 14% self-reported initiation of statins (n=14), aspirins (n=18), diabetic-medication (n=5) and/or anti-hypertensive medication (n=12) 52 weeks after the CVD risk factor screening.

Paper III

The aim was to evaluate the 62-item VISA-FFQ for relative validity of milk fat and for overall reproducibility.

In a subsample of 307 participants, we evaluated the VISA-FFQ to be acceptable valid in its estimation of milk fat, presented as a correlations between dietary 15:0 (estimated from the VISA-FFQ adjusted for total intake of foods) and whole-blood 15:0 (assayed from the DBS) of r=0.32 and r=0.30, at time 1 and 2 respectively. In a sub-sample of 122 individuals, we found that 55 out of 62 items in the VISA-FFQ presented satisfactory and consistent reproducibility, defined as correlations ≥0.5 between first and second completion of the VISA-FFQ, and with no large significant difference in intake. This comprised a variety of foods, smoking and physical activity.

The VISA-FFQ also seemed to be a convenient questionnaire to assess intake of foods and lifestyle factors associated with CVD risk, both in pharmacy and at home.

Paper IV

The aim was to describe a sub-population of MH and MU subjects in regards to differences in fatty acid profile and the impact of BMI.

We divided a subsample of 321 participants according to metabolic status defined by Telle-Hansen *et al.*(162); 150 were MH, 52 were MU, and 119 were none of the above. As we found that metabolic status was related to BMI, we further grouped MH and MU subjects according to normal weight, overweight and obesity. Normal weight MU subjects had significantly lower plasma HDL-C and higher triglycerides and HbA1c than MH subjects. Whereas the opposite was observed for obese MH subjects. Furthermore, MH obese were more than three times as physical active as MU obese. Whole-blood fatty acids 16:0, 16:1, 18:1 and stearoyl-CoA desaturase-1 activity (ratio of 16:1/16:0) (SCD-1) were significantly related to metabolic status and BMI. MU obese seemed to have higher 16:0, 16:1 and SCD-1 compared to MH subjects. The differences were present but not statistical significant for and normal weight subjects (BMI 18.5-24.9 kg/m^2) (43). The results illustrates the importance of assessing CVD risk, irrespectively of BMI.

4 Materials and methods

4.1 Study design

The VISA study was a multicenter study conducted in Boots pharmacies between 2012 and 2015. For simplicity, we describe the VISA study in three parts with overlapping visits (V1-V4); The Screening effectiveness study (V1), the Alert/advice intervention (V1, V2 and V3) and the Heart age intervention (V3 and V4) (Figure 5).

Screening effectiveness study	**Alert/advice intervention study**	**Heart age intervention**
(Screening/V1)	(V1, V2, V3)	(V3, V4)

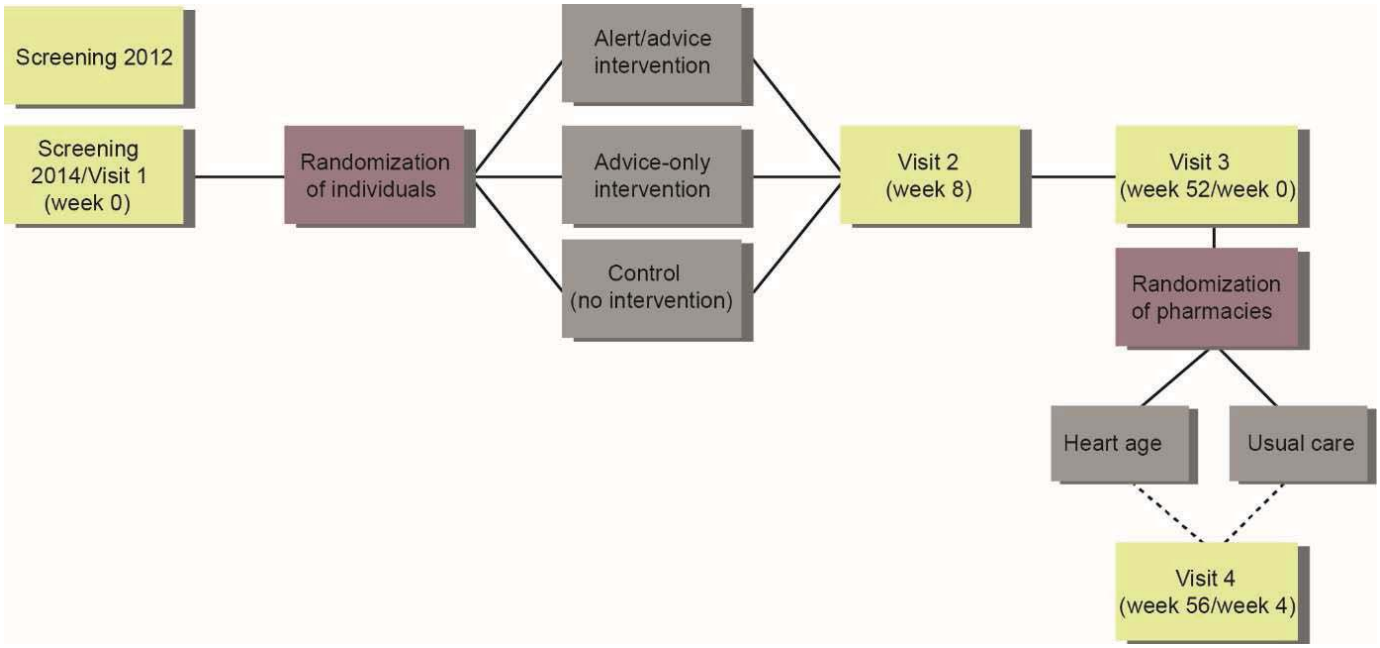


Figure 5. Overview of the Vascular lifestyle-Intervention and Screening in phArmacies (VISA) study. Figure made by Carina Knudsen, Institute of Basic Medical Sciences, UiO. V= Visit.

4.1.1 Screening effectiveness study

The Screening effectiveness study presented in *paper I* had a cross-sectional study design and comprised measurements of capillary TC concentrations and collection of anonymous data from the screening questionnaire. Data were collected during six days in each of May 2012 and September 2014 in 148 (2012) and 149 (2014) Boots pharmacies. Figure 6 presents the geographical distribution of pharmacies. Healthcare personnel in pharmacies (pharmacists, technicians or nurses) executed the study. Point-of-care measurements of TC were followed by a brief consultation regarding interpreting of the TC concentration and subsequently tailored diet and lifestyle advice.

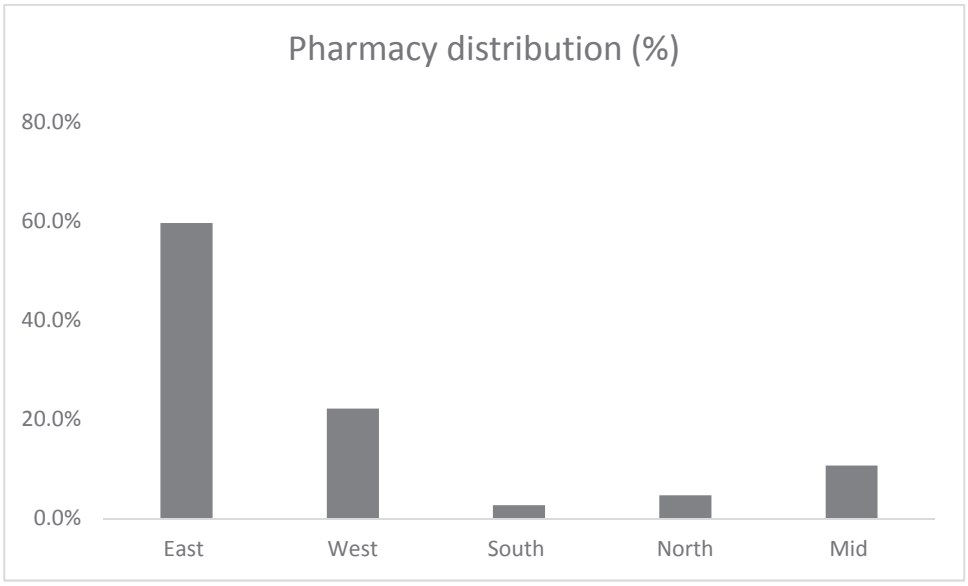


Figure 6. Geographical distribution of 149 Boots pharmacies according to regions in Norway.

4.1.2 Alert/advice intervention study

The Alert/advice intervention study with CVD risk factor screening presented in *paper II* was implemented in 50 out of 149 pharmacies (as an additional option to the Screening effectiveness study). The design was an 8-week RCT (V1-V2) with a follow-up visit 52 weeks after baseline at V3 (Figure 5).

The CVD risk factor screening included point-of-care measurements of HbA1c, plasma TC, HDL-C, LDL-C, triglycerides, blood pressure, height and weight, and resulted in calculation of an ad hoc CVD risk score (CVD risk score). Individuals with a predefined, elevated, CVD risk score were randomized to one of two interventions or control in the ratio 1.1:1 (block size 9: stratified by pharmacy and gender). In the main intervention group (Alert/advice), participants were immediately after the CVD risk factor screening at V1 alerted to their screening result and given risk-modifying advice, both verbally and through various written intervention materials. Participants randomized to the Advice-only intervention were not alerted of their screening result until at V2, but received risk-modifying advice at V1. Participants randomized to the Control group received no risk alert, nor advice until at V2. Effects of interventions were measured at V2 when participants returned to pharmacies to repeat the CVD risk factor screening, and all participants received the Alert/advice intervention. The screening for CVD risk factors, risk alert and consultation with advice were also repeated at V3. Participants completed the screening questionnaire at V1 (same as in the Screening effectiveness study) and the VISA-FFQ at V1, V2 and V3, and the follow-up questionnaire at V3. Each visit took on average 30 minutes. Results from the Alert/advice intervention study are presented in *paper II.*

4.1.3 Heart age intervention study

As shown in Figure 5, V3 operated both as the follow-up visit of the Alert/advice intervention study, and as baseline for the Heart age intervention study. Results from the Heart age intervention has not yet been presented, but data from V3 and V4 were utilized to provide cross-sectional data to *paper III and IV*.

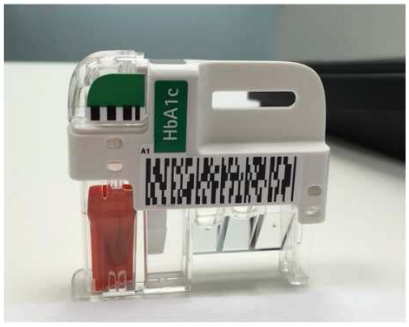
For the purpose of the Heart age intervention, pharmacy was the unit of randomization (paired-clustered). The randomization process was executed in excel by Svendsen and Jacobs Jr.; Pharmacies were sorted by size (number of participants) in pairs, and each pair was randomized to either intervention (heart age) or control (usual care) pharmacies. Heart age was calculated from several CVD risk factors, and is a visual, and apparently understandable, risk communication tool developed by the British Heart Foundation (163). In the intervention pharmacies, results from the CVD risk factor screening was conveyed as heart age compared to biological age (163). Whereas in the usual care pharmacies, counselling after the CVD risk factor screening was provided in accordance with the Advice/alert procedure from V2.

To measure the effect of heart age, diet and lifestyle habits were assessed with the VISA-FFQ, whereas whole-blood TC and fatty acid concentrations were obtained from the blood sampling method dried blood spots (DBS). DBS-samples were obtained from participants by pharmacy staff at V3, and self-sampled by participants at V4 (hence, V4 was no actual visit, but named V4 to ensure consistency in names).

4.2 Measurements

Pharmacy staff completed a training program prior to each study and to each research visit. The training program consisted of a standard operation procedure, an e-learning course and practical training. The practical training comprised biochemical and anthropometric measurements and the proposed dialog with the customer, giving advice to reduce measurement levels if necessary. The Training manager in Boots Norge AS, Lisa T. Mørch-Reiersen, was responsible in Boots pharmacies for developing training programs for the entire VISA-study.

4.2.1 Biochemical measurements



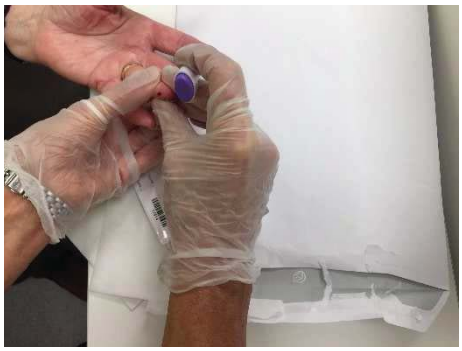
Casett with blood for HbA1c measurement. **Photo:** Beate Østengen

TC measurement using Accurent plus. **Photo:** Boots Norge AS

The VISA-study included several biochemical and anthropometric measurements. Generally, fasting samples were not required, but hours since the last meal was recorded in the Alert/advice and Heart age intervention studies. In the Screening effectiveness study, the main device for analyzing TC was the portable Roche Diagnostic's, Accutrend plus™. The upper limit for TC concentrations was 7.76 mmol/L and the lower limit 3.88 mmol/L. In the Alert/advice and Heart age intervention studies, Alere Afinion AS100 was used to measure HbA1c (using standard immunoturbidemitric method (164) and plasma TC, triglycerides and HDL-C (except if triglycerides were >7.34 mmol/L). LDL-C was calculated with Friedewald's formula (except if triglycerides >4.52 mmol/L). Afinion' s upper limit of TC concentrations was 12.95 mmol/L and the lower limit was 2.59 mmol/L.

Dried blood spots

In the Heart age intervention study, finger-prick blood samples were collected on a DBS card (VITAS Analytical Services, Oslo, Norway). Two spots of blood (~60 µl) per DBS card were considered satisfactory amount of blood. Pharmacy staff were instructed to dry the sample for 2-5 hours before it was put in an airtight aluminum bag and stored in the refrigerator if not immediately shipped to VITAS laboratory, Oslo, for analysis. Blood sample from DBS were used to analyze fatty acid profile and TC from whole-blood (165). Fatty acids in whole-blood were separated and determined by extracting Fatty Acid Methyl Esters (FAME) and therefore expressed as % of FAME. Participants were not offered DBS sampling if they reported taking omega 3- supplements or had eaten fatty fish within the last 12 hours.



Illustrations of fatty acids obtained from the method of dried blood spots (VITAS Analytical Services) **Photos:** Beate Østengen.

4.2.2 Anthropometric measurements

Blood pressure

A&D Medical blood pressure Monitor TM Model UA-767 Plus 30 was used for blood pressure measurements. Blood pressure was measured in accordance with general guidelines (166); two seated consecutive measurements were performed after resting for about five minutes. The average of two blood pressure measurements was recorded.

Illustration of blood pressure measurement as performed in the VISA-study. **Photo:** Karianne Svendsen.

Height and weight

For height and weight measurements, we used any digital scale with precision of 0.1 kg, and any mounted height board that were available in the pharmacy. Standing height was measured in erect posture and with feet against the baseboard. Weight was measured in light clothing without shoes. Both measures were in accordance with procedures from the National Health and Nutrition Examination Survey (NHANES) (167). Weight (kilograms) and height (meters) were recorded, and BMI was calculated and recorded as: weight (kg)/height (meters)^2.

Illustration of height measurement as performed in the VISA-study. **Photo:** Tove Rusvik.

4.3 Questionnaires

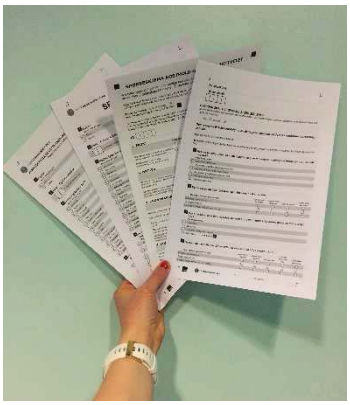


Photo: Karianne Svendsen.

The VISA-study included three questionnaires, all were developed by the VISA-study investigators and all were optical readable and self-administered by participants (except for recording of results from CVD risk factor screenings). Completion time for each questionnaire was ≤ 15 minutes.

The screening questionnaire was completed at V1, anonymous in the Screening effectiveness study, and with identification number in the Alert/advice intervention study. The screening questionnaire included a demographic assessment as well as questions related to previous measurements of TC, blood glucose and blood pressure. Results were included in *paper I and II* and the questionnaires (2012 and 2014 versions) were appendices to *paper I*).

The 62-item VISA-FFQ was a study-specific FFQ, adapted from the NORDIET-FFQ (168). The VISA-FFQ was developed to assess habitual dietary intake of foods and lifestyle factors with particular emphasize on capturing intake of foods and prevalence of lifestyle factors associated with CVD risk. The VISA-FFQ was completed at V1, V2, V3 and V4. An evaluation of the VISA-FFQ was presented in *paper III*, and data obtained from the VISA-FFQ was included in *paper II, III and IV.* The VISA-FFQ is attached as Appendix 1.

The follow-up questionnaire was administered at V3. The questionnaire was intended to tell how participants perceived the result of the CVD risk factor screening, and also to study one-year effects of the Alert/advice intervention study. Results from the follow-up questionnaire was included in *paper II*. The follow-up questionnaire (in Norwegian) is Appendix 2.

4.4 Intervention material

The intervention material provided to the Alert/advice group and partly to the Advice-only group at V1, consisted of one “know your risk factors-card” and one intervention brochure. Intervention materials were developed by the VISA-study investigators.

The “know your risk factors-card” separated concentrations/values of each risk factor into predefined color-zones complying with general recommendations (28); green (favorable), yellow (slightly unfavorable), orange (unfavorable) and red (clearly unfavorable). The card also contained risk-factor specific strategies to risk modification such as; choose healthy fats (unsaturated fatty acids in favor of SFAs), eat less sugar and more whole grains to improve lipids. The card also emphasized the potential large impact on small dietary and lifestyle changes. Similar, that *“losing weight if overweight, being physically active, eating more fruits and vegetables, and quitting smoking would be beneficial for all risk factors”*. The card was translated to English by Svendsen in collaboration with fluent English and Norwegian speaker Tonje Røhr Skjærvik, and is appendix to *paper II*.

The brochure contained information about the VISA-study and simple advice on lifestyle and diet to reduce risk of CVD. The focus of the brochure was to improve health-related behaviors, such as choosing food sources of unsaturated fats and whole grains, eat less sugar, quit smoking and exercise more. The brochure was also given to participants in the Screening effectiveness study. The brochure is attached as Appendix 3.

4.5 Statistics

Data processing and analyses in all papers were mainly performed by SAS software version 9.4 for Windows, whereas Microsoft Excel 2010-2016, IBM SPSS Statistics 24 and R software were used occasionally. Significance level was set to 5% (two-sided). Normally distribution was assessed visually by histograms and Q-Q plots. Data were expressed as means and standard deviations (SDs) when judged normally distributed, and as median and 25th and 75th percentiles when not (169).

Paper I

In *paper I*, the primary analysis was logistic regression. The primary outcome was previous measurements (yes/no) of TC, blood glucose and blood pressure (each analyzed separately) and included several categorical covariates; groups of age, BMI, education, physical activity, smoking, gender and previous measurement of the other risk factors. Probabilities and odds ratios were calculated with 95% CI that were back transformed from their estimated logits.

Paper II

Power calculation

A simple sample size calculation was performed in Excel following the convention of Laake *et al.* (170). Effect estimate was 10% change in CVD risk score (primary outcome) between the Alert/Advice group and the Control group. With 5% significance level and 80% power, this resulted in an estimated sample size of 200 in each of the groups. With three groups in total, wethen estimated that we needed 50 pharmacies in order to include 600 participants.

Analyses of outcomes

To assess 8-week change in the primary outcome between intervention and control groups, we used an unadjusted linear regression model to analyze complete cases. The two degrees of freedom F test with p-value was the formal test of difference in CVD risk score between groups. We performed a series of sensitivity analysis in order to ensure consistency in results from the complete case analysis, and to adjust for possible variation within- and among pharmacies. First, we used lineal mixed models. The model included the unstructured

covariates time (week 0, week 8, week 52), visits (V1, V2, V3) and interaction between visit and time as fixed effects, and identification number as random effect. Next, we added pharmacies (n=48) as an additional random effect variable to the model. Lastly, we analyzed data using the intention to treat principle. The methods baseline-carried forward method and multiple imputations methods (10 imputations using the MIANALYZE Procedure in SAS) (171), were used to include the individuals who did not return to V2. All the models included change in CVD risk score as dependent variables and age and gender as covariates. Secondary outcomes were change in CVD risk factors and health-related behaviors between V1, V2 and V3 within and between groups. Unadjusted linear regression analysis was used to assess change in CVD risk factors, whereas Wilcoxon Signed rank test was used for repeated measures of health-related behaviors within groups and Kruskal Wallis test of differences between groups.

We enrolled participants with elevated CVD risk and performed repeated measurements of CVD risk factors. In such situations, the repeated measures are likely to be closer to the mean than the initial measurement, due to the statistical phenomena regression towards the mean (RTM) (161). Therefore, we calculated how much of the change in CVD risk score for the total (uncontrolled) sample could be explained by RTM, and subtracted the estimated effect from the observed change in CVD risk score. RTM was calculated following the proposed method of Hannan *et al.* (161), and 95% CI for RTM was calculated based on 10000 bootstrap samples.

Paper III

Power calculation

Following the convention of Hulley, we estimated that a sample size of 41 subjects would be sufficient to detect significant correlation coefficients (rho) of 0.5 or higher as a measure of reproducibility of intake estimated by the VISA-FFQ (172). This implied a significance level of 5% and power of 80%.

Analyses of outcomes

Data obtained from V3 was analyzed cross-sectional in this paper. For the purpose of evaluating relative validity of milk fat, partial Spearman rank order correlation (rho) was calculated between dietary 15:0 and 17:0 (estimated from intake of milk, milk products and cheese except for fat-free products in the VISA-FFQ) and whole-blood biomarker 15:0 and 17:0 % of FAME. The correlations were adjusted for total amount of foods and drinks (except tap water) estimated from the VISA-FFQ. Reproducibility of intake of foods and drinks between the test and retest completion of the VISA-FFQ was measured by Spearman's rho (or weighted kappa correlations for categorical data), of which correlation coefficients >0.5 were considered satisfactory or good (173). Whereas Wilcoxon signed rank test (or McNemar test for categorical data) was used to test differences between test and retest intakes. The degree of agreement (including presence of outliers, 95% CI of observations) was evaluated through the creation of Bland Altman plots (174).

Paper IV

Data obtained from V3 was analyzed cross-sectional in this paper. We first stratified participants according to metabolic status (MH and MU). We used linear regression model with metabolic status, BMI and their interaction product term (status x BMI) to study if fatty acid profile between MH and MU were dependent on BMI. Age and gender were added to the model to adjust for confounding. Consequently, the MH and MU were further stratified according to BMI category (normal weight, overweight and obese), creating three subgroups within each metabolic status group. We descriptively explored differences in fatty acid profile, SCD-1, CVD risk factors and demographic factors within each of the BMI-categories. We log-transformed non-normal variables and used T-tests to assess differences in continuous variables, whereas Chi-Square tests were used for categorical variables. Since we had an exploratory approach to analyses, neither results were adjusted for multiple testing.

4.6 Ethical aspects

The VISA study has received ethical approval from the Norwegian Regional Ethical Committee (reference 2013/1660). The VISA-study was also reported to the Norwegian Social Science Data Services with concession from the Norwegian Data Protection Authority to perform couplings to national health registries. The Alert/advice intervention study was registered in clinicalTrials.gov with identifier: NCT02223793.

The VISA-study was conducted in accordance with The Code of Ethics of the World Medical Association (Helsinki Declaration). With reference to the ethical committee, consent to utilize data for statistical analysis in the Screening effectiveness study was assumed by filling out the questionnaire. Informed consent was obtained for all participants in the Alert/advice intervention study, and a simplified consent (to obtain DBS samples) was obtained in the Heart age intervention study.

The VISA-study investigators (pharmacists, medical doctor, nutritionists), in close contact with the ethical committee, carefully considered the counselling following the CVD risk factor screening including the consideration of at what values referral to GP was appropriate. In the screening effectiveness, pharmacy staff recommended the participant to follow-up the screening result with their GP if TC concentrations was ≥7.76 mmol/L (upper limit of the Accutrend device). In the Alert/advice intervention, those with HbA1c <7.0% (n=5), TC <12.00 mmol/L (n=1) and systolic (n=35) and/or diastolic (n=57) blood pressure <170mmHg/100) were recommended to visit their GP at a suitable time. Furthermore, we informed participants that were lost to follow-up at V2 of their screening result from V1. Participants in the Alert/advice intervention were also encouraged to contact Svendsen by mail or phone if they had any queries.

4.6.1 The role of the sponsors

Boots Norge AS and MILLS AS were the main sponsors of the study and investigators in the VISA-study. Boots pharmacies provided expenses to staff, equipment related to the screening and biochemical measurements and similar, and contributed to funding of the study in collaboration with Mills. Mills sponsored the optical reading and scanning of the screening questionnaire, and contributed financially (through the Vita hjertego' grant) to the evaluation of the VISA-FFQ.

We are aware that there are several conflict of interest in this study. After the VISA-study, Boots pharmacies was the first pharmacy chain in Norway to introduce a pay-service named "Heart health" with similarities to the alert/advice intervention. It is clearly in the interest of Boots pharmacies to sell this service, and results from the VISA-study is likely to be used in this regards. Mills will also clearly benefit from any attention on CVD risk because they sell functional food products such as Vita hjertego' proaktive margarine that has been demonstrated in clinical studies to reduce TC concentrations (175). The sponsors furthermore contributed with incentives in the form of a few products to participants who completed the Alert/advice intervention study. Mills also gave coupons on Vita proactive to participants in the Screening effectiveness study in 2012. These potential conflicts of interests are stated in the funding statement of each paper, and employees in Mills and Boots pharmacies have co-authored *paper I and II.* These two papers were the only ones that were directly related to results from the VISA-study. The sponsors had no influence on the decision to submit the papers.

5 Study populations

5.1 Study centers: Pharmacies

All Boots pharmacies in Norway at the time of study initiation, performed the Screening effectiveness study. Of them, 50 pharmacies were selected to perform the Alert/advice intervention study, and 47 completed the Heart age intervention study (Figure 7).

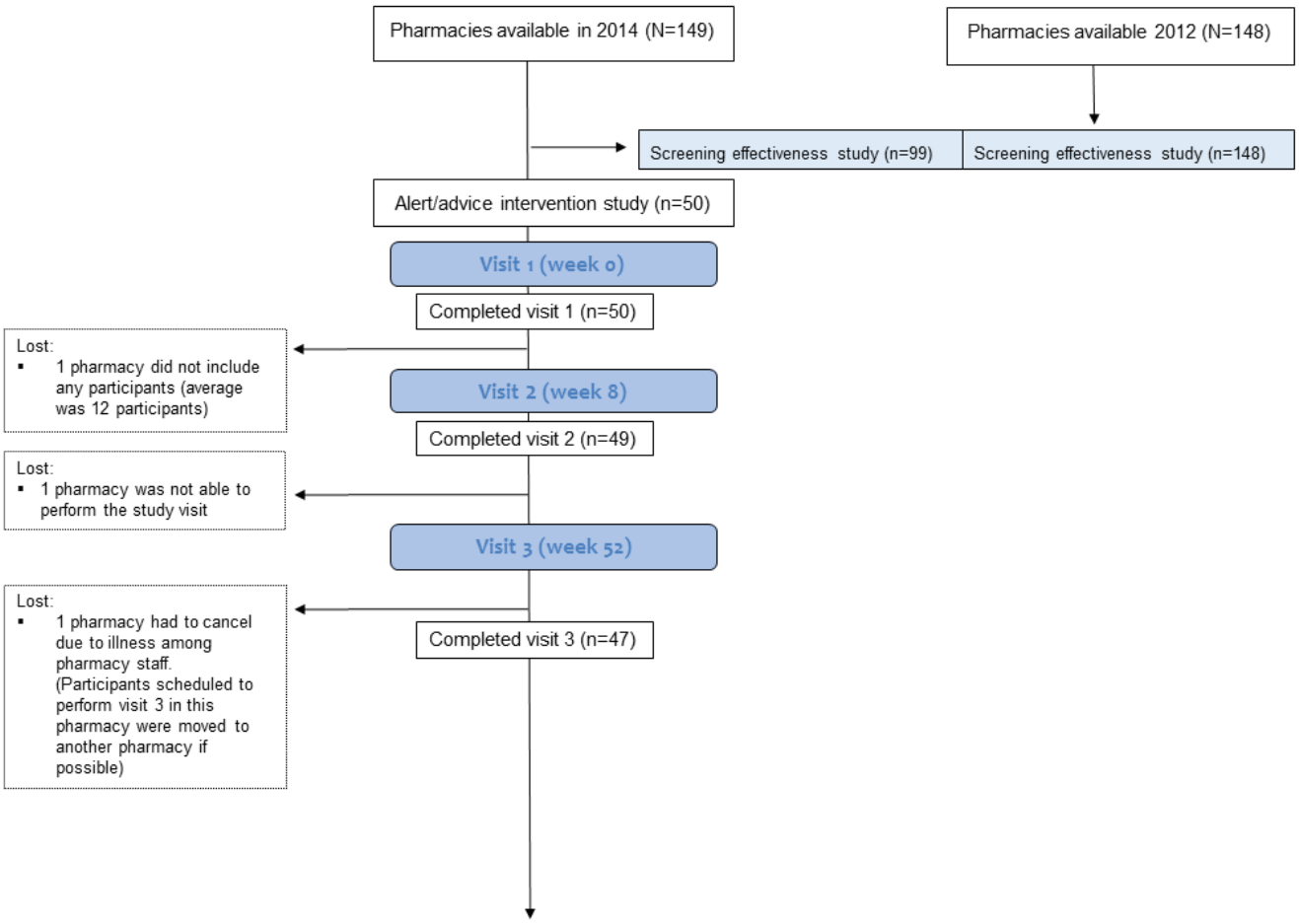


Figure 7. Number of pharmacies included in different parts of the VISA-study.

5.2 Screening effectiveness study sample

During the period of the Screening effectiveness study, 39 788 point-of-care measurements of TC were performed. Of them, 71% (n=28 263) answered the screening questionnaire (18 624 in 2012 and 7 834 in 2014). Eligible criteria for participating in the Screening effectiveness study included age ≥18 years, not pregnant or lactating women, no use of lipid lowering medication and satisfactory completion of the screening questionnaire. The final sample in the Screening effectiveness study described in *paper I* was 21 090 participant*s* (Figure 8).

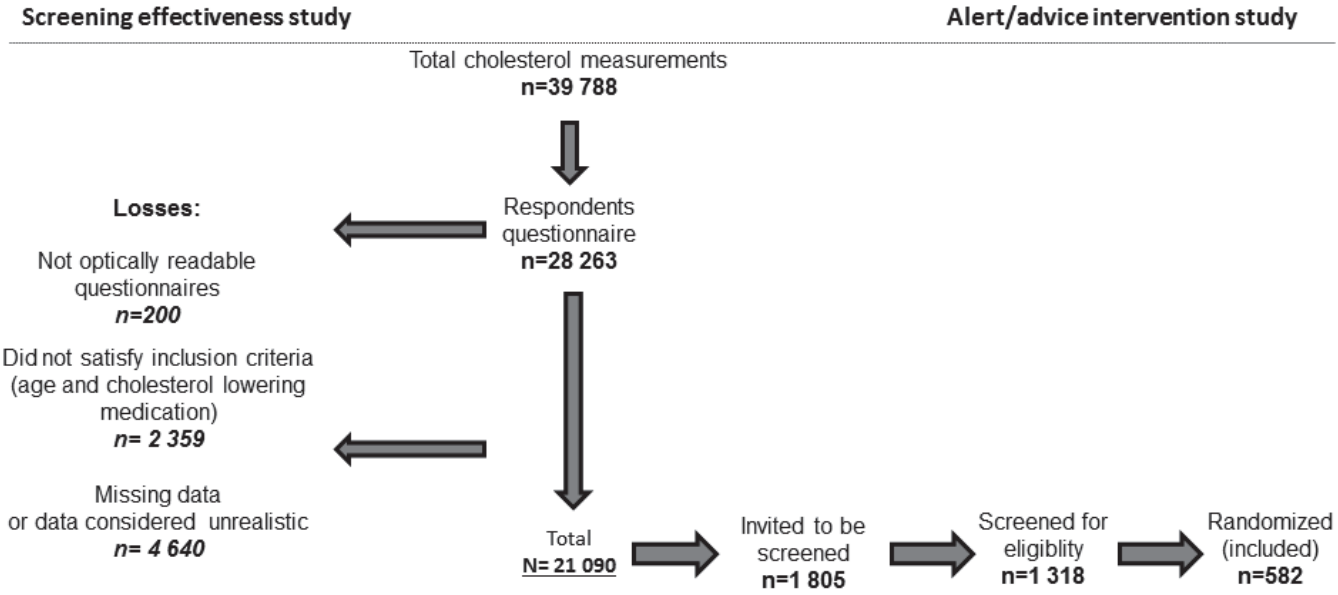


Figure 8. Overview of participants in the Screening effectiveness study and the Alert/advice intervention study.

5.3 Alert/advice intervention study sample

As illustrated in Figure 8, a sub sample of the Screening effectiveness study sample (n=1318) consented and were screened for eligibility to participate in the Alert/advice intervention study. Inclusion criteria were no CVD-relevant medication[1], no history of CVD events[2], understanding Norwegian and having a calculated ad hoc risk score (CVD risk score) of ≥ 4 according to Table 3 (except if; HbA1c ≥7.0% (n=5), TC ≥12.00 mmol/L (n=1) and systolic (n=35) and/or diastolic (n=57) blood pressure ≥170/100 mmHg).

Eligible participants (n=582) were randomized to either one of two interventions, the Alert/advice group (n=198), the Advice-only group (n=185), or the Control group (n=199). In total 93.3% (n=543) completed the intervention by returning to pharmacies at V2. The numbers in each group were; Alert/advice group (n=185), Advice-only group (n=168) and the Control group (n=190). In total 377 of 508 invited attended V3. Samples from V1, V2 and V3 were included in *paper II,* whereas the V3 sample was also utilized for cross-sectional analyses in *paper III and IV.*

Table 3. Calculation of CVD risk score based on score (0-4) for each of the CVD risk factors.

	Score			
	0	**1**	**2**	**4**
Systolic and diastolic blood pressure[1]	SYS <131 and/or <86 DIA mmHg	SYS ≥131 and/or DIA ≥86 mmHg	SYS ≥140 and/or DIA ≥90 mmHg	SYS ≥160 and/or DIA ≥100 mmHg
Total cholesterol	<5 mmol/L	≥5.00 mmol/L	≥6.00 mmol/L	≥7.00 mmol/L
HDL-cholesterol[2]	>1.0 mmol/L	<1.0 mmol/L		
HbA1c	<5.6 %	≥5.6 %	≥5.8 %	≥6.4 %
Body mass index	<30 kg/m2	>30 kg/m2		
Age	>50 years	<50 years	≤40 years	

CVD, Cardiovascular disease; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin A1c; BMI, Body mass index; SYS, systolic; DIA, diastolic.
[1]Mean of two measurements was recorded. Only the highest value of Systolic and diastolic blood pressure was included in risk score calculation.
[2] If HDL was not calculated (triglycerides were>7.34 mmol/L), score 0 was assigned HDL.

[1] Lipid lowering-, blood pressure lowering-, and anti-T2D-medication
[2] Cardiac stenting, percutaneous coronary intervention, T2D and diabetes type 1, coronary artery by-pass operation, heart attack, stroke, heart catheterization, or chest pain/angina pectoris

5.4 Heart age intervention study sample

Prior to V3, 48 pharmacies were randomized to either heart age intervention pharmacies (N=23 pharmacies, 251 participants) or usual care pharmacies (N=25 pharmacies, 257 participants). In the intervention pharmacies, 192 attended V3 of which 178 completed DBS sampling at V3, and 138 self-sampled DBS at V4. In the usual care pharmacies, 185 attended V3 of which 148 completed DBS sampling at V3, and 123 self-sampled DBS at V4.

In the pooled intervention and usual care pharmacies, a sub sample of 307 participants from V3, and 241 from V4, comprised the relative validity sample in *paper III.* Inclusion criteria were available data from both DBS and the VISA-FFQ. In the usual care pharmacies, 122 participants were included in the test-retest sample in *paper III*. The inclusion criteria was available data from VISA-FFQ completed at both V3 (test) and V4 (retest).

In total 321 with available DBS-samples at V3 were included in *paper IV.* These subjects were further characterized as MH or MU, following a modified definition by Telle-Hansen *et al.* (162). In total 150 were characterized as MH, having at least three of the following five criteria: TC <5.2 mmol/L, LDL-C <2.6 mmol/L, HDL-C >1.3 mmol/L, triglycerides (<1.7 mmol/L (fasting) or <2.1 mmol/L (non-fasting)) or HbA1c <5.7%. Whereas 52 were characterized as MU, defined as having ≥4 of the following five criteria; TC ≥5.2 mmol/L, LDL-C ≥2.6 mmol/L, HDL-C ≤1.3 mmol/L, triglycerides ≥1.7 mmol/l (or <2.1 mmol/L if non-fasting) or HbA1c ≥5.7%. Intermediate between MH and MU were 119 participants.

6 Discussion

6.1 Methodological considerations

The methodological implications apply to the overall VISA-study if not otherwise specified.

6.1.1 Multicenter studies

The VISA-study was a multicenter study encompassing 148-159 pharmacies in the Screening effectiveness study, of which 50 pharmacies were included in the Alert/advice intervention study, and 47 in the Heart age intervention study (Figure 7). All pharmacies belonged to the same pharmacy chain (Boots Norge AS). In this way, we ensured a broad geographical distribution of participants, and successfully enrolled the approximate sample size needed (n=600). The involving of pharmacies within the same chain facilitated the low-cost, web-based training of pharmacy staff, and ensured an efficient communication platform throughout the study period. The disadvantages of having multiple centers, are that each pharmacy might vary in regards to organization, size (number of staff and number of customers), compliance to the protocol, quality of care/interventions provided and similar. These similarities and differences between centers are called contextual effects (176).
In addition to these contextual effects, each center also differs in respect to participant characteristics. For several reasons, participants belonging to one center tends to be similar to each other than individuals belonging to other centers (the compositional effect) (169, 177). Consequence of compositional and contextual effects might be correlated outcomes within each pharmacy (177). This assumption of correlated outcomes within pharmacies were confirmed with calculation of intraclass correlation coefficient (ICC) of 0.41[3] for repeated measures (V1, V2, V3) of the primary outcome CVD risk score (169). This indicates substantial within-pharmacy clustering of participants (178). Hence, the variation in the data can, to a relative large extent, be due to differences within individuals, rather than from differences over time (intervention effect) as it can directly affect the variance and therefore the p-values (169, 176). However, after adjusting for multiple centers (assuming the 48

[3] Between pharmacies variance (Covariance Parameter Estimates) = 1.14, Within-pharmacies variance (Residual variance) = 1.64. ICC = 1.14 / (1.14 +1.64) =0.41

pharmacies to be a random of all Boots pharmacies (despite that we know that this is not completely true)), we found that the estimated high ICC did not alter the observed result for change in CVD risk score between groups (*paper II)*.

6.1.2 Validity and reproducibility

In order to accurately assess relationships between exposure and outcome, the tools for measuring the relationships needs to be valid (accurate) and reproducible (precise) (179, 180). In order to be valid and reproducible, measurement errors, defined as deviations from the true value, needs to be satisfactory and controllable (181). The main sources of errors in health assessments are systematic errors and within-subject random errors (182).

Systematic errors can arise due to errors in the measurements tool that can result in assessment of the wrong outcome. Systematic errors can also occur if the study is conducted in discordance with the protocol (183). We have documentation that pharmacy staff in the VISA-study completed the training prior to the visits, but accordance to the protocol can still have varied. Pharmacy staff in the VISA-study (who were health care personnel) were familiar with TC measurements, but not with measurements of lipids and HbA1c using Afinion, nor blood pressure, height, weight and DBS measurements. However, we observed (from visiting a few pharmacies in Oslo and from talking to pharmacy staff), that the procedure for CVD risk factor screening was easy to comply with. Random errors can occur during the implementing and analysis phases of a study (183), and could be due to errors in the analyzer or device, or errors in reporting of data by both the participant and the researcher. Several random errors can threaten the reproducibility of the study, and can result in less precise estimations and larger variation in the outcome (170). In the VISA-study, we limited possible biases related to the measurement devices by controlling them daily, and we reduced researcher bias related to recording of questionnaire data by having optical readable questioners that were machine-scanned.

VISA-FFQ

Evaluation studies are necessary in determining degree of measurement errors (184). In *paper III,* we evaluated the dietary assessment tool, the VISA-FFQ, and found that it was relatively valid to assess intake of milk fat from milk, milk products and cheese except for fat-free products. Relative validity was displayed as significant correlation of 0.32 between (whole-blood) 15:0 % of FAME, and estimated, total food-adjusted dietary 15:0. We considered this correlation acceptable, and comparable to other studies using whole-blood or serum biomarker 15:0 as reference for intake of milk fat (69, 70, 185). The results are also supported by an evaluation study demonstrating that 15:0 assayed in DBS have sensitivity to capture changes in intake of high-fat dairy products (186). However, when 15:0 was analyzed from serum or plasma samples, higher correlation with dairy fat were observed (70, 185). The VISA-FFQ was also considered reproducible to assess intake of most food and lifestyle factors, in accordance with results from other short-FFQs (187, 188), and found convenient to use in several settings (*paper III*).

Biochemical measures

Two different devices were used for capillary measurements of TC; one assayed TC in plasma (Alere Afinion^{TM}AS 100) and one assayed TC in whole-blood (Accutrend plus of Roche diagnostics ltd). Generally, capillary, finger prick sampling has been shown to only slightly (2.9%) overestimate TC concentrations compared to venous blood samples (189).
Both Afinion and Accurend showed high reproducibility compared to reference laboratory methods (190, 191). Accutrend also showed high sensitivity and specificity in the discrimination of high values (191). However, Afinion seemed to slightly underestimate (by 0.2 mmol/L) TC in the measuring interval 4.7-7.6 mmol/L, compared to the laboratory method. This underestimation (called concentration-dependent biases) were however negligible for TG and HDL (190). Both devices had satisfactory precision with within day imprecision of ≤3% for Afinion (190) and intra-assay precision of ≤5% for Accutrend (192), however the day- to-day reproducibility of Accutrend was not satisfactory (192).
However, the control range of the measuring device was much wider for Afinion (2.59-12.95 mmol/L) than Accutrend (3.88-7.76 mmol/L).

Satisfactory reproducibility of measurements of HbA1c has also been reported for Afinion (190). Imprecision for HbA1c was presented as ≤2.0% (193), and the concentration-dependent bias was overall acceptable in particular in the middle and highest measurement range (190). However, the presence of biases and outliers outside the total error limits, diminishes the analytical quality of the analyses (194).

Fatty acids in whole-blood were assayed from DBS, and the method has demonstrated high ICC and therefore good reproducibility over time for measurements of 15:0% of FAME, but not satisfactory agreement for 17:0 (186). Measures of within-subject coefficients of variation has been shown to be relative low for 15:0 (16.6%) indicating lower within-person change across time (186). Fasting fatty acids assayed from DBS is comparable to fasting plasma concentrations of fatty acids (195).

6.1.3 Completers versus non-completers

Valid assessment of outcomes can also be affected by the phenomena of confounding. Confounding is a situation that can occur when a variable is associated with both the exposure and the outcome, and can alter the relationship between the two (169). Randomization performed accurately limits the effect of confounders at baseline, by equally distributing possible confounders in the randomized groups (196). Only then can differences between groups be described as casual effects (197, 198). In the Alert/advice intervention study, the 582 participants randomized to one of three groups at baseline were not statistically significantly different, and the 93% (n=543) that were retained at V2 had similar number of dropouts in each group (*paper II*). Results from sensitivity analyses also confirmed that the results from complete case analysis did not seem to be affected by the number of dropouts (*paper II*) (199-202). However, there could be selection bias concerning the sample that consented to be screened for the Alert/advice intervention (n=1 318) and those who did not consent (n=487). We do not know whether the 487 did not want to participate or could not participate due to the inclusion criteria of no previously CVD event or medication use.

Prior to V3, 35% were lost to follow-up. This could be considered a substantial proportion of missing data that can introduce confounders and lead to biased estimates (176). In such cases, any approach to analyze data and to handling missing data will most likely be biased

(176). Nevertheless, 52 weeks is a long time and higher losses of follow-ups are not unusual (203). In a feasibility study of HbA1c measurements and risk assessment in Norwegian pharmacies (not Boots pharmacies), 65% were lost prior to a two-month follow-up (204). Importantly, due to various logistic issues, only 508 out of 543 who attended V2 were invited to V3. Hence, non-intentional lost to follow-ups can be considered as 26% (377/508) in our study. Yet, the sample remaining is also likely to weaken the validity and conclusions drawn, because non-participants tends to differ from participants (180, 199). However, as reported in *paper III,* we found that although most characteristics were similar, there were more smokers and lower age in participants at V3 compared to non-participants, as also observed in a similar RCT in pharmacies (205) (*paper III*). In contrast to the HUNT study, we did not find differences in any socioeconomic factors between participants and non-participants (206).

6.1.4 Generalizability

Selection bias occurring due to voluntary enrollment and selection criteria can be a real threat to generalizability of results (207, 208), hence limiting to what extent the results can be representative for a larger population than the one studied (207, 208). In order to evaluate the generalizability of the Screening effectiveness sample, we compared the sample to data from the general Norwegian population usually according to data from Statistics Norway, or to the longitudinal health studies, HUNT 3 (2006-08) and Tromsø 7 (2015-16) in Table 2. Table 2 was updated from the previous version published in *paper I* in order to include results from Tromsø 7. We found that the Screening sample were similar to the general population in terms of proportion of individuals with BMI ≥27 kg/m^2 and physical inactive (Table 1). Additionally, it seemed as though the percentage with high school as highest attained education level (41%) and percent smokers (20%) in the Screening effectiveness study were more alike Statistics Norway (41% and 21% respectively) (159) than the sample in Tromsø 7 (28% and 14% respectively) (152) (Table 2). However, the screening study oversampled older women compared with the average numbers in the general Norwegian population. Female dominance is also observed in other health surveys (209), including outreach efforts (aiming to reach people that do not seek help) (210). Characteristics were also comparable to a very similar, ongoing, health survey in Swedish

pharmacies that over six years have included 23 890 people of which 65% were women (211). However, the population was younger (mean age 42 years) than the Screening effectiveness study (55 years) (*paper I*) (211). In contrast to the HUNT and Tromsø studies, the representativeness of the Screening effectiveness study is logically enhanced by the inclusion of participants from 18 out of 19 counties, hence representing both urban and rural Norway. Still, the eastern region of Norway (in particular Oslo and Akershus) comprised 60% of the study sample (Figure 6). However, the number of participants included from each region presented generally similar ratios to the total number of participants living in that region, as presented in the candidate's master thesis (151). Results from effectiveness studies are easily transferred to the population because they measure effects in real life, community or clinical settings (212). In summary, we are confident that results from the Screening effectiveness study can be considered relatively representative for a large sample of non-medicated adults, in particular young Norwegian women that are non-pregnant/lactating (*paper I*).

6.2 General discussion of results

6.2.1 Population-based surveillance

Government-initiated, population based, screening programs and routine health check programs contribute with valuable surveillance of the population's health status, and to epidemiological research of association between exposures and risk of disease (22, 116).

Similar to the previous age-40 program in Norway (116), surveillance of risk factor levels in the population is ensured with health checks in the United Kingdom (the National Health Service) and in Australia from age 40 (213, 214). Whereas in the USA, population based surveillance of risk factors are obtained through NHANES on an apparently representative populations of adults (215). Although the HUNT and Tromsø studies yield important information on health status in Norway, only 2 out of 19 counties in Norway are represented. There are therefore currently no population based screening programs for CVD risk factors in Norway. This observation was the main reason for implementing the nationwide VISA-study. Recently, the Ministry of Health and Care Service has acknowledged

the need for population-based surveillance of health status in Norway (140). However, the Ministry have not proposed to implement CVD risk factor screening (140) that could yield objective information on health status. Recent national data from Finland imply that population-based monitoring of CVD risk factors is vital to detect unfavorable changes in CVD risk factors that needs public attention (216).

During the last decade, Finland and Sweden both experienced a shift towards higher serum TC concentrations across genders and educational groups between (216, 217). Mean TC in the Screening effectiveness study was 5.6 mmol/L (5.4 mmol/L for men and 5.7 mmol/L for women) (Table 2). TC was marginally lower in HUNT 3 (2006-08) and in Tromsø 7 (2015-2016) with serum TC of 5.5 mmol/L in both studies (152, 218). Comparison of the different TC concentrations is however influenced by difference in methods to analyze capillary blood samples between pharmacies, and the slight overestimation of capillary blood samples to venous blood samples obtained in HUNT and Tromsø (189). Difference in gender and use of lipid lowering medication in the HUNT and Tromsø studies in contrast to the Screening effectiveness study, might also have affect the comparison in particular in the older age groups (86, 152, 153). Within the age groups 21-31 years, we observed TC of 4.7 mmol/L in men and 4.8 mmol/L in women (*paper I*). These concentrations were slightly higher than the TC concentrations obtained upon request (personal information from Erik Arnesen) from the largest medical laboratory in Norway, Fürst, demonstrating TC 4.6 mmol/L for both genders in 2012 (*paper I*). Because of the resembling with the general Norwegian population, our results supported by TC concentrations obtained in HUNT 3 (2006-08) and Tromsø 7, suggest almost no change in TC concentrations in Norway after 2006, mirrors the observed trend for other European countries from 2008 to 2014 (219). Said in another way, TC in Norway do not seem to reflect the decreasing TC concentrations observed in USA (220), nor might it reflect the worrying increase in TC concentrations observed in Finland and Sweden (216, 217).

6.2.2 Effectiveness of screening and alerting to CVD risk

Because screening for CVD risk factors have not been found effective in reducing CVD morbidity and mortality (110, 221, 222), it is not generally recommended in European and Norwegian guidelines for CVD prevention in practice (28, 115). Despite this, there is no doubt that population based screening programs have resulted in reduced risk factors and subsequently reduced CVD morbidity and mortality throughout the years (119, 224-226), of which some screening programs have had larger effects (22) than others (223). Atherosclerosis leading to CVD can be accelerated by long term-exposure to high risk factors (102). Hence, early detection of high risk factors can still be effective in preventing premature disease (14), even though systematic reviews and population based RCTs are not able to demonstrate results on reduced morbidity and mortality (110, 221, 222). We found that a nationwide, screening of TC in an apparently healthy population, resulted in identification of 11% that were unaware of a high TC of ≥7 mmol/L (*paper I*). As we found the study sample to resemble the Norwegian population, this result would imply that a large proportion of the population have hyperlipidemia without being aware of it (39, 40). With today's knowledge in preventive medicine we must be aware that many people have not received necessary information to make an informed choice regarding targeted prevention. A similar in-pharmacy CVD screening as the Screening effectiveness study, reported substantial number of screen-detected prevalence of high TC of 34% (n=52) (224). Whereas Rohla and colleagues found that of 6800 participants, 30% were confronted with CVD risk factor levels that they were not previously aware of (34). However, these studies defined CVD risk at lower levels. In our study, CVD risk factor screening identified 6% with either possible T2D (HbA1c ≥7.0%), hyperlipidemia (TC ≥12 mmol/L) or severely hypertension (≥170/100 mmHg). These individuals were not included in the study but strongly recommended to visit (*paper II*). Furthermore, of 582 individuals included in the intervention, 1.2% had HbA1c of ≥6.5% suggestive of T2D (225), 36.4% had TC ≥7.0 mmol/L and 4.8% had systolic blood pressure ≥160 mmHg, both indicating that treatment might be necessary (115) (unpublished results). Identification of high risk is a clear benefit of screening, as individuals identified with high risk are given the opportunity to make informed choices that potential can prevent or change development of disease (226). In this regard, we also demonstrated, in line with results from a secondary prevention trial in Norwegian

pharmacies (227), that the CVD risk factor screening resulted in a small reduction in CVD risk for the total (uncontrolled, n=543) sample after two months. The effect size was though small, because the majority of the reduction was estimated to be explained by regression towards the mean (*paper II*). Other studies have also observed reduction in CVD risk after in-pharmacy screenings (139, 228, 229). The risk reduction could have been mediated through small, observed improvements in health-related behaviors such as reduction in intake of foods high in sugar and dairy SFA and more exercise after 8 weeks (*paper II*). Result for SFA dairy assessed by the VISA-FFQ was considered relative valid, and exercise was evaluated to have good reproducibility in *paper II*, and to be relative valid compared to an objective measurement by Henriksen *et al*. (230). Furthermore, we found that reduction in CVD risk score was highly correlated with reduction in TC ($r=0.6$, $p<0.05$), hence supporting that pharmacies successfully can have a role in primary prevention by detecting and controlling hyperlipidemia (138, 231). Reduction in HbA1c and blood pressure levels were also comparable to other pharmacy-based intervention studies (232, 233). Although the sample present after 52 weeks might not be entirely representative for the sample enrolled at baseline, it should be considered a clear long-term benefit of the CVD risk factor screening that 14% had started CVD preventive medicine after the screening. Particular because it was not a specific intervention target and because all participants were medication-free at baseline *(paper II)*. These results were superior to what observed in a very similar RCT in pharmacies in Canada (150). However, in contrast to our study, Tsuyuki and colleagues found that a pharmacy-led intervention of CVD risk assessment and education (also including components of medication management) was successful in reducing LDL-C, blood pressure, HbA1c and make people quit smoking after three months compared to usual care (150). Hence, the effectiveness of CVD risk factor screening in the VISA-study was limited by the non-effective intervention of alerting to elevated CVD risk identified by screening. In contrast to what was our a priori hypothesis supported by others (147, 234), we found that the Control group seemed to have larger CVD risk score reduction than participants in the primary intervention group, the Alert/advice intervention group (*paper II*). There are several possible explanations for the ineffective Alert/advice intervention. Primary prevention intervention studies that have resulted in substantial reductions in CVD events share the features of enrolling participants with high risk of CVD (22, 76, 235). Hence, although participants in the Alert/advice intervention study had moderately elevated risk, greater risk

could have resulted in greater intention to change behavior (236). Unpublished results from the follow-up questionnaire revealed that at least 50% reported that the CVD risk factor screening result at baseline was in accordance with their expectation. This could have limited the alerting effect of the intervention (237). Still, we did not find that expectations towards measurement levels were significantly related to reduction in CVD risk score *(paper II*). There is also the possibility that participants in the Alert/advice group, intentionally or unintentionally, underestimated or misinterpreted the assessed CVD risk (237, 238). Perception and interpretation of risk can be affected by numeracy (239, 240) which again is related to the ability to interpret health information (241). There are indications that low numeracy is more prevalent in samples somewhat reflecting the intervention sample, such as those with low socioeconomic status, and minority groups (242, 243). We attempted to circumvent the numeracy issue by using colors to demonstrated comparative risk (74) in the "know your risk factors-card", followed by clear and simple explanation of risk factors (244). However, if CVD risk was interpreted as dichotomous rather than a continuum (74) or if the amount of information was too much, (80, 242) the card might have had limited effect.

There is also a possibility that the Control group might not have acted as a control group. Consequently, the intervention can erroneously appear to be less effective than it really was (200). In this regard, we can speculate that CVD risk factors screening followed by the feedback that *"your results from the CVD risk factor measurements will be available in 8 weeks"* could have been interpreted as a self-directed approach of doing all the work of studying what risk is and how to reduce it. The protection motivation theory was developed in an attempt to explain how fear could affect and motivate to attitude change indirectly through the belief in severity of disease (57, 245). However, as stated by Webster and Heeley, it is unlikely that one theory can explain all decision-making behavior (74). We also have to consider that pharmacy staff are not researchers, so that other methods for altering risk identified by screening in pharmacies should be devised.

From a different point of view, results from the Screening effectiveness study can also be interpreted as 81-89% were redundant to screen, because they either had low TC or already knew their TC was high (*paper I*). This alternative interpretation, in addition to the possible psychological aspects of both positive and negative test results and false results (not assessed in the VISA-study), should be deliberated in a more extensive evaluation of the

effectiveness of a pharmacy-based screening (222). Although screenings for cancer and CVD risk factors are dissimilar, a Norwegian study found that a negative cancer screening result was associated with increased weight (246). Mirroring results from the HUNT study (247), we found that reduction in lipids and blood pressure level were accompanied by increased BMI (*paper II*). In this regard, the authors speculate to whether this data might support the "healthy obese" hypothesis. e.g. that subgroups in the population can sustain obese without serious health consequences (247). In support of this hypothesis, in *paper IV*, we identified 67% (n=34) of obese at V3 as metabolically healthy obese (248) with significantly higher HDL-C and lower triglycerides than their counterpart, MU obese (*paper IV*). Opposite, and equally interesting, 15% (n=11) of normal weight individuals were defined as MU (249), with significantly higher HbA1c, triglycerides and lower HDL-cholesterol, despite generally similar BMI (*paper IV*). Distinguishing between MH and MU obese and normal weight, could potential be important in understanding the biological mechanisms in disease development irrespectively of, and beyond, BMI (250), although not all seem agree on this matter (51). Either way, these findings should not be used to limit the importance of BMI as a risk factor, (251), but rather to emphasize the importance of measuring CVD risk factors despite lack of physical symptoms, and also not to judge risk by physical symptoms.

6.2.3 Screening and intervention studies in pharmacies

The rising global prevalence of CVD, T2D and other non-communicable diseases, will logically lead to a higher incidence of people at risk and those needing treatment and help to adhere to described medication (123, 149, 252). Nevertheless, there is an estimated shortage of 4.3 million health professionals worldwide including but not limited to GPs (252). This shortage imply that the future health care system could benefit from utilizing existing health care providers (252), as it would logically reduce the use of resources associated with training and education (252). In unison, pharmacies seemed to be an underused resources in the primary health care system (253), that in Norway continues to growth in numbers and size (254). Pharmacies are present in a wide range of locations, and offer convenient drop-in services with long opening hours even in the weekends. These features make pharmacies accessible (136) as demonstrated with the numerous of visits in pharmacies yearly (129, 136, 255), that surpasses the number of GP visits per year (146). In countries without government-initiated

health checks, it has been suggested that pharmacy staff could deliver routine care such as screening for, and control of, CVD risk factors (34, 252).

The Norwegian guidelines for preventive medicine suggest that lipids could be considered measures at age 40 or older if not previously measured (115), because hyperlipidemia seldom gives symptoms or gives symptoms that are easily ignored. Nevertheless, there are indications that GPs in Norway might down prioritize measuring CVD risk factors if not considered relevant (256). Pharmacies are accessible to both physicians and patients and typically with longer opening ours than a GP (257). There is therefore a pending opportunity for developing a working relationship between pharmacists and GPs, where pharmacists screen and refer high-risk individuals to GPs. This could potential result in more efficient and targeted GP-visit. On the other hand, screening in pharmacies might also increase the burden on GPs. Exemplified, a CVD screening in pharmacies in England, resulted in 70% of clients being referred to GP (258). Willis and colleagues found that the referral rates have increased over the years (149). In the Alert/advice intervention, we found that on private initiative 31.4% (n=114), 14.3% (n=52) and 39.1% (n=142) had controlled their TC, HbA1c/blood glucose and/or blood pressure respectively (not limited to GPs) after the CVD risk factor screening (unpublished results). The challenge, when transferring results to practice, will therefore be to consider the appropriate cut-off levels for referral to GP. The age-adjusted NORRISK score could be appropriate to use as guidance in this matter (97). A working collaboration between pharmacist and GP would be in line with the national call for an interdisciplinary collaboration of tomorrow's health care where health care providers find a common ground and acknowledge each other's strengths and limitations (124).

Nevertheless, it is important to evaluate of pharmacy staff today are interested in expanding their services, and to gain the public acknowledgment in this process (259). To further broaden the use of pharmacies, some suggest that pharmacists could prescribe medication (134). However, conflicts of interest arise when medication is prescribed the same place as it is dispensed. We have not assessed, nor considered the cost and cost-effectiveness of approaches to pharmacy-based screening and monitoring of CVD risk factors levels. Although the CVD risk assessment and treatment have become cheaper (252), screening are costly, and the disease being screened for needs to affect a substantial amount of people, with low drop our rates to assure more value per screened in order to be cost effective

(213). Nevertheless, results from studies in Canada, with similar health care system as Norway, suggest that pharmacist care of CVD risk factors can be both health beneficial and cost saving (148, 149).

Unequal access to high quality health care has been identified as an important contributor to health disparities (252, 260). We found that screening for CVD risk factors in pharmacies attracted those who have not previously had their TC and blood glucose measured (*paper I*). Waaseth and colleagues suggest that there is a clear need for pharmacist counselling also in the follow-up of patients with high blood glucose (261). We also found that the low awareness of TC and blood glucose measurements was related to low education, and had gender and age differences *(paper I)*. Data from Statistics Norway also indicates that characteristics of the VISA-study sample, to some degree reflect those who are less likely to regularly see their doctor (146, 262). Taken together, these findings support the idea that services provided in pharmacies and on similar retail clinics, have the potential to attract those who are less likely to otherwise have accessed these services (127, 133, 210). Once high risk is detected, access to proper care and preventive medicine is available for all in Norway. This suggests, as supported by Willis et al., that by being accessible, screening in pharmacies have the potential to contribute to reduced inequalities in CVD and T2D, and therefore merit further study (149). Considering the urgent need for health care providers and the accessibility of pharmacies and results from the VISA-study overall, supports the statement by Tsuyuki and coworkers saying that utilizing pharmacies in the health care system *is; "an opportunity that we cannot ignore"* (136).

7 Conclusions

In a pharmacy-based nationwide screening for CVD risk factors, we identified a significant number of individuals with previously unknown hyperlipidemia, impaired blood glucose tolerance and hypertension. Even though it was not a pre-specified intervention-target, we observed that several individuals had been prescribed preventive medicine by their physician after the screening. These findings, in addition to characterizing individuals into MH obese and MU normal weight individuals, support the value of assessing CVD risk factors in otherwise healthy individuals in order to reveal high risk factors that can otherwise easily be ignored. Given that we did not find any clear effect of alerting to elevated CVD risk in pharmacies, other methods for intervention to reduce risk identified by screening would have to be devised.

With the present VISA-study, we cannot evaluate whether the observed benefits of detecting high risk, that in principle could result in keeping individuals healthier longer, outweigh several possible negative effects of screening in general. However, we found that low awareness for TC and blood glucose was generally common and, importantly, associated with gender and educational level. Results from the VISA-study indicates that pharmacies have a potential to attract a broad range of the population that are useful to screen for CVD risk. We conclude that pharmacies should be considered as an important public health provider and that further work should be done to enhance their value in potentiating risk reduction.

8 Future work and perspective

Since the intervention of alerting to risk of cardiovascular disease (CVD) was not effective in reducing risk, the next step is to evaluate if the risk communication tool heart age (163), will potentiate risk reduction. We will therefore analyze results from the Heart age intervention study. Furthermore, we will perform subgroup analysis to investigate possible explanatory factors that might have affected the observed CVD risk score reduction.
As Apoteket AB pharmacies in Sweden offer an similar service as the Heart health service in Boots pharmacies (211), there is possibilities to collaborate across borders in order to further explore and enhance the role of pharmacies in primary prevention of CVDs.
We should also assess the cost effectiveness of pharmacy-based risk assessments and/or screenings. Additionally, possible differences in TC, educational level and other socioeconomic parameters, and previous measurements of CVD risk factors between Norwegian counties will be explored in an ongoing master project. We have also been granted access, and obtained consent from participants to couple data from the Alert/advice intervention with The Cause of Death and the Norwegian Prescription Database. With comparison to an age- and gender-adjusted cohort, we aim to yield novel findings of the long-term effects of pharmacy-based screening for CVD risk factors.

Finally yet importantly, we will prioritize to communicate the following main results and their interpretation to different stakeholders, local and national authorities, and to the public:

- We recommend that CVD risk factors should be measured once in early adulthood for all, because high CVD risk seldom gives symptoms, and long-term exposure to high levels might be harmful.

- Pharmacies are suitable to screen for CVD risk and identifying high risk. To maximize the yield of the screening, a referral collaboration with physicians should be considered, in line with the recent governmental *report; The Primary health and care services of tomorrow*.

- The focus in risk assessments should be on measuring total cholesterol and blood glucose rather than blood pressure, because the overall awareness is substantially lower for these two risk factors.

- Pharmacies seems to both attract a broad range of a healthy population, and importantly those who seem to benefit the most from assessing CVD risk factors. The role of pharmacies in primary prevention of CVD therefore merit more attention.

9 Reference list

1. Svendsen K, Telle-Hansen V, Mørch-Reiersen LT, Garstad KW, Gran JM, Jacobs Jr. DR, et al. Changes in lifestyle and risk factor levels after identification of and alerting to high cardiovascular risk: a randomized controlled trial of healthy subjects visiting Norwegian pharmacies. 2017.
2. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. European heart journal. 2016;37(42):3232-45.
3. World Health Organization. Global status report on noncommunicable diseases 2010: Description of the global burden of NCDs, their risk factors and determinants. Genevé; 2010.
4. World Health Organization. Cardiovascular diseases (CVDs) 2017 [updated May 2017; cited 2018 21.4.]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/.
5. Mannsverk J, Wilsgaard T, Mathiesen EB, Lochen ML, Rasmussen K, Thelle DS, et al. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016;133(1):74-81.
6. Global Burden of Disease Mortality Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544.
7. Norwegian Institute of Public Health. Cardiovascular disease in Norway. 2016 [cited 21.2.2018]. Norwegian Institute of Public Health, [cited 21.2.2018]. Available from: https://www.fhi.no/en/op/hin/health--disease/cardiovascular-disease-in-norway---/.
8. Luepker RV. Falling Coronary Heart Disease Rates: A Better Explanation? Circulation. 2016;133(1):8-11.
9. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.
10. Bobryshev YV, Ivanova EA, Chistiakov DA, Nikiforov NG, Orekhov AN. Macrophages and Their Role in Atherosclerosis: Pathophysiology and Transcriptome Analysis. BioMed Research International. 2016;2016:9582430.
11. Ferrier DR. Biochemistry. 6th ed. ed. Philadelphia: Wolters Kluwer; 2014.
12. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid Intima-Media Thickness for Atherosclerosis. Journal of atherosclerosis and thrombosis. 2016;23(1):18-31.
13. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338(23):1650-6.
14. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
15. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. 2017;0:1-14.
16. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. Circulation. 2017.
17. Goldstein JL, Brown MS. A Century of Cholesterol and Coronaries: From Plaques to Genes to Statins. Cell. 2015;161(1):161-72.

18. Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. Circulation. 1993;87(6):1781-91.
19. National Heart Lung and Blood Institute. https://www.nhlbi.nih.gov/health-topics/atherosclerosis: U.S Department of Health and Human Services [cited 2018 10.4]. Available from: https://www.nhlbi.nih.gov/health-topics/atherosclerosis.
20. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J, 3rd. Factors of risk in the development of coronary heart disease-six year follow-up experience. The Framingham Study. Annals of internal medicine. 1961;55:33-50.
21. Keys A BH, Menotti A,. Coronary heart disease in seven countries. Summary. Circulation. 1970;41(4 Suppl):I186-95.
22. Jousilahti P, Laatikainen T, Salomaa V, Pietila A, Vartiainen E, Puska P. 40-Year CHD Mortality Trends and the Role of Risk Factors in Mortality Decline: The North Karelia Project Experience. Global heart. 2016;11(2):207-12.
23. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217(1):3-46.
24. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008;118(20):2047-56.
25. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Archives of internal medicine. 2010;170(17):1566-75.
26. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Archives of internal medicine. 2004;164(19):2147-55.
27. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European heart journal. 2011;32(14):1769-818.
28. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;252:207-74.
29. Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings. Public health and medical care implications. Hypertension (Dallas, Tex : 1979). 1989;14(5):570-7.
30. World Health Organization. Global status report on noncommunicable diseases. Geneva: World Health Organization; 2014.
31. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet. 2005;365(9457):434-41.
32. Catapano AL, Wiklund O. Think Again About Cholesterol Survey. Atherosclerosis Supplements. 2015;20:1-5.
33. Angus J, Evans S, Lapum J, Rukholm E, St Onge R, Nolan R, et al. "Sneaky disease": the body and health knowledge for people at risk for coronary heart disease in Ontario, Canada. Social science & medicine (1982). 2005;60(9):2117-28.
34. Rohla M, Haberfeld H, Sinzinger H, Kritz H, Tscharre M, Freynhofer MK, et al. Systematic screening for cardiovascular risk at pharmacies. Open heart. 2016;3(2):e000497.

35. Alm CS, Warmbrodt N, Klemsdal TO. Kan forebygge tidelig død: Enkle tiltak gjør det mulig å kartlegge risikofaktorer for hjerte- og karsykdom. Sykepleieren 2. 2012.
36. Mooney LA, Franks AM. Impact of health screening and education on knowledge of coronary heart disease risk factors. Journal of American Pharmacy Association. 2011;51(6):713-8.
37. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice. 2011;94(3):311-21.
38. Diabetesforbundet. Diabetes in Norway 2016 29.1.2018 [cited 2018 29.1]. Available from: http://www.diabetes.no/en/.
39. NKT for FH. Hjelp oss å finne alle (forside) [updated 2018; cited 2018 29.1]. Available from: http://www.nktforfh.no/.
40. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. European heart journal. 2013;34(45):3478-90a.
41. Mundal L, Veierod MB, Halvorsen T, Holven KB, Ose L, Iversen PO, et al. Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994-2009, a registry study. European journal of preventive cardiology. 2016;23(18):1962-9.
42. Johnson KC, Bray GA, Cheskin LJ, Clark JM, Egan CM, Foreyt JP, et al. The Effect of Intentional Weight Loss on Fracture Risk in Persons With Diabetes: Results From the Look AHEAD Randomized Clinical Trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2017.
43. World Health Organization. BMI classification Geneva: World Health Organization; 2006 [updated 6.9.2012. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
44. World Health Organization. Prevalence of overweight among adults, BMI ≥ 25, crude Estimates by WHO Region 2017 [cited 2018 5.2]. Available from: http://apps.who.int/gho/data/view.main.BMI25CREGv?lang=en.
45. The Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388(10046):776-86.
46. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. Frontiers in Endocrinology. 2016;7:30.
47. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. Jama. 2003;289(1):76-9.
48. Crump C, Sundquist J, Winkleby MA, Sundquist K. Interactive effects of obesity and physical fitness on risk of ischemic heart disease. International journal of obesity (2005). 2017;41(2):255-61.
49. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, et al. Characterizing the profile of obese patients who are metabolically healthy. International journal of obesity (2005). 2011;35(7):971-81.
50. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in metabolically benign obese individuals. Obesity (Silver Spring, Md). 2012;20(3):651-9.
51. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. Journal of the American College of Cardiology. 2017;70(12):1429-37.
52. Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: Understanding metabolically unhealthy normal weight or metabolically healthy obese patients. Metabolism: clinical and experimental. 2016;65(1):73-80.
53. Micha R, Penalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. Jama. 2017;317(9):912-24.
54. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. Circulation. 2011;123(24):2870-91.

55. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Experimental & Clinical Cardiology. 2005;10(4):229-49.
56. Lawrence M, Kerr S, McVey C, Godwin J. The effectiveness of secondary prevention lifestyle interventions designed to change lifestyle behavior following stroke: summary of a systematic review. International journal of stroke : official journal of the International Stroke Society. 2012;7(3):243-7.
57. Conner M, Norman P. Predicting and changing health behaviour : research and practice with social cognition models. 3rd ed. ed. Maidenhead: McGraw-Hill Education; 2015.
58. Micha R, Shulkin ML, Penalvo JL, Khatibzadeh S, Singh GM, Rao M, et al. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS ONE. 2017;12(4):e0175149.
59. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Public Health Service: Office of the Surgeon General; 2014.
60. Huth PJ, Fulgoni VL, Keast DR, Park K, Auestad N. Major food sources of calories, added sugars, and saturated fat and their contribution to essential nutrient intakes in the U.S. diet: data from the National Health and Nutrition Examination Survey (2003-2006). Nutr J. 2013;12:116.
61. Masana L, Ros E, Sudano I, Angoulvant D. Is there a role for lifestyle changes in cardiovascular prevention? What, when and how? Atherosclerosis Supplements. 2017;26:2-15.
62. Bowen KJ, Sullivan VK, Kris-Etherton PM, Petersen KS. Nutrition and Cardiovascular Disease—an Update. Current atherosclerosis reports. 2018;20(2):8.
63. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines. Advances in nutrition (Bethesda, Md). 2016;7(3):445-54.
64. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans 2015 [8.:[Available from: https://health.gov/dietaryguidelines/2015/guidelines/
65. Nasjonalt råd for ernæring. Food-based dietary guidelines for public health promotion and prevention of chronic diseases - Methodology and scientific evidence (in Norwegian). Oslo: Helsedirektoratet; 2011. 353 p.
66. Risérus U, Marklund M. Milk fat biomarkers and cardiometabolic disease. Current Opinion in Lipidology. 2017;28(1):46-51.
67. Lordan R, Tsoupras A, Mitra B, Zabetakis I. Dairy Fats and Cardiovascular Disease: Do We Really Need to be Concerned? Foods (Basel, Switzerland). 2018;7(3).
68. de Oliveira Otto MC, Nettleton JA, Lemaitre RN, Steffen LM, Kromhout D, Rich SS, et al. Biomarkers of dairy fatty acids and risk of cardiovascular disease in the Multi-ethnic Study of Atherosclerosis. Journal of the American Heart Association. 2013;2(4):e000092.
69. Albani V, Celis-Morales C, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, et al. Exploring the association of dairy product intake with the fatty acids C15:0 and C17:0 measured from dried blood spots in a multipopulation cohort: Findings from the Food4Me study. Molecular nutrition & food research. 2016;60(4):834-45.
70. Brevik A, Veierod MB, Drevon CA, Andersen LF. Evaluation of the odd fatty acids 15:0 and 17:0 in serum and adipose tissue as markers of intake of milk and dairy fat. European journal of clinical nutrition. 2005;59(12):1417-22.
71. Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM. Dietary biomarkers: advances, limitations and future directions. Nutr J. 2012;11:109.
72. Warensjö Lemming E, Nälsén C, Becker W, Ridefelt P, Mattisson I, Lindroos AK. Relative validation of the dietary intake of fatty acids among adults in the Swedish National Dietary Survey using plasma phospholipid fatty acid composition. Journal of Nutritional Science. 2015;4.
73. Vlaeminck B, Fievez V, Cabrita ARJ, Fonseca AJM, Dewhurst RJ. Factors affecting odd- and branched-chain fatty acids in milk: A review. Animal Feed Science and Technology. 2006;131(3):389-417.

74. Webster R, Heeley E. Perceptions of risk: understanding cardiovascular disease. Risk Management and Healthcare Policy. 2010;3:49-60.
75. World Health Organization. World Health Report 2002 – Reducing Risks, Promoting Healthy Life. 2002.
76. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. New England Journal of Medicine. 2013;368(14):1279-90.
77. Pi-Sunyer X. The Look AHEAD Trial: A Review and Discussion Of Its Outcomes. Current nutrition reports. 2014;3(4):387-91.
78. Nielsen JB, Leppin A, Gyrd-Hansen DE, Jarbol DE, Sondergaard J, Larsen PV. Barriers to lifestyle changes for prevention of cardiovascular disease - a survey among 40-60-year old Danes. BMC cardiovascular disorders. 2017;17(1):245.
79. van der Weijden T, Bos LB, Koelewijn-van Loon MS. Primary care patients' recognition of their own risk for cardiovascular disease: implications for risk communication in practice. Current opinion in cardiology. 2008;23(5):471-6.
80. Zelan K. The risks of knowing : developmental impediments to school learning. New York: Plenum Press; 1991.
81. Rothman RL, Montori VM, Cherrington A, Pignone MP. Perspective: the role of numeracy in health care. Journal of health communication. 2008;13(6):583-95.
82. Global Burden of Disease 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544.
83. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
84. Bennett A, Chow CK, Chou M, Dehbi HM, Webster R, Salam A, et al. Efficacy and Safety of Quarter-Dose Blood Pressure-Lowering Agents: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hypertension (Dallas, Tex : 1979). 2017;70(1):85-93.
85. Folkehelseinstituttet. Velkommen til Reseptregisteret 2012 25.10.2012 [cited 2016 2.5.]. Available from: http://www.reseptregisteret.no/.
86. Hopstock LA, Bonaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Lochen ML, et al. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromso Study 1979-2016. BMJ open. 2017;7(8):e015001.
87. Thorsson B, Steingrimsdottir L, Halldorsdottir S, Andersen K, Sigurdsson G, Aspelund T, et al. Changes in total cholesterol levels in Western societies are not related to statin, but rather dietary factors: the example of the Icelandic population. Eur Heart J. 2013;34(24):1778-82.
88. Masters R, Anwar E, Collins B, Cookson R, Capewell S. Return on investment of public health interventions: a systematic review. J Epidemiol Community Health. 2017;71(8):827-34.
89. Jeet G, Thakur JS, Prinja S, Singh M. Community health workers for non-communicable diseases prevention and control in developing countries: Evidence and implications. PLoS ONE. 2017;12(7):e0180640.
90. European Society of Cardiology. European heart health charter, 2009 [Available from: http://www.heartcharter.org/download/toolkit/EHHC%20English.pdf.
91. Folkehelseinstituttet. Dødsårsakregisteret Oslo: Folkehelseinstituttet; 2016 [cited 2017 2.4]. Available from: http://statistikkbank.fhi.no/dar/
92. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. Heart (British Cardiac Society). 2016;102(24):1945-52.
93. Guo X, Li Z, Vittinghoff E, Sun Y, Pletcher MJ. Trends in rate of acute myocardial infarction among patients aged <30 years. Nature Reviews Cardiology. 2017;15:119.

94. Gupta A, Wang Y, Spertus JA, Geda M, Lorenze N, Nkonde-Price C, et al. Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010. Journal of the American College of Cardiology. 2014;64(4):337-45.
95. Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. Bmj. 2012;344:e356.
96. Sulo G, Igland J, Nygard O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. European journal of preventive cardiology. 2013.
97. Selmer R, Igland J, Ariansen I, Tverdal A, Njolstad I, Furu K, et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. European journal of preventive cardiology. 2017;24(7):773-82.
98. Ridker PM, Cook N. Should age and time be eliminated from cardiovascular risk prediction models? Rationale for the creation of a new national risk detection program. Circulation. 2005;111(5):657-8.
99. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nature reviews Cardiology. 2018;15(4):230-40.
100. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
101. Hughes GH, Cutter G, Donahue R, Friedman GD, Hulley S, Hunkeler E, et al. Recruitment in the Coronary Artery Disease Risk Development in Young Adults (CARDIA) Study. Controlled clinical trials. 1987;8(4 Suppl):68s-73s.
102. Brown MS, Goldstein JL. Biomedicine. Lowering LDL--not only how low, but how long? Science. 2006;311(5768):1721-3.
103. Gidding SS, McMahan CA, McGill HC, Colangelo LA, Schreiner PJ, Williams OD, et al. Prediction of coronary artery calcium in young adults using the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score: the CARDIA study. Archives of internal medicine. 2006;166(21):2341-7.
104. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes care. 2013;36(12):3863-9.
105. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. The new England journal of medicine. 2012;366(4):321-9.
106. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. Bmj. 2008;336(7659):1475-82.
107. Helsedirektoratet. Nasjonalt screeningprogram mot tarmkreft: Status og anbefalinger. Divisjon spesialisthelsetjenester Avdeling sykehustjenester; 2017.
108. Milne RJ, Gregory D. Gamble. Cardiovascular risk screening and lipid lowering treatment in their economic context. New Zeland: New Zealand Guidelines Group Cardiovascular Modelling Group; 2003.
109. Prochazka AV, Caverly T. General Health Checks in Adults for Reducing Morbidity and Mortality From Disease: Summary Review of Primary Findings and Conclusions. JAMA internal medicine. 2013:1-2.
110. Dyakova M, Shantikumar S, Colquitt JL, Drew CM, Sime M, MacIver J, et al. Systematic versus opportunistic risk assessment for the primary prevention of cardiovascular disease. Cochrane database of systematic reviews. 2016;1:Cd010411.
111. Wong MC, Ching JY, Chan VC, Lam TY, Luk AK, Ng SS, et al. Factors associated with false-positive and false-negative fecal immunochemical test results for colorectal cancer screening. Gastrointestinal endoscopy. 2015;81(3):596-607.

112. Collins RE, Lopez LM, Marteau TM. Emotional impact of screening: a systematic review and meta-analysis. BMC Public Health. 2011;11(1):603.
113. American Heart Association. Heart-Health Screenings 2017 [Available from: http://www.heart.org/HEARTORG/Conditions/Heart-HealthScreenings_UCM_428687_Article.jsp#.WZwVoD4jGpp.
114. National Institute for Health and Clinical Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). 2014.
115. Helsedirektoratet. Forebygging av hjerte- og karsykdom: Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom. Oslo: Helsedirektoratet; 2017.
116. Bjartveit K, Stensvold I, Lund-Larsen PG, Graff-Iversen S, Urdal P. [Cardiovascular screenings in Norwegian counties. Trends in risk pattern during the period 1985-90 among persons aged 40-42 in 4 counties]. Tidsskr Nor Laegeforen. 1991;111(17):2072-6.
117. Folkehelseinstituttet. 40-åringsundersøkelsene 1985-1999. 2013. In: Regionale helseundersøkelser 1974-2009 [Internet]. Folkehelseinstituttet Available from: https://www.fhi.no/studier/helseundersokelser/40-aringsundersokelsene/.
118. Tverdal A, Selmer RM. 40-åringsundersøkelsene-400 000 menn og kvinner har møtt opp. Tidsskr Nor Laegeforen. 2002;122(27):2641-2.
119. Kreftregisteret. Mammografiprogrammet [updated 5.3.2018; cited 2018 20.4]. Available from: https://www.kreftregisteret.no/screening/Mammografiprogrammet/.
120. World report on Ageing and Health [Internet]. 2015. Available from: http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1].
121. Nayor M, Vasan RS. Recent Update to the US Cholesterol Treatment Guidelines: A Comparison With International Guidelines. Circulation. 2016;133(18):1795-806.
122. Aluttis C, Bishaw T, Frank MW. The workforce for health in a globalized context - global shortages and international migration. Global health action. 2014;7(1):23611.
123. World Health Organization. The World Health Report 2013: Research for Universal Health Coverage.; 2013.
124. Meld. St. 26 (2014–2015). The primary health and care services of tomorrow – localised and integrated. Oslo: Ministry of Health and Care Services; 2014.
125. Goodman RA, Bunnell R, Posner SF. What is "community health"? Examining the meaning of an evolving field in public health. Preventive medicine. 2014;67 Suppl 1:S58-61.
126. Rawlins MD. Extending the role of the community pharmacist. BMJ. 1991;302(6774):427-8.
127. Department of Health. Pharmacy in England: Building on strengths, delivering the future. London: Department of Health; 2008.
128. Hypertension Canada. Hypertension Canada. Mission and vision [cited 2018 21.2.]. Available from: https://www.hypertension.ca/en/mission-and-vision.
129. Shiu JR, Simpson SH, Johnson JA, Tsuyuki RT. Quantifying opportunities to affect diabetes management in the community2006. 37-8 p.
130. Via-Sosa MA, Toro C, Trave P, March MA. Screening premorbid metabolic syndrome in community pharmacies: a cross-sectional descriptive study. BMC Public Health. 2014;14:487.
131. Brown TJ, Todd A, O'Malley CL, Moore HJ, Husband AK, Bambra C, et al. Community pharmacy interventions for public health priorities: a systematic review of community pharmacy-delivered smoking, alcohol and weight management interventions Southampton (UK): NIHR Journals Library; 2016.
132. Blenkinsopp A, Anderson C, Armstrong M. Systematic review of the effectiveness of community pharmacy-based interventions to reduce risk behaviours and risk factors for coronary heart disease. Journal of public health medicine. 2003;25(2):144-53.
133. Laws M, Scott MK. The emergence of retail-based clinics in the United States: early 460 observations. (Project Hope). Health affairs. 2008;27:5.
134. Bluml BM, McKenney JM, Cziraky MJ. Pharmaceutical care services and results in project ImPACT: hyperlipidemia. Journal of the American Pharmaceutical Association (Washington,DC : 1996). 2000;40(2):157-65.

135. Kjome RLS, Wright DJ, Bjaaen AB, Garstad KW, Valeur M. Dermatological cancer screening: Evaluation of a new community pharmacy service. Research in social & administrative pharmacy : RSAP. 2017;13(6):1214-7.
136. Tsuyuki RT, Beahm NP, Okada H, Al Hamarneh YN. Pharmacists as accessible primary health care providers: Review of the evidence. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC. 2018;151(1):4-5.
137. Al Hamarneh YN, Hemmelgarn BR, Hassan I, Jones CA, Tsuyuki RT. The Effectiveness of Pharmacist Interventions on Cardiovascular Risk in Adult Patients with Type 2 Diabetes: The Multicentre Randomized Controlled RxEACH Trial. Canadian journal of diabetes. 2017;41(6):580-6.
138. Tsuyuki RT, Johnson JA, Teo KK, Simpson SH, Ackman ML, Biggs RS, et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). Archives of internal medicine. 2002;162(10):1149-55.
139. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Archives of internal medicine. 2011;171(16):1441-53.
140. Grøtvedt L GE, Hesselberg Ø, Johansen R, Reneflot A. Fylkesundersøkelser blant voksne - forslag for gjennomføring. Folkehelseinstituttet; 2016. Contract No.: ISBN (elektronisk) 978-82-8082-750-0
141. Bjartveit K, Wøien G. Risikofaktorer for hjerte- og karsykdom i Norge. Resultater fra undersøkelser i 18 fylker. Oslo: Statens Helseundersøkelser; 1997.
142. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Grete H.Bratberg LV, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi. 2003;13(1):19-23.
143. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-7.
144. McNamara CL, Balaj M, Thomson KH, Eikemo TA, Solheim EF, Bambra C. The socioeconomic distribution of non-communicable diseases in Europe: findings from the European Social Survey (2014) special module on the social determinants of health. European journal of public health. 2017;27(suppl_1):22-6.
145. Lim KK, Kwan YH, Tan CS, Low LL, Chua AP, Lee WY, et al. The association between distance to public amenities and cardiovascular risk factors among lower income Singaporeans. Preventive medicine reports. 2017;8:116-21.
146. Statistics Norway. GPs and emergency primary health care Statistics Norway 2015 [updated 8.6.2016; cited 2018 12.3]. Available from: https://www.ssb.no/en/helse/statistikker/fastlegetj/aar/2016-06-08.
147. Waldron CA, van der Weijden T, Ludt S, Gallacher J, Elwyn G. What are effective strategies to communicate cardiovascular risk information to patients? A systematic review. Patient education and counseling. 2011;82(2):169-81.
148. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes care. 2007;30(6):1374-83.
149. Willis A, Rivers P, Gray LJ, Davies M, Khunti K. The effectiveness of screening for diabetes and cardiovascular disease risk factors in a community pharmacy setting. PLoS ONE. 2014;9(4):e91157.
150. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The Effectiveness of Pharmacist Interventions on Cardiovascular Risk: The Multicenter Randomized Controlled RxEACH Trial. Journal of the American College of Cardiology. 2016;67(24):2846-54.
151. Svendsen K. Kolesterolnivå i grupper av Norges befolkning- resultater fra lavterskel kolesterolmålinger i apotek. Universitetet i Oslo; 2013.
152. The Tromsø Study. Tromsø 7-desciption of variables 2015-16 [cited 2018 1.2]. Available from: http://tromsoundersokelsen.uit.no/tromso/.

153. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-77.
154. NTNU: Hunt research center. HUNT 321.2.2018. Available from: https://hunt-db.medisin.ntnu.no/hunt-db/#/studypart/77.
155. Statistics Norway. Dette er Norge 2014: Hva tallene forteller: Statistics Norway; 2014 [cited 2018 27.2]. Available from: https://www.ssb.no/befolkning/artikler-og-publikasjoner/_attachment/188232?_ts=1475e7ac938.
156. Mean age 2014 [Internet]. http://www.kommuneprofilen.no/Profil/Befolkning/DinRegion/bef_alder_region.aspx 2014. Available from: http://www.kommuneprofilen.no/Profil/Befolkning/DinRegion/bef_alder_region.aspx
157. Graff-Iversen S, Jenum AK, Grotvedt L, Bakken B, Selmer RM, Sogaard AJ. Risk factors for myocardial infarction, stroke and diabetes in Norway. Tidsskrift for Den norske legeforening. 2007;127(19):2537-41.
158. Helseforhold, levekårsundersøkelsen [Internet]. https://www.ssb.no/helse/statistikker/helseforhold. 2015. Available from: https://www.ssb.no/helse/statistikker/helseforhold.
159. Statistics Norway. Population´s level of education, 1 October 2014.: Statistics Norway

2015 [updated 18 June 2015. Available from: http://www.ssb.no/en/utdanning/statistikker/utniv/aar/2015-06-18?fane=tabell&sort=nummer&tabell=225181.
160. Smoking habits [Internet]. 2015 [cited 12.04.2017]. Available from: https://www.ssb.no/helse/statistikker/royk.
161. Hannan PJ, Jacobs DR, Jr., McGovern P, Klepp KI, Elmer P. Estimating the effect of regression toward the mean under stochastic censoring. American journal of epidemiology. 1994;139(4):422-31.
162. Telle-Hansen VH, Halvorsen B, Dalen KT, Narverud I, Wesseltoft-Rao N, Granlund L, et al. Altered expression of genes involved in lipid metabolism in obese subjects with unfavourable phenotype. Genes & nutrition. 2013;8(4):425-34.
163. Joint British Societies for the prevention of cardiovascular disease. Risk calculator 2015 [cited 2015 03.06]. Available from: http://www.jbs3risk.com/pages/risk_calculator.htm
164. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. Biomarker Insights. 2016;11:95-104.
165. Sakhi AK, Bastani NE, Ellingjord-Dale M, Gundersen TE, Blomhoff R, Ursin G. Feasibility of self-sampled dried blood spot and saliva samples sent by mail in a population-based study. BMC cancer. 2015;15(1):265.
166. Frese EM, Fick A, Sadowsky HS. Blood Pressure Measurement Guidelines for Physical Therapists. Cardiopulmonary Physical Therapy Journal. 2011;22(2):5-12.
167. National Health and Nutrition Examination Survey. Anthropometry procedures manual NHANES; 2004 [cited 2018 5.4].
168. Henriksen HB, Carlsen MH, Paur I, Berntsen S, Bøhn SK, Skjetne AJ, et al. Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients. Food and nutrition Research. 2018;62(1306):1306.
169. Field A. Discovering statistics using SPSS : (and sex and drugs and rock 'n' roll). 3 ed. Los Angeles: SAGE; 2009.
170. Laake P, Hjartåker A, Thelle DS, Veierød MB. Epidemiologiske og kliniske forskningsmetoder. 1. ed. Oslo: Gyldendal akademisk; 2007. 551 p.
171. IDRE Statistical Consulting Group. Missing data techniques with SAS 2016. Available from: https://stats.idre.ucla.edu/wp-content/uploads/2016/09/Missing-Data-Techniques_UCLA_Stata.pdf
172. Hulley SB. Designing clinical research: an epidemiologic approach. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

173. Hankin JH, Wilkens LR, Kolonel LN, Yoshizawa CN. Validation of a quantitative diet history method in Hawaii. American journal of epidemiology. 1991;133(6):616-28.
174. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. International Journal of Nursing Studies. 2010;47(8):931-6.
175. Pedersen JI, Kirkhus B, Muller H. Serum cholesterol predictive equations in product development. EurJMedRes. 2003;8(8):325-31.
176. Friedman LM, Furberg, C. D , DeMets, D. L. Issues in Data Analysis. Fundamentals of clinical trials 4. ed. New York: Springer; 2010
177. Kahan BC, Morris TP. Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? Statistics in Medicine 2013;32(7):1136-49.
178. Thompson DM, Fernald DH, Mold JW. Intraclass Correlation Coefficients Typical of Cluster-Randomized Studies: Estimates From the Robert Wood Johnson Prescription for Health Projects. Annals of family medicine. 2012;10(3):235-40.
179. Slack MK, Draugalis JR. Establishing the internal and external validity of experimental studies. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2001;58(22):2173-81; quiz 82-3.
180. Willet W. Nutritional Epidemiology. Oxford: Oxford University Press; 2013.
181. Slimani N, Freisling H, Illner AK, Huybrechts I. Methods to Determine Dietary Intake.
182. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, et al. Structure of dietary measurement error: results of the OPEN biomarker study. American journal of epidemiology. 2003;158(1):14-21; discussion 2-6.
183. Laake P, Thoresen M, Veierød MB. Målefeilsproblemer. Oslo: Gyldendal akademisk; 2007. p. [128]-[68].
184. Willet W, Lenart E. Reproducibility and validity of food-frequency questionnaires. Nutritional epidemiology. New York: Oxford University Press; 1998. p. 101-47.
185. Sofie Biong A, Berstad P, Pedersen JI. Biomarkers for intake of dairy fat and dairy products. European Journal of Lipid Science and Technology. 2006;108(10):827-34.
186. Albani V, Celis-Morales C, O'Donovan CB, Walsh MC, Woolhead C, Forster H, et al. Within-person reproducibility and sensitivity to dietary change of C15:0 and C17:0 levels in dried blood spots: data from the European Food4Me Study. Molecular nutrition & food research. 2017.
187. England CY, Andrews RC, Jago R, Thompson JL. A systematic review of brief dietary questionnaires suitable for clinical use in the prevention and management of obesity, cardiovascular disease and type 2 diabetes. European journal of clinical nutrition. 2015;69(9):977-1003.
188. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutrition research reviews. 2004;17(1):5-22.
189. Sblendorio V, Palmieri B, Riccioni G. Blood cholesterol concentration measured by CR3000: fingerstick versus venous sampling. International journal of immunopathology and pharmacology. 2008;21(3):729-33.
190. Jain A, Rao N, Sharifi M, Bhatt N, Patel P, Nirmal D, et al. Evaluation of the point of care Afinion AS100 analyser in a community setting. Annals of clinical biochemistry. 2017;54(3):331-41.
191. Coqueiro RdS, Santos MC, Neto JdSL, Queiroz BMd, Brügger NAJ, Barbosa AR. Validity of a Portable Glucose, Total Cholesterol, and Triglycerides Multi-Analyzer in Adults. Biological Research For Nursing. 2014;16(3):288-94.
192. Scafoglieri A, Tresignie J, Provyn S, Clarys JP, Bautmans I. Reproducibility, accuracy and concordance of Accutrend Plus for measuring circulating lipid concentration in adults. Biochemia medica : casopis Hrvatskoga drustva medicinskih biokemicara / HDMB. 2012;22(1):100-8.
193. Sølvik UØ, Røraas T, Christensen NG, Sandberg S. Diagnosing Diabetes Mellitus: Performance of Hemoglobin A: Point-of-Care Instruments in General Practice Offices. Clinical chemistry. 2013;59(12):1790-801.
194. Scandinavian evaluation of laboratory equipment for primary health care (SKUP). Afinion™ system for HbA1c. A system for measurement of B—Haemoglobin A1c manufactured by Axis-Shield PoC AS , Norway.

195. Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, et al. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. American journal of epidemiology. 2005;162(4):373-81.
196. Attia AM. Bias in RCTs: Confounders, selection bias and allocation concealment2005. 258-60 p.
197. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343.
198. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008;336(7644):601-5.
199. Wagner J. The Fraction of Missing Information as a Tool for Monitoring the Quality of Survey Data. Public Opinion Quarterly. 2010;74(2):223-43.
200. A.R. Jadad MWE. Bias in Randomized Controlled Trials. 2008.
201. Liu G, Gould AL. Comparison of alternative strategies for analysis of longitudinal trials with dropouts. Journal of biopharmaceutical statistics. 2002;12(2):207-26.
202. Hayati Rezvan P, Lee KJ, Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research. BMC medical research methodology. 2015;15:30.
203. Rothman K.J. GS, Lash T.L. Modern Epidemiology. 3. ed: Lippincott Williams & Wilkins; 2008.
204. Risoy AJ, Kjome RLS, Sandberg S, Solvik UO. Risk assessment and HbA1c measurement in Norwegian community pharmacies to identify people with undiagnosed type 2 diabetes - A feasibility study. PLoS ONE. 2018;13(2):e0191316.
205. Rozenfeld Y, Hunt JS. Effect of patient withdrawal on a study evaluating pharmacist management of hypertension. Pharmacotherapy. 2006;26(11):1565-71.
206. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC medical research methodology. 2012;12:143.
207. Kahan BC, Rehal S, Cro S. Risk of selection bias in randomised trials. Trials. 2015;16.
208. Friedman LM, Furberg, C. D , DeMets, D. L. Fundamentals of clinical trials 4. ed. New York: Springer; 2010
209. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: Collaborative research in the interface between clinical medicine and epidemiology: Study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scandinavian journal of public health. 2013;41(1):65-80.
210. Isaacs D, Riley AC, Prasad-Reddy L, Castner R, Fields H, Harper-Brown D, et al. Jazzin' Healthy: Interdisciplinary Health Outreach Events Focused on Disease Prevention and Health Promotion. Journal of racial and ethnic health disparities. 2017;4(2):223-32.
211. Perk JN, M. Relative cardiovascular risk, a valuable additional tool in prevention. EuroPrevent; Malaga 2016.
212. Gartlehner G HR, Nissman D, et al. Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Rockville. 2006. Rockville (MD): Agency for Healthcare Research and Quality (US). Available from: https://www.ncbi.nlm.nih.gov/books/NBK44024/.
213. Department of Health. Putting prevention first. NHS Health Checks: Vascular Risk Assesssment and Management. London Department of Health; 2009.
214. Amoroso C, Harris MF, Ampt A, Laws RA, McKenzie S, Williams AM, et al. The 45 year old health check - feasibility and impact on practices and patient behaviour. Australian family physician. 2009;38(5):358-62.
215. Center for Disease Control and Prevention. National Health and Nutrition Examination Survey: About the National Health and Nutrition Examination Survey2013 6.5.2013 [cited 2016 16.4]. Available from: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

216. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. European journal of public health. 2015;25(3):539-46.
217. Ng N, Johnson O, Lindahl B, Norberg M. A reversal of decreasing trends in population cholesterol levels in Vasterbotten County, Sweden. Global health action. 2012;5.
218. Serum Cholesterol [Internet]. NTNU. [cited 12.4.2017]. Available from: https://hunt-db.medisin.ntnu.no/hunt-db/#variab152.
219. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet. 2011;377(9765):578-86.
220. Carroll MD, Fryar CD, Kit BK. Total and High-density Lipoprotein Cholesterol in Adults: United States, 2011-2014. NCHS data brief. 2015(226):1-8.
221. Jorgensen T, Jacobsen RK, Toft U, Aadahl M, Glumer C, Pisinger C. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. BMJ. 2014;348:g3617.
222. Krogsboll LT, Jorgensen KJ, Gronhoj Larsen C, Gotzsche PC. General health checks in adults for reducing morbidity and mortality from disease: Cochrane systematic review and meta-analysis. BMJ. 2012;345:e7191.
223. Luepker RV, Rastam L, Hannan PJ, Murray DM, Gray C, Baker WL, et al. Community education for cardiovascular disease prevention. Morbidity and mortality results from the Minnesota Heart Health Program. American journal of epidemiology. 1996;144(4):351-62.
224. Jafari M, Masih M, Emerson JF. The Value of Pharmacist Involvement in a Point-of-Care Service, Walk-In Lipid Screening Program. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2001;21(11):1403-6.
225. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation2011 18.3.2014. Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf?ua=1.
226. Stene LC SH, Gulseth HL. D. Diabetes in Norway. 2014 8.8.2017 [cited 21.2.2018]. In: Public Health Report [Internet]. Norwegian Institute of Public Health, [cited 21.2.2018]. Available from: https://www.fhi.no/en/op/hin/health--disease/diabetes-in-norway---public-health-/.
227. Garcia BH, Giverhaug T, Hogli JU, Skjold F, Smabrekke L. A pharmacist-led follow-up program for patients with established coronary heart disease in North Norway - a randomized controlled trial. Pharmacy practice. 2015;13(2):575.
228. Mc Namara KP, Dunbar JA, Philpot B, Marriott JL, Reddy P, Janus ED. Potential of pharmacists to help reduce the burden of poorly managed cardiovascular risk. The Australian journal of rural health. 2012;20(2):67-73.
229. Ladhani NN, Majumdar SR, Johnson JA, Tsuyuki RT, Lewanczuk RZ, Spooner R, et al. Adding pharmacists to primary care teams reduces predicted long-term risk of cardiovascular events in type 2 diabetic patients without established cardiovascular disease: results from a randomized trial. Diabetic medicine : a journal of the British Diabetic Association. 2012;29(11):1433-9.
230. Henriksen HB, et al. Validation of two short questionnaires assessing physical activity in colorectal cancer patients. BMC Sports Science, Medicine and Rehabilitation (In press). 2018.
231. Charrois TL, Zolezzi M, Koshman SL, Pearson G, Makowsky M, Durec T, et al. A systematic review of the evidence for pharmacist care of patients with dyslipidemia. Pharmacotherapy. 2012;32(3):222-33.
232. van Eikenhorst L, Taxis K, van Dijk L, de Gier H. Pharmacist-Led Self-management Interventions to Improve Diabetes Outcomes. A Systematic Literature Review and Meta-Analysis. Frontiers in pharmacology. 2017;8:891.
233. Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC. 2017;150(3):184-97.

234. Olenak JL, Calpin M. Establishing a cardiovascular health and wellness program in a community pharmacy: screening for metabolic syndrome. J Am Pharm Assoc (2003). 2010;50(1):32-6.
235. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet. 1981;2(8259):1303-10.
236. Frileux S, Munoz Sastre MT, Mullet E, Sorum PC. The impact of the preventive medical message on intention to change behavior. Patient education and counseling. 2004;52(1):79-88.
237. Cheong AT, Khoo EM, Tong SF, Liew SM. To Check or Not to Check? A Qualitative Study on How the Public Decides on Health Checks for Cardiovascular Disease Prevention. PLoS ONE. 2016;11(7):e0159438.
238. Helou TN, Santos RD, Laurinavicius AG, Bittencourt MS, Pesaro AEP, Franco FGM, et al. Association between clinical factors and self-underestimation of cardiovascular risk in subjects submitted to a routine health evaluation. Clinical cardiology. 2018.
239. van der Weijden T, van Steenkiste B, Stoffers HE, Timmermans DR, Grol R. Primary prevention of cardiovascular diseases in general practice: mismatch between cardiovascular risk and patients' risk perceptions. Medical decision making : an international journal of the Society for Medical Decision Making. 2007;27(6):754-61.
240. Goldman RE, Parker DR, Eaton CB, Borkan JM, Gramling R, Cover RT, et al. Patients' perceptions of cholesterol, cardiovascular disease risk, and risk communication strategies. Annals of family medicine. 2006;4(3):205-12.
241. Damman OC, Vonk SI, Van den Haak MJ, van Hooijdonk CMJ, Timmermans DRM. The effects of infographics and several quantitative versus qualitative formats for cardiovascular disease risk, including heart age, on people's risk understanding. Patient education and counseling. 2018.
242. N Bleich S, Herring B, Flagg D, Gary-Webb T. Reduction in Purchases of Sugar-Sweetened Beverages Among Low-Income Black Adolescents After Exposure to Caloric Information2012. 329-35 p.
243. Woloshin S, Schwartz LM, Moncur M, Gabriel S, Tosteson AN. Assessing values for health: numeracy matters. Medical decision making : an international journal of the Society for Medical Decision Making. 2001;21(5):382-90.
244. Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. Medical decision making : an international journal of the Society for Medical Decision Making. 2007;27(5):696-713.
245. Tunner JF, Day E, Crask MR. Protection motivation theory: An extension of fear appeals theory in communication. Journal of Business Research. 1989;19(4):267-76.
246. Berstad P, Loberg M, Larsen IK, Kalager M, Holme O, Botteri E, et al. Long-term lifestyle changes after colorectal cancer screening: randomised controlled trial. Gut. 2015;64(8):1268-76.
247. Holmen J, Holmen TL, Tverdal A, Holmen OL, Sund ER, Midthjell K. Blood pressure changes during 22-year of follow-up in large general population - the HUNT Study, Norway. BMC cardiovascular disorders. 2016;16:94.
248. Karelis AD, Brochu M, Rabasa-Lhoret R. Can we identify metabolically healthy but obese individuals (MHO)? Diabetes & metabolism. 2004;30(6):569-72.
249. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. Metabolic and body composition factors in subgroups of obesity: what do we know? The Journal of clinical endocrinology and metabolism. 2004;89(6):2569-75.
250. Vinknes KJ, Elshorbagy AK, Nurk E, Drevon CA, Gjesdal CG, Tell GS, et al. Plasma stearoyl-CoA desaturase indices: association with lifestyle, diet, and body composition. Obesity (Silver Spring, Md). 2013;21(3):E294-302.
251. van Dam RM, Willett WC. Unmet potential for cardiovascular disease prevention in the United States. Circulation. 2009;120(13):1171-3.
252. Yusuf S. Improving worldwide access to inexpensive and effective treatments for common cardiovascular diseases. European Heart Journal Supplements. 2018;20(suppl_C):C18-C22.

253. Anderson C. Health promotion in community pharmacy: the UK situation. Patient education and counseling. 2000;39(2-3):285-91.
254. The Norwegian Pharmacy Association. Pharmacies in Norway 2016 [cited 2016 05.09.]. Available from: https://www.apotek.no/fakta-og-ressurser/statistikk-for-2016/1--apotek/1-1-apotek-i-norge.
255. The Norwegian Pharmacy Association. Pharmacy costumers and reciepe expeditions 2016 [updated 2017; cited 2017 11.11]. Available from: https://www.apotek.no/fakta-og-ressurser/statistikk-for-2016/3--apotekkunden/3-1-apotekkunder-og-reseptekspedisjoner.
256. Den norske legeforeningen. Gjør kloke valg-kampanjen (Choosing Wisely) 2017 [cited 2018 23.3]. Available from: http://legeforeningen.no/Emner/Andre-emner/Tillitsvalgt/Fagmedisinske-foreninger/nyhetsbrev/Nyhetsbrev-mai-2017/Gjor-kloke-valg-kampanjen-Choosing-Wisely/.
257. Manigault KR, Lewis KA. Pharmacists role in cholesterol management: addressing challenges and barriers. Journal of pharmacy practice. 2015;28(1):35-43.
258. Horgan JM, Blenkinsopp A, McManus RJ. Evaluation of a cardiovascular disease opportunistic risk assessment pilot ('Heart MOT' service) in community pharmacies. Journal of public health. 2010;32(1):110-6.
259. Krska J, Morecroft C. Views of the general public on the role of pharmacy in public health. Journal of Pharmaceutical Health Services Research. 2010;1:33-8.
260. Cruz-Flores S, Rabinstein A, Biller J, Elkind MS, Griffith P, Gorelick PB, et al. Racial-ethnic disparities in stroke care: the American experience: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(7):2091-116.
261. Waaseth M, Nilsen T, Kjome L, Halvorsen K. Apotekkunder med diabetes: Egenmåling av blodglukose og behov for farmasøytisk rådgivning. Norsk Farmaceutisk Tidsskrift 2017;9.
262. Helsedirektoratet. Brukere og kontakter-fastlege [cited 2018 12.4]. Available from: https://statistikk.helsedirektoratet.no/bi/Dashboard/cd950f51-51ea-4422-af77-c0f1bff7baf5?e=false&vo=viewonly.

I

Pharmacies offer a potential high-yield and convenient arena for total cholesterol and CVD risk screening

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Abstract

Background: Moderately elevated blood total cholesterol (TC), blood glucose and blood pressure are rarely symptomatic and as such many individuals remain untreated.
We studied the yield of an in-pharmacy screening in terms of identifying undetected high TC and absence of prior measurements of TC, glucose and blood pressure.

Methods: A cross sectional TC screening study was conducted for one week in each of May 2012 and September 2014 in 148 and 149 Boots^{TM} Norge AS pharmacies in Norway.

Results: Participants (n=21090) with mean age 54.5±16.0 were included. Participant characteristics resembled the general population over a similar age range. 11% (n=2337) were unaware of their high TC ≥ 7.0 mmol/L, and an additional 8% were unaware of TC ≥ 6.2 mmol/L. The absolute yield of unknown high TC was highest at age 60-69 year; however, considering long exposure-time to high TC in the young, their small yield (<1%) is also important. Prior measurement of one risk factor was associated with prior measurement of the others. The probability of not having had measured glucose was large (~50%), independent of age.

Conclusions: Identification of treatable high TC in a non-medicated sample was substantial in absolute number, although only 11%-19% were unaware of their high levels. Except for glucose, the awareness and hence probability of having had the risk factors measured increased with age. Consequently, and since long exposures to high values are common and can be harmful, early screening for glucose and TC should be considered. Pharmacies are capable to perform this service.

Key words: Screening, pharmacy, cholesterol-yield, cardiovascular disease, cholesterol

Introduction

Cardiovascular disease (CVD) is a major contributor to death worldwide (1), affected by the atherosclerotic process that has already started in childhood (2). Thus, for risk factors such as high blood total cholesterol (TC), blood glucose or blood pressure, it is important both to reduce high levels and to maintain low values (2). However, moderately elevated levels of these risk factors are rarely symptomatic. Although early diagnosis of elevated levels can be accomplished through relatively inexpensive blood pressure measurement and testing of TC and glucose, many people remain untreated. The majority of individuals with familial hypercholesterolemia and over 50% of individuals with type 2 diabetes mellitus are undiagnosed (3, 4). World Health Organization (WHO) estimates that 80% of all CVDs can be prevented by appropriate lifestyle and diet and/or adequate drug treatment (5). However, without knowing one's risk factor levels, targeted decisions to lower risk are not possible (6). The lower thresholds being recommended in current guidelines for medical treatment of elevated risk factors in an aging world population, imply that even more people will need treatment in the years to come (7, 8). Existing health care services may not easily have the capacity to deal with the increasing number of medical visits (9). Thus, WHO calls for local, novel approaches to deliver health care services, such as convenient screening programs (10). Pharmacies have been suggested for a role in CVD prevention (11), as they now perform some services some of which had earlier been reserved for physicians (12). This includes, among many others, measurements of TC and other lipids, glucose and blood pressure, in addition to providing lifestyle advice and counseling on smoking cessation (13).

Using TC concentrations and questionnaire information obtained in an in-pharmacy screening study, our aim was to investigate yield in terms of detecting unknown high TC and characteristics and prevalence of those whose TC, glucose and blood pressure had not previously been measured. We had the following hypotheses:

I) Pharmacy screening attracts individuals with characteristics similar to the general population.

II) Pharmacy screening identifies people whose TC, glucose and blood pressure have not been measured before and where a substantial number get new and useful information on their TC level.

Methods

This cross sectional TC screening study is part of the "Vascular lifestyle-Intervention and Screening in phArmacies" (VISA) study. A complete and detailed description of the VISA study design is appended (Appendix 1). Briefly, the data analyzed in this paper arose from complementary TC measurements offered six days in both May 2012 and September 2014 in Boots™ Norge AS pharmacies. Pharmacies (148 pharmacies in 2012 and 149 in 2014) were distributed nationwide except for one county in Norway. The screening was planned and conducted by the University of Oslo in collaboration with the for-profit organizations Boots Norge AS, Mills AS, Grete Roede™, and a non-profit organization, the Norwegian Health Association. Participants became aware of the screening through national and local advertisements or by being advised of the possibility of measuring their TC during a visit to the pharmacy. Health care providers in pharmacies (pharmacist, technicians or nurses) who had completed a training program executed the study.

The initial step in the screening was to undergo point-of-care finger-prick TC measurements in a consultation room within each pharmacy. TC was measured using the Roche Diagnostics AS Accutrend Plus™ (available in all pharmacies) or the Alere AS Afinion™ AS100 (available in 50 pharmacies). Accutrend Plus captured TC concentrations of 3.88-7.76 mmol/L, and Afinion AS100 in the interval 2.59-12.95 mmol/L. Values that were outside the range of the device were assigned to the corresponding extreme value in the measurement range. All screenees were immediately provided with their TC value on completion of the

assay along with an interpretive brochure with diet and lifestyle advice for CVD prevention. For those with TC ≥ 7.76 mmol/L, a follow-up visit with a general practitioner (GP) was recommended.

Research study participation also depended on filling out an anonymous optically readable pre-coded questionnaire that was solicited when convenient during screening. (The translated questionnaires edition 2012 and 2014 are appended). This screening questionnaire was developed by the VISA-study investigators, however, wording of the questions were borrowed from several validated questionnaires and from Statistics Norway (www.ssb.no). As approved by the Norwegian Regional Ethical Committee, consent for research participation was assumed by filling out the questionnaire. For statistical analyses, we used the items that both editions of the questionnaire shared. These items were TC level, age, sex, educational attainment, height and weight (from which we computed body mass index (BMI) as kg/m^2), physical activity level, smoking status, prior measurement of TC, glucose and blood pressure and prior knowledge of TC, glucose and blood pressure level. Participants spent on average 15-20 minutes on TC measurement and the questionnaire (not counting waiting time).

Reporting of this paper follows the STROBE checklist for observational studies.

Data analysis

Descriptive statistics for the continuous variables were given as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. For comparison with the Norwegian population, the majority of data were obtained from either Statistics Norway (the agency which has responsibility for official statistics in Norway), or the longitudinal population health surveys: The North Trøndelag Health study (HUNT) and the Tromsø-study, considered representative for an adult Northern-European population (14, 15). We utilized two cut offs for high TC: ≥ 7.0 mmol/L and ≥ 6.2 mmol/L. TC concentrations of

≥ 7.0 mmol/L indicated a probable need for treatment,(16) while TC ≥ 6.2 mmol/L indicated that TC should be monitored because of the risk of developing higher TC (17). Missing values for smoking were assumed to indicate non-smoking, because the smoking question in the 2012 edition was constructed as if it should only be checked if smokers: “Do you smoke? About how many per day:” Similar, missing values indicated “not measured” for previously measured TC, glucose and blood pressure.

Statistical analysis included descriptive statistics, chi-square test, independent sample t-test and logistic regression. For logistic regression, estimated probabilities back transformed from their estimated logit and odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were presented. The difference between age- and sex adjusted models and more fully adjusted models was minor, and the fully adjusted models (categories of age, gender, BMI and education, smoking, physical inactivity and previous measures of the other two risk factors and TC categories for TC) were presented. All analyses were conducted using SAS version 9.4 for Windows. The significance level was set at ≤ 0.05.

Study sample

Research participants were required to be at least 18 years of age and not lactating or pregnant. Only people who were not taking lipid lowering medication were screened in 2014; consequently all those reported using lipid lowering medication in 2012 were excluded from these analyses. Those with multiple unrealistically high/low/missing values or had an unreadable questionnaire were also omitted, leading to a final inclusion of 21090 participants (Figure 1).

Results

Population characteristics

Table 1 shows background characteristics for the 21090 participants. The majority (68.9%) was women, and mean age was 54.5 years (±16.0). Overweight/obesity defined as BMI ≥ 27 kg/m^2 (following the convention of Statistics Norway), was more prevalent in men (37.4%, n=2356) than women (26.0%, n=3529). Compared to data for the general Norwegian population, the VISA study attracted older women and people who were slightly better educated, but smoking prevalence, BMI ≥ 27 kg/m^2 and inactivity were similar to national data (Table 1).

Prevalence of high TC defined as ≥ 7.0 mmol/L was observed in 0.9%, (n=18) of women and 1.4% (n=8) of men aged 18-29. As well as in 38.2% (n=779) and 30.1% (n=167) of women and men respectively, aged 60-69 years (Figure 2).

Yield of screening

Total cholesterol

Table 2 presents the yield of the screening for unknown high TC. In total, 11.4% (n=2337) learned that their TC level was high (≥ 7.0 mmol/L), while an additional 1.6% (n=335) had a reinforced message, given that they already knew their TC was high. With high TC defined as ≥ 6.2 mmol/L, 19.4% (N=3975) of the total sample learned about a high TC, while 7.3% (n=1501) already knew that their TC was high. Supplementary figure 3 shows the yield divided by age groups. Here, 0.24% (n=50) aged 18-29 years were made aware of an unknown elevated TC. The yield of detecting unknown high TC was however largest for 60-69 years old with 5.7% (n=1174) .

Blood glucose and blood pressure

Supplementary Figure 4 illustrates findings about prior measurement of glucose and blood pressure. Between 68.7% (n=378) of men aged 18-29 years and 46.7% (n=677) of men aged 60-69 years had not previously had their glucose measured. For women, the corresponding prevalence was between 51.5% (n=592), aged 18-29 years and 40.5% (n=1435), aged 60-69 years. It was common that blood pressure had previously been measured for both genders and in all age groups.

Likelihood of previous measurement

In total, 36.2% (n=7638) had measured all three risk factors before, while 6.6% (n=1401) had not measured any. Measuring one risk factor before was the strongest predictor of whether or not either of the others had been measured. If TC had not been measured before, there was an observed 53% probability (OR 2.61 (95% CI: 2.43-2.80)) that glucose neither had been measured, and a 64% probability (OR 3.00 (95% CI: 2.65-3.39)) that blood pressure had not

been measured before. Being young, inactive, having low education and being overweight/obese were all characteristics that were significantly associated with the odds of not having had TC measured before. Those whose measured TC ≤ 5.0 mmol/L (which was only known after the screening in the present study) had a two-fold increased odds of not having had TC measured before (OR 2.01 (95% CI: 1.80-2.32)) compared to those who measured TC ≥ 7.0 mmol/L. In contrast to TC and blood pressure, age was not a strong predictor for the probability of previous glucose measurement, but being male was. Furthermore, obese participants were 15% more likely than normal weight to have previously measured glucose (OR 0.55 (0.49-0.61) (supplementary Table 3, supplementary Table 4 and supplementary Table 5).

Discussion

In line with our objectives, we found that a complementary TC screening in Norwegian pharmacies was a popular offer that attracted individuals with similarities to the general Norwegian population except for an overrepresentation of older women. Furthermore, we demonstrated that the screening resulted in 11% of screenees being altered of a TC value that, according to national recommendations, needs immediate attention (18). According to our data, particular attention should be paid to measurements of TC and blood glucose.

In Norway, this is the most recent screening for CVD risk factors that includes individuals across urban and rural populations. Like any other study based on voluntary enrollment of participants, screening in pharmacies may be subject to selection bias. However, we showed that age, gender, and education biases may be similar as other conventional screenings (19-21), and highly comparable to another pharmacy-based screening program in Austria (13). Even with an overrepresentation of older women, smoking, physical activity habits, BMI and educational distribution seemed similar to the general Norwegian population. Young women

were especially similar to the general Norwegian population in terms of educational level (Supplementary Figure 5). Pharmacies and other retail-based clinics have longer opening hours and offer affordable drop-in appointments for health services (22). These features may attract young people and those with lower education who previously have reported "lack of time" and "inconvenient time for appointment" as barriers for participating in health surveys (23). We also note that pharmacies have a broad product assortment in addition to prescription medicines, and that the customers are accordingly not limited to medicated patients with a diagnosis (22). Hence, our results can be representative for a large proportion of the Norwegian population, with emphasize on, but not restricted to, women.

We replicated what is well established, (24) and recently confirmed in the Tromsø Study (25), that women's TC level peaks later than men. In Norway, the latest information on measured TC in multiple counties were reported more than ten years ago, and the present study report that TC remains the same (5.6 mmol/L) (26). Compared to county-specific studies with similar age (but more equal gender distribution), TC in the nationwide VISA study was higher than in HUNT 3 (15) according to the online HUNT database (5.4 mmol/L) and the seventh survey of the Tromsø Study (5.5 mmol/L) (25). Further, prevalence of high TC was highest in women and higher than other pharmacy screenings (27). Compared to health surveys in Sweden (1986-2009), we observed similar prevalence of TC $\geq$ 7.0 mmol/L for women, but slightly lower prevalence for men (28). A large proportion of the Norwegian population used lipid lowering medication in the study period (29). However, < 1% of adults < 30 years used statins (29). Thus, our results on TC level in a non-medicated population are more accurately representative in the young than in the older age groups. While data from five counties in Norway (2000-03) showed that 0.9% of men and 0.8% of women under 30 years had TC $\geq$ 8 mmol/L (26), we found that 0.9% of women and 1.4% of men in the same age group had TC $\geq$ 7 mmol/L.

Yield of identifying high TC should be discussed as to 1) whether useful and new knowledge of TC level was given and 2) whether information on a high TC led to CVD preventive actions with lifestyle and/or medication. We found that 11% received new information, and 2 % got repeated information about a TC level $\geq$ 7.0 mmol/L that should be treated (16). An additional 8% were informed about a previously unknown TC $\geq$ 6.2 mmol/L that should be monitored given the tendency for TC to increase with age, and the risks associated with long term exposure of high TC (2). Thus, the 0.3% young who were identified with a previously unknown TC of $\geq$ 6.2 mmol/L may be of special importance despite that the yield is low in absolute numbers. Attention to high risk in the young may also be of special importance in Norway given a reported recent increase in first myocardial infarction among people aged $\leq$ 45 years (30). Only physicians can diagnose and prescribe medication. Hence, yields of an in-pharmacy screening in a public health perspective also depend on ability to collaborate with physicians and other appropriate professionals.

According to our data, measurement of one risk factor was associated with measuring other risk factors. These findings call attention to the importance of initial screening for CVD risk factors. Emphasize should be put on glucose measurements because the probability (~50% as supported by others (13)) of not having had glucose measured before was high and not associated with age, in contrast to the other risk factors. Introducing nationwide examinations for CVD risk factors should also be considered in light of the recent observed unfavorable increase in TC levels in Finland (31) and in Sweden (32). Future studies should explore possible barriers for why finger-prick measurements of TC and glucose seems to be less frequent measures than blood pressure.

Limitations

First, we acknowledge that pharmacies are not research institutions. On the other hand, pharmacies seems highly accessible and successful in recruiting participants across geographical regions, age, sex and educational status. Questionnaire limitations include that it was not validated and it was self-administered and all variables except TC level were self-reported. There are several errors associated with self-reporting. However, self-report is quick and inexpensive and with few questions considered to be sensitive, this limitation may not be of great impact (33). Though, we found some peculiar finding that might indicate that the participants interpreted the question of previously measured TC incorrectly (for instance that subsequently measured low TC was associated with being less likely to have measured TC before). Although, our results were in line with similar studies. Another limitation was that we omitted all participants with an unreadable questionnaire and with unrealistic values of key variables. Also, different exclusion criteria in the two screening periods lead to later exclusion of potential participants. This could be corrected with re-contact of participants if the screening captured personal identity, as would be the case if the screening were linked to the participant's medical record. Exclusions were however executed to improve data quality and for comparison basis. Inconsistency in which time of the day and time of the year TC was measured, and inconsistency between measurement devices could have affected the level of the TC measurement.

Potential role of pharmacies

The present study demonstrates potential for pharmacies to complement the health care system by providing the important initial screening and advice for CVD risk factors, as also suggested by others (11). Such pharmacist-provided interventions are demonstrated to be successful in reducing risk of CVDs (12). This potential role of pharmacies should be

recognized in countries were the health care system already is stressed with long waiting times, and where an aging population will further stress the expansion of current health care systems (8). Results from a study in Canada, with similar universal health care system as Norway, found that adding pharmacists to primary care also was a cost effective strategy for reducing CVD risk (34). Expenses for marketing, staff and blood tests and the pharmacies' willingness to assess CVD risk factors must be considered and compared to potential yields, before recommending or implementing public screening for CVD risk factors in pharmacies any further.

Conclusion

We present a screening study for TC and CVD risk factors in pharmacies that seem convenient for a large heterogeneous proportion of the general population.

We found that prior measurement of glucose and TC were less common than for blood pressure. To increase the yield in terms of attracting those whose glucose and TC are more likely not to have been measured before, our results suggests that young, overweight/obese, inactive and lower educated should be targeted for TC screening, and all ages, low educated, and males for blood glucose screening. The yield of identifying high TC that may need treatment in a non-medicated sample was substantial in absolute numbers, even though only 11%- 19% were unaware of their high TC levels. It seems like point-of-care testing in pharmacies is convenient, attractive and found to be cost-effective, pharmacy-screening could be an asset to the health care system.

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Conflict of interests

MGB is, and LG was employed by Mills AS and KWG and LTMR were employees in Boots Norge AS at the time of the study initiation. Boots and Mills were involved in the design of the study but had no influence on the decision to submit the paper. KR, KS and VTH have received funding from Mills AS. KS has also received grant from Vita hjertego' (MILLS AS brand). DRJ is consultants for California Walnut Commission. KR has received honorariums for meeting in advisory boards and lectures for Amgen, Chiesi, Sanofi, Mills AS, MSD (Norway) and for participation in meetings for Norwegian Directorate of Health and the Norwegian Medical Association.

Key points:

- In-pharmacy screening was efficient and successful in recruiting > 20 000 that seemed representative for at least, but not limited to, a young, female Norwegian population

- In-pharmacy screening resulted in alerting 11-19% of total cholesterol concentrations that need attention
- The results emphasize the importance of initial screening for CVD risk factors and to tailor screening to target groups to achieve the highest yield
- Pharmacies in Norway may be a valuable arena to attract a low socioeconomic population

Author's contributions

KS KWG LTMR MGB LG VHTH and KR were responsible for the conceptual design of the study. DRJ KS ITR VHTH and KR were responsible for analyzing and interpreting data. DRJ, KS, VHTH and KR had the major responsible for the review of the study and input on revisions. All authors read and approved the final manuscript.

Reference list

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1459-544.
2. Brown MS, Goldstein JL. Biomedicine. Lowering LDL--not only how low, but how long? Science. 2006;311(5768):1721-3.
3. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. European heart journal. 2013;34(45):3478-90a.
4. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice. 2011;94(3):311-21.
5. World Health Organization. Global status report on noncommunicable diseases 2010: Description of the global burden of NCDs, their risk factors and determinants. Genevé; 2010.
6. Mooney LA, Franks AM. Impact of health screening and education on knowledge of coronary heart disease risk factors. Journal of American Pharmacy Association. 2011;51(6):713-8.
7. Nayor M, Vasan RS. Recent Update to the US Cholesterol Treatment Guidelines: A Comparison With International Guidelines. Circulation. 2016;133(18):1795-806.
8. World Health Organization. World report on ageing and health 2015 [Available from: http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1.

9. Claudi T, Midthjell K, Holmen J, Fougner K, Kruger O, Wiseth R. Cardiovascular disease and risk factors in persons with type 2 diabetes diagnosed in a large population screening: the Nord-Trondelag Diabetes Study, Norway. JInternMed. 2000;248(6):492-500.
10. World Health Organization. The World Health Report 2013: Research for Universal Health Coverage.; 2013.
11. Tsuyuki RT, Beahm NP, Okada H, Al Hamarneh YN. Pharmacists as accessible primary health care providers: Review of the evidence. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC. 2018;151(1):4-5.
12. Tsuyuki RT, Johnson JA, Teo KK, Simpson SH, Ackman ML, Biggs RS, et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). Archives of internal medicine. 2002;162(10):1149-55.
13. Rohla M, Haberfeld H, Sinzinger H, Kritz H, Tscharre M, Freynhofer MK, et al. Systematic screening for cardiovascular risk at pharmacies. Open heart. 2016;3(2):e000497.
14. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-7.
15. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-77.
16. Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom Oppfølging og mål for kontroll ved forebygging av hjerte- og karsykdom(2016).
17. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63(25 Pt B):2935-59.
18. Helsedirektoratet. Forebygging av hjerte- og karsykdom: Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom. Oslo: Helsedirektoratet; 2017.
19. The Tromsø Study. Tromsø 7-desciption of variables 2015-16 [Available from: http://tromsoundersokelsen.uit.no/tromso/.
20. Bjorngaard JH, Vie GA, Krokstad S, Janszky I, Romundstad PR, Vatten LJ. Cardiovascular mortality - Comparing risk factor associations within couples and in the total population - The HUNT Study. International journal of cardiology. 2017;232:127-33.
21. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: Collaborative research in the interface between clinical medicine and epidemiology: Study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scandinavian journal of public health. 2013;41(1):65-80.
22. Via-Sosa MA, Toro C, Trave P, March MA. Screening premorbid metabolic syndrome in community pharmacies: a cross-sectional descriptive study. BMC Public Health. 2014;14:487.
23. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC medical research methodology. 2012;12:143.
24. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. The new England journal of medicine. 2012;366(4):321-9.
25. Hopstock LA, Bonaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Lochen ML, et al. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromso Study 1979-2016. BMJ open. 2017;7(8):e015001.
26. Graff-Iversen S, Jenum AK, Grotvedt L, Bakken B, Selmer RM, Sogaard AJ. Risk factors for myocardial infarction, stroke and diabetes in Norway. Tidsskrift for Den norske legeforening. 2007;127(19):2537-41.
27. Peterson GM, Fitzmaurice KD, Kruup H, Jackson SL, Rasiah RL. Cardiovascular risk screening program in Australian community pharmacies. Pharmacy world & science : PWS. 2010;32(3):373-80.

28. Eriksson M, Holmgren L, Janlert U, Jansson JH, Lundblad D, Stegmayr B, et al. Large improvements in major cardiovascular risk factors in the population of northern Sweden: the MONICA study 1986-2009. Journal of internal medicine. 2011;269(2):219-31.
29. Sakshaug S, Strøm H, Berg C, Blix HS, Litleskare I, Granum T. Drug Consumption in Norway 2011–2015: Folkehelseinstituttet; 2016 [cited 2016 19.11.]. Available from: http://www.legemiddelforbruk.no/english/
30. Sulo G, Igland J, Nygard O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. European journal of preventive cardiology. 2013.
31. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. European journal of public health. 2015;25(3):539-46.
32. Ng N, Johnson O, Lindahl B, Norberg M. A reversal of decreasing trends in population cholesterol levels in Vasterbotten County, Sweden. Global health action. 2012;5.
33. Wright FL, Green J, Reeves G, Beral V, Cairns BJ. Validity over time of self-reported anthropometric variables during follow-up of a large cohort of UK women. BMC medical research methodology. 2015;15:81.
34. Simpson SH, Lier DA, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, et al. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: results from a randomized controlled trial. Diabetic medicine : a journal of the British Diabetic Association. 2015;32(7):899-906.
35. Statistics Norway. Dette er Norge 2014: Hva tallene forteller: Statistics Norway; 2014 [cited 2018 27.2]. Available from: https://www.ssb.no/befolkning/artikler-og-publikasjoner/_attachment/188232?_ts=1475e7ac938.
36. KommuneProfilen. Mean age 2014 Statistics Norway: Statistics Norway; 2014 [updated 11.1.2017. Available from: http://www.kommuneprofilen.no/Profil/Befolkning/DinRegion/bef_alder_region.aspx.
37. NTNU: Hunt research center. Available from: http://www.ntnu.no/c/document_library/get_file?uuid=65b9ce4f-c712-4cdd-a1b1-ff67a6df42c8&groupId=10304.
38. Statistics Norway. Helseforhold, levekårsundersøkelsen 2015 [Available from: https://www.ssb.no/helse/statistikker/helseforhold
39. Statistics Norway. Educational attainment of the population, 1 October 20142014 27.2.2018. Available from: http://ssb.no/utdanning/statistikker/utniv.
40. Smoking habits [Internet]. 2015 [cited 12.04.2017]. Available from: https://www.ssb.no/helse/statistikker/royk.

Table 1 Background characteristics of participants in the VISA study and the general Norwegian population.

	Norwegian population Mean±SD %	**Total, VISA N=21,090** Mean±SD % (n/N)	**Men, VISA N=6,516** Mean±SD % (n/N)	**Women, VISA N=14,285** Mean±SD % (n/N)	p-value[1]
Women, %	49.7[4]	68.9			
Age, years	39.4[5]	54.5±16.0	53.9±16.4	54.8±15.8	0.0004
TC, mmol/L	5.6[6]	5.5±1.1	5.4±1.0	5.7±1.1	<0.0001
BMI, kg/m	27.2[7]	25.4 ±4.0	26.3±3.6	25.0±4.1	<0.0001
Age ≤39 years, %	31.9[5*]	19.2 (3985/20706)	21.7 (1401/6445)	18.2 (2562/14066)	<0.0001
BMI≥27 kg/m, %	28.0[8]	29.6 (5953/20090)	37.4 (2356/6292)	26.0 (3529/13587)	<0.0001
Highest attained education level:					0.0333
Primary school, %	27.3[9]	15.6 (3149/20168)	15.5 (969/6252)	15.5 (2125/13671)	
High school, %	41.3[9]	41.3 (8325/20168)	40.0 (2499/6252)	41.8 (5720/13671)	
University/college 1-3 years, %	22.7[9]	25.0 (5034/20168)	26.2 (1639/6252)	24.5 (3351/13671)	

University college >3 years, %	8.7[9]	18.2 (3660/20168)	18.3 (1145/6252)	18.1 (2475/13671)	
Inactive[2], %	17 [7]	17.5 (3629/20727)	20.7 (1331/6421)	16.0 (2248/14056)	<0.0001
Smokers[3], %	21[10]	19.8 (4186/21090)	17.2 (1118/6516)	20.9 (2996/14285)	<0.0001

N= of all available data for analysis for total, men and women.

VISA, Vascular lifestyle-Intervention and Screening in phArmacies; TC, Total cholesterol; BMI, Body Mass Index.

-TC was measured in pharmacy; all other data were self-reported.

- 289 people with missing gender are included in the total column.

[1] Independent sample t-test or Pearson chi-square for sex difference.

[2] Exercise, ≤1 time/week.

[3] Every day and occasional smoking.

[4-10] References (data available that were considered as representative to the Norwegian population in terms of data source and time were utilized): **4:(35)**, **5:(36)** *16-39 years, **6:(25)**, 7:**(37)**, **8**:(38), **9**:(39), **10:(40)**.

468

469

Table 2 Description of yield for various subgroups with available total cholesterol (TC) measurements.

Screened and with available TC values **N= 20473**								
	TC previously measured						**TC not previously measured**	
n/N (%)	12095/20473 (59.1%)						8378/20473 (40.9%)	
	Recalled TC was high (≥7)		**Recalled TC was normal (<7)**		**Did not recall TC**			
n/N (%)	781/20473 (3.8%)		7941/20473 (38.8%)		3373/20473 (16.5%)			
	Measured TC ≥7	Measured TC <7	Measured TC≥7	Measured TC <7	Measured TC ≥7	Measured TC <7	Measured TC ≥7	Measured TC <7
n/N (%)	335/20473 (1.6%)	446/20473 (2.2%)	1142/20473 (5.6%)	6799/20473 (33.2%)	553/20473 (2.7%)	2820/20473 (13.8%)	642/20473 (3.1%)	7736/20473 (37.8%)
Comment on yield	**Useful** (better monitioring needed)	**Reassured**	**Useful**	Not useful	**Useful**	Not useful	**Useful**	Not useful

TC, total cholesterol, measured in mmol/L.

-Missing values are included in "TC not previously measured".

-For the purpose of yield, presentages are computed of the total available for analysis (n=20473).

470

471

Figure titles and legends:

Figure 1 Simplified flowchart of the study design and inclusion of participants in an in-pharmacy screening for total cholesterol.

Figure 2 Illustrating mean total cholesterol (mmol/L) and prevalence (%) of total cholesterol ≥7 mmol/L according to gender and age groups (N=20473).

Supplementary figure titles and legends:

Figure 3 Yield of screening presented as who (of the total population) got knew information about a measured total cholesterol of ≥6.2 mmol/L, according to age groups and compared to those who already knew that their TC was high (N= 20473).

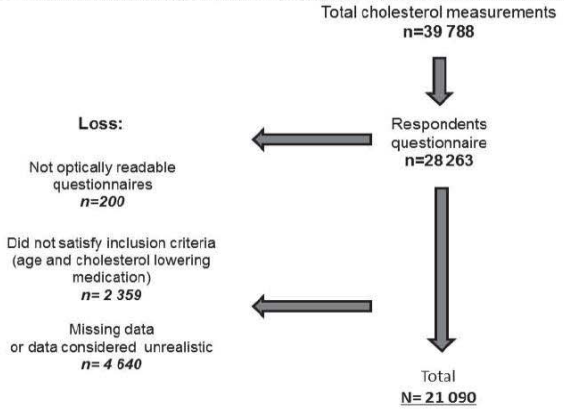
Figure 4 Prevalence of participants who reported no previously measured blood pressure (1) and glucose (2) compared to those who had measured it before, according to gender and age groups (N=21090).

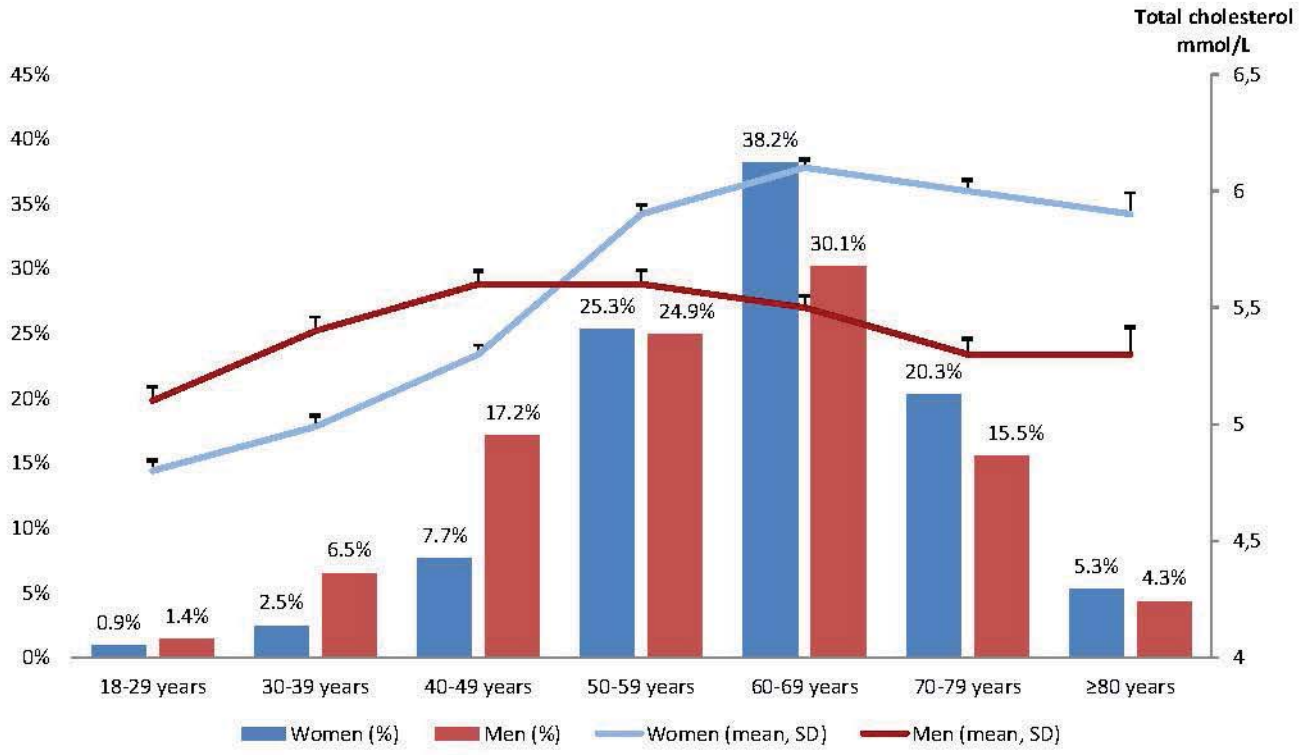
Figure 5 Prevalence of participants who have attained a higher educational level (college/university minimum 1 year) for the Norwegian population reported by statistics Norway (2012-14) and the present study (VISA) (2012-14) according to age and gender.

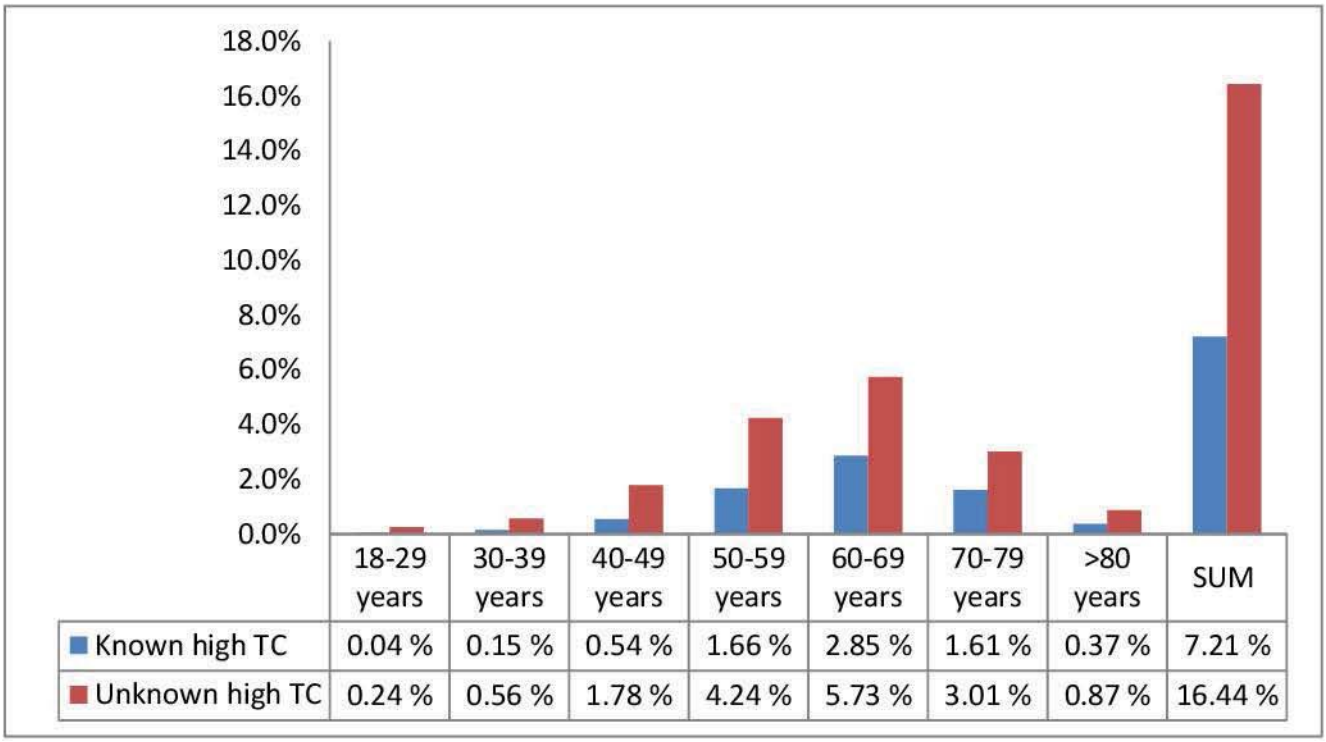
Supplementary files:

1. Appendix1_Complete description of the VISA study.pdf
2. Questionnaire 2012-pdf
3. Questionnaire 2014 –pdf

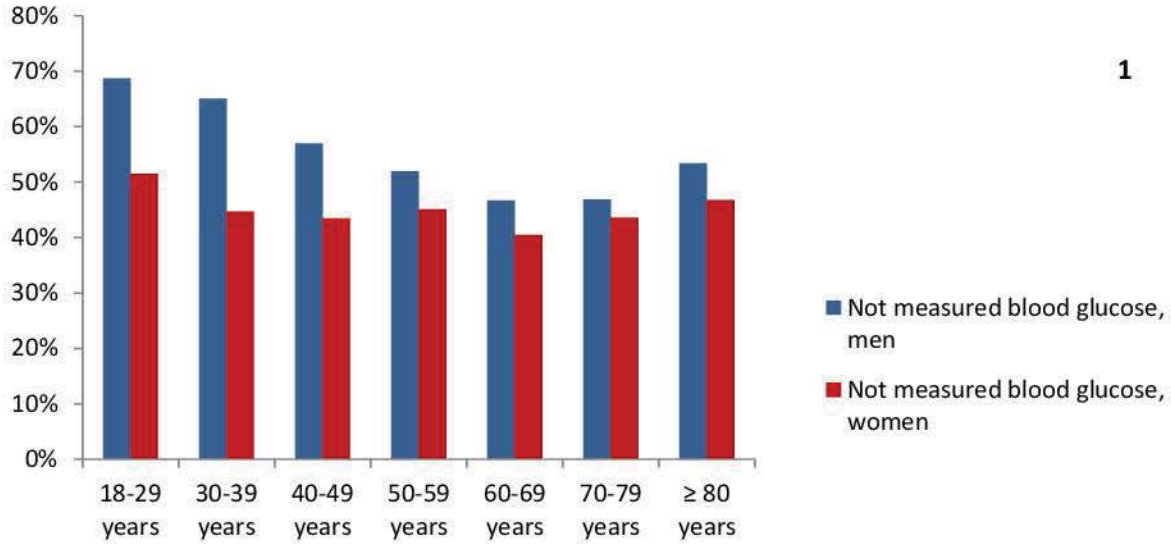
TC screening study



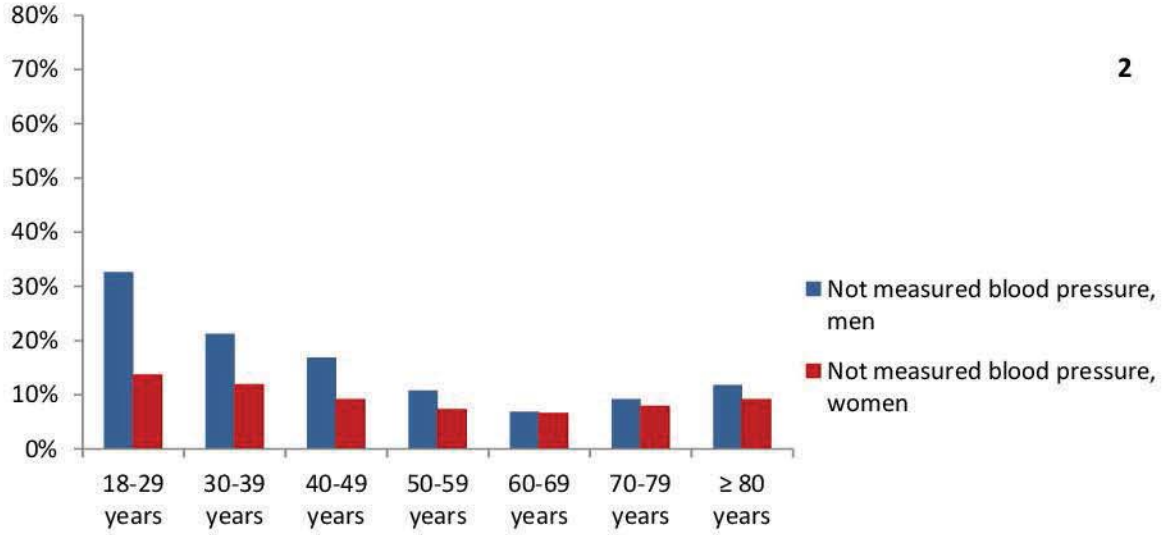

Total cholesterol mmol/L
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
6,5
6
5,5
5
4,5
4
0.9%
1.4%
2.5%
6.5%
7.7%
17.2%
25.3%
24.9%
38.2%
30.1%
20.3%
15.5%
5.3%
4.3%
18-29 years
30-39 years
40-49 years
50-59 years
60-69 years
70-79 years
≥80 years
Women (%)
Men (%)
Women (mean, SD)
Men (mean, SD)



	18-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	>80 years	SUM
Known high TC	0.04 %	0.15 %	0.54 %	1.66 %	2.85 %	1.61 %	0.37 %	7.21 %
Unknown high TC	0.24 %	0.56 %	1.78 %	4.24 %	5.73 %	3.01 %	0.87 %	16.44 %


80%
70%
60%
50%
40%
30%
20%
10%
0%
18-29 years
30-39 years
40-49 years
50-59 years
60-69 years
70-79 years
≥ 80 years
Not measured blood glucose, men
Not measured blood glucose, women

1


80%
70%
60%
50%
40%
30%
20%
10%
0%
18-29 years
30-39 years
40-49 years
50-59 years
60-69 years
70-79 years
≥ 80 years
Not measured blood pressure, men
Not measured blood pressure, women

2

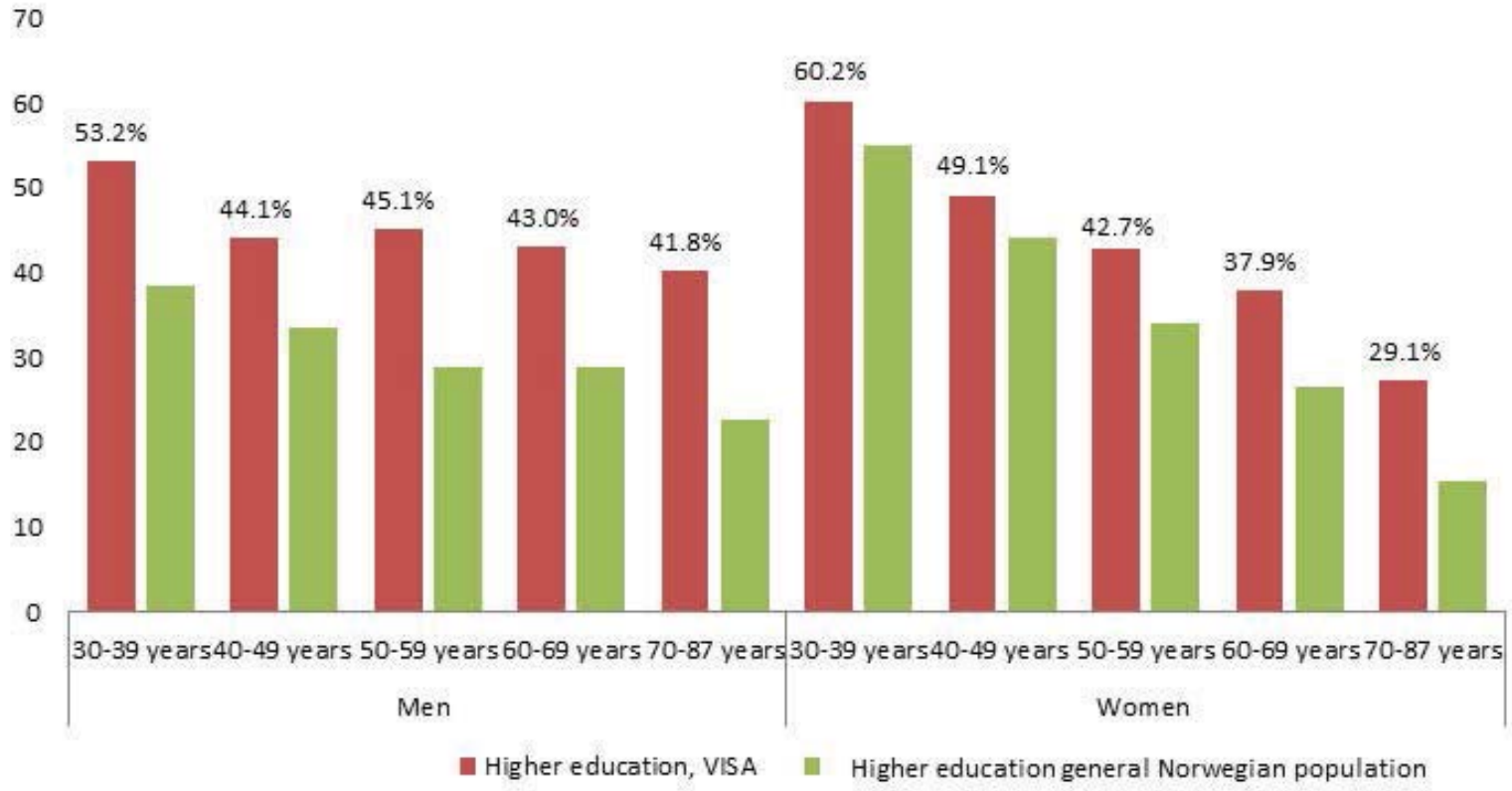

70
60
50
40
30
20
10
0
53.2%
44.1%
45.1%
43.0%
41.8%
60.2%
49.1%
42.7%
37.9%
29.1%
30-39 years
40-49 years
50-59 years
60-69 years
70-87 years
30-39 years
40-49 years
50-59 years
60-69 years
70-87 years
Men
Women
Higher education, VISA
Higher education general Norwegian population

Table 3 Probability (p) and odds ratio (OR) for difference between variables for not having had total cholesterol measured before (n=8611).

Variables	Prob. (p)	Odds ratio (OR)	95%CI OR	95%CI OR	P for any diff*
Smoking					0.0039
SMK, no	0.40	1			
SMK, yes	0.43	1.14	1.04	1.24	
Activity level					<0.0001
Active	0.39	1			
Inactive	0.45	1.26	1.15	1.37	
BMI-categories					<0.0001
Normalweight	0.38	1			
Obesity	0.44	1.28	1.14	1.42	
Overweight	0.42	1.16	1.08	1.26	
Underweight	0.34	0.85	0.63	1.14	
Education					0.0024
High school	0.40	1			
Primary school	0.43	1.16	1.04	1.28	
University/college 1-3 years	0.40	1.03	0.94	1.12	
University/college > 3 years	0.38	0.92	0.83	1.01	
Gender					0.0001
Male	0.38	1			
Female	0.41	0.41	1.16	1.07	
Agegroup					<0.0001
18-29 years	0.81	1			
30-39 years	0.67	0.48	0.41	0.57	
40-49 years	0.51	0.24	0.21	0.28	
50-59 years	0.35	0.13	0.11	0.15	
60-69 years	0.24	0.07	0.06	0.09	
70-79 years	0.23	0.07	0.06	0.08	
>80 years	0.26	0.08	0.07	0.10	
Blood glucose					<0.0001
Yes, measured	0.30	1			
Not measured	0.53	2.61	2.43	2.80	
Blood pressure					<0.0001
Yes, measured	0.38	1			

Not Measured	0.64	3.00	2.65	3.39	
Total cholesterol level					<0.0001
≥7.00	0.30	1			
6.01-7.00	0.36	1.30	1.14	1.48	
5.01-6.00	0.41	1.61	1.42	1.82	
≤5 mmol/L	0.46	2.05	1.80	2.32	

- BMI= Body Mass Index.
-Total cholesterol level was measured in pharmacy; all other data were self-reported.
*p-value for any difference (F7, large df.)
-Odds Ratio and probabilities are adjusted for all other variables in the model

Table 4 Probability (p) and odds ratio for not having had blood glucose measured before (n=9967).

Variables	Prob (p)	Odds ratio (OR)	95%CI OR	95%CI OR	P for any diff*
Smoking					0.6164
SMK, yes	0.47	1			
SMK, no	0.47	1.02	0.94	1.10	
Activity level					0.3364
Active	0.47	1			
Inactive	0.48	1.04	0.96	1.13	
BMI-categories					<0.001
Normalweight	0.51	1			
Obesity	0.36	0.55	0.49	0.61	
Overweight	0.46	0.82	0.77	0.88	
Underweight	0.48	0.89	0.69	1.15	
Education					0.1138
High school	0.47	1			
Primary school	0.49	1.06	0.96	1.16	
University/college 1-3 years	0.46	0.94	0.87	1.01	
University/college > 3 years	0.47	0.97	0.89	1.06	
Gender					0.0001
Male	0.54	1			
Female	0.44	0.66	0.62	0.71	
Agegroup					0.0021
18-29 years	0.45	1			
30-39 years	0.45	1.00	0.87	1.15	
40-49 years	0.45	1.03	0.90	1.17	
50-59 years	0.50	1.22	1.08	1.40	
60-69 years	0.47	1.12	0.98	1.27	
70-79 years	0.48	1.15	0.99	1.32	
>80 years	0.49	1.22	1.00	1.48	
Total cholesterol					<.0001
Yes, measured	0.37	1.00			
Not measured	0.61	2.59	2.42	2.77	
Blood pressure					<.0001
yes, measured	0.43	1.00			
Not Measured	0.77	4.46	3.93	5.06	

*p-value for any difference (F7, large df.)

- BMI= Body Mass Index- All data are self-reported.
- Odds Ratio and probabilities are adjusted for all other variables in the model

Table 5 Probability (p) and odds ratio for not having had blood pressure measured before (n=2260).

Variables	Prob (p)	Odds ratio (OR)	95%CI OR	95%CI OR	P for any diff*
Smoking					0.5407
SMK, yes	0.06	1			
SMK, no	0.06	0.96	0.84	1.09	
Activity level					0.5058
Active	0.06	1			
Inactive	0.07	1.05	0.92	1.19	
BMI-categories					0.0437
Normalweight	0.07	1			
Obesity	0.06	0.91	0.77	1.09	
Overweight	0.06	0.92	0.82	1.03	
Underweight	0.10	1.53	1.05	2.25	
Education					<.0001
High school	0.06	1.00			
Primary school	0.08	1.33	1.14	1.54	
University/college 1-3 years	0.06	0.90	0.79	1.02	
University/college > 3 years	0.06	0.88	0.76	1.02	
Gender					<.0001
Male	0.08	1			
Female	0.06	0.65	0.59	0.73	
Agegroup					<.0001
18-29 years	0.09	1			
30-39 years	0.07	0.74	0.61	0.89	
40-49 years	0.07	0.71	0.59	0.84	
50-59 years	0.06	0.57	0.48	0.69	
60-69 years	0.05	0.55	0.46	0.67	
70-79 years	0.06	0.65	0.53	0.81	
>80 years	0.07	0.70	0.52	0.94	
Total cholesterol					<.0001
Yes, measured	0.04	1.00			
Not measured	0.11	2.96	2.63	3.34	
Blood glucose					<.0001
Yes, measured	0.03	1.00			
Not Measured	0.13	4.43	3.90	5.02	

*p-value for any difference (F7, large df.)

- BMI= Body Mass Index
- All data are self-reported.

Odds Ratio and probabilities are adjusted for all other variables in the model

Complete Description of the VISA-Study design

"The Vascular lifestyle-Intervention and Screening in phArmacies" (VISA) study is a Norwegian pharmacy-based with the overall aim of studying the effect of screening for TC in pharmacies and to evaluate the effect of alerting individuals to elevated, asymptomatic cardiovascular risk factors (CVDs). We describe the VISA study in two parts: the total cholesterol (TC) screening study (**part 1**). The 8-week randomized controlled trial (RCT) that emanated from the TC screening study and resulted in follow-up visits including conducting a new intervention study (**part 2**).

The overall aim of part 1 is to contribute with new knowledge about participants in an in-pharmacy screening study for TC. The overall aim of part 2 was to study the short- and long-term effects of assessing CVD risk in pharmacies and alerting individuals to elevated CVD risk factors. Flowchart of research visits within part 1 and part 2 of the VISA-study is illustrated in **Figure 1**. Participant flow is further illustrated in **Figure 2**.

The VISA study has approval from the Norwegian Regional Ethical Committee (reference 2013/1660), and concession from the Norwegian Data Protection Authority to perform couplings to national health registries. The intervention study is registered in clinicaltrials.gov with identifier: NCT02223793.

Part 1a: TC screening study in 2012

A TC screening study was conducted for one week in May 2012 in 148 Boots™ Norge AS pharmacies (part of Walgreens Boots Alliance) in 18 (out of 19) counties in Norway.
The screening study was planned and conducted by the University of Oslo in collaboration with the for-profit organizations Boots Norge AS, Mills DA (food and brand warehouse), Grete Roede™ (weight loss program), and a non-profit organization, the Norwegian Health Association. The organizers joint aim was to make the public aware of the importance of knowing personal TC value as it is a major risk factor for CVD [1]. Participants became aware of the TC screening study through advertisements (newsletter, social media, local and national newspapers and radio commercials and outside boards) or by being advised of the possibility of screening at the time of a visit to the pharmacy. The study was executed by health care providers in pharmacies (pharmacist, technicians or nurses) who had completed a training program (a web-based educational module, procedure for each activity and self-training of TC measurements a minimum of five times).

The initial step of the screening was to undergo a point-of-care finger-prick TC measurement in a consultation room within each pharmacy. To measure TC, individuals were required to be at least 18 years of age and not lactating or pregnant. TC measurements were obtained using Roche Diagnostic's, Accutrend Plus™. Accutrend Plus could assess TC values between 3.88 mmol/L and 7.76 mmol/L. Measurements that were outside the range of the device were assigned to the extreme lowest or highest value in the measurement range. All screenees were immediately provided with their TC value, explained roughly in categories as followed

<5.0 = satisfactory, 5.0-6.5 = slightly elevated, 6.6-7.6= elevated, and ≥7.76 = severely elevated. The participants received a *"know your cholesterol card"* containing their TC result with general explanation of each of the four TC categories. They also received an interpretive brochure regarding recommended lifestyle and diet for CVD prevention. For those whose measured TC was ≥7.76 mmol/L, follow-up visit with general practitioner (GP) was recommended.

The research aspects of the TC screening study started with an anonymous optically readable pre-coded questionnaire. As approved by the Norwegian Regional Ethical Committee, consent for research participation was assumed by filling out the questionnaire. Research participation was solicited when convenient during screening. Thus, if there was a long queue for the measurement, individuals were asked if they would like to respond to a questionnaire during their wait; while if the queue was short, they were asked to participate after their TC measurement was complete. Occasionally, people were allowed to take the questionnaire home and return it the day after in person or by surface mail. The TC measurement and questionnaire took on average 15-20 minutes per participant, not counting waiting time.

Part 1b: TC screening study in 2014

In 2014, the TC screening study was once more conducted in Boots pharmacies. Overall, the TC screening study in 2012 and 2014 were similar but there were some differences:

1) The TC screening in 2014 was conducted in September.
2) 149 pharmacies were involved.
3) Use of cholesterol lowering medication was an additional exclusion criteria for participation.
4) The 2014 budget for advertisement was about 1/6 of the 2012 budget, consequently radio, newspaper notices/advertisements, and billboards were omitted.
5) In 50 of the 149 pharmacies TC was measured using Alere Afinion^{TM}AS100 that captured measurement levels in the interval 2.59-12.95 mmol/L in addition to Accutrend Plus^{TM}. This device is designed to enable quick and easy on-the-spot testing regardless of blood sample type [2].
6) Participants received a revised edition of the questionnaire used in 2012.
   The main differences were: re-phrasing of the questions on smoking habits and physical activity level, postal number was replaced with counties, questions on marital status, ethnicity and income were included and a question on grading of agreement on whether or not Norway should re-introduce health checks at the age of 40 years was deleted.

Part 2: Screening for the RCT (week 0, starting in 2014)

In 50 of the 149 pharmacies in 2014, individuals who expressed interest in measuring TC were rather invited to an extended screening including measures of multiple risk factors for CVD. The extended screening was simultaneous a screening for eligibility to participate in an 8-week RCT. If the offer was declined, individuals were instead offered the TC screening as described in 1b. Prior to the RCT, pharmacy staff underwent practical training and an electronically education module had to be completed prior to each research visit.

The aims of the intervention study (as stated to the participant after the RCT) were as follows:

- Studying the effect of alerting to measured CVD risk factors that were considered elevated: TC, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides, glycated hemoglobin (HbA1c) and blood pressure.
- To measure the impact of knowing the risk of CVD on different risk factors (TC, HDL-C, LDL-C, triglycerides, HbA1c, blood pressure, diet and lifestyle after 8 and 52 weeks and to perform coupling to central registry after 2 and 5 years.

The timing of the screening and invitation to participate in the intervention study is designated week 0. The next steps were as follows:

Information about the intervention study (where: waiting area)

Those who expressed interest in the extended screening for the intervention study received an informed consent to read and a questionnaire to complete while waiting. The questionnaire was similar to the screening questionnaire described in 1b, but with additional space to record date, assigned group number (criteria described later) and values of TC, HDL- C, LDL-C, triglycerides, HbA1c, blood pressure, weight, height and body mass index (BMI) for visit 1 (V1) and visit 2 (V2).

Informed consent (where: consultation room)

The initial step was to inform the potential participant about the study, after which informed consent was signed by both the participant and pharmacy staff, and one copy was provided to each. Personal information recorded included email address, telephone number, mailing address and the participant's unique 11-digits personal identification number.

Checking for eligibility to be screened

An electronic program made explicitly for the VISA study designed by LINK Medical Research™ Oslo (not otherwise included in the study) was used to: 1) check participants for eligibility to be screened for the intervention study and 2), if eligible to be screened, then also to allocate participants to one of five groups based on measured risk factor levels and 3), if eligible to participate in the intervention study, then additional randomize participants to groups.

Only persons who were not taking lipid lowering-, blood pressure lowering-, and anti-diabetic-medication and did not report a history of any CVD events, such as cardiac stenting, coronary artery by-pass operation, heart attack, stroke, heart catheterization, or chest

pain/angina pectoris, could be screened for the intervention study. Participants also had to understand and speak Norwegian.

If the participant was *not* eligible to be screened, then TC measurement was offered as described in 1b (if inclusion criteria for TC measurement was satisfied).

Screening for CVD risk factors/ checking eligibility for the intervention study

If eligible, the extended screening was performed in the following order:

1. **HbA1c and lipids**
   HbA1c and lipids were obtained first by finger-pricks, using two different cassettes (panels) in the device Alere Afinion™AS100. In one of the panels, TC, HDL-C and triglycerides (lipids) were measured and LDL-C was calculated using Friedewald's formula. Analysis of HbA1c took 3 minutes and lipids, 8 minutes. The error range of Afinion AS100 was ≤3 % for HbA1c and ≤5 % for lipids. This is considered acceptable by the European CE-standards. HbA1c was recorded with one decimal, lipids with two.

2. **Blood pressure**
   After measurements of HbA1c and lipids, two consecutive measurements of blood pressure were performed by A&D Medical blood pressure Monitor ™ Model UA-767Plus30. Blood pressure measurement was performed seated resting according to European recommendations **[3].** Average of the two last measurements was recorded without any decimals.

3. **Height and weight**
   Standing height was measured using a wall mounted height board with erect posture and feet against the baseboard and weight by using a digital scale [4]. Participants were weighed in light clothing without shoes. Height and weight were recorded with one decimal. BMI was calculated in the program from height and weight.

The screening results were recorded in the electronic program by LINK medical, and on the participant's questionnaire. Hour(s) since last meal defined in four categories was recorded, and the result could assist in clarification of possible elevated levels of triglycerides to the participant.

Calculation of ad hoc risk score and group allocation

Immediately after recording of the measurement levels in the electronic program, an ad hoc risk score was calculated. Scores ranging from 1-4 points according to criteria in **Table 1** were assigned for each of the measures values of HbA1c, TC, HDL-C, blood pressure (average of two measurements), BMI and age. Points were summarized to an ***ad hoc risk score*** and participants were assigned to 1 of 5 groups based on the following criteria and scores:

- **Group 1, 2 and 3 (high risk):** Total score of ≥ 4 points (intermediate between low and very high risk)
- **Group 4 (low risk) :** <4 points in total score

- **Group 5 (very high risk):** Independently of score, if one or more of the following were satisfied: HbA1c ⩾ 7.0%, TC ⩾ 12.00 mmol/L, Systolic blood pressure ⩾ 170mmHg, Diastolic blood pressure ⩾100mmHg

Group allocation and randomization Visit 1 (V1) (week 0)

Group allocations were only visible for pharmacy staff. Health care professional were given a detailed and illustrative description in the electronic program of what type of information that should be provided participants depending on their group allocation.

If the participant was assigned to **group 5**, one of the measured risk factors was severely elevated and the participant was recommended to visit their GP at their earliest convenience. Participants in this group received ***CVD lowering advice material*** that consisted of:
1) an interpreted brochure with lifestyle and diet information for CVD prevention (brochure)
2) a "know your risk factors" card to record measurement levels on one side with additional key information on specific risk-factor recommendations (e.g. reduce salt for lowering blood pressure) on the other side. Lastly, they were told that their participation in the intervention study was ended.

If assigned to **group 4,** the participant was informed about their measured risk factor levels and given the CVD lowering advice material with additional motivational statement to keep the levels low and favorable. They were also told that their participation in the intervention study was ended.

Those with an ad hoc risk score that was intermediate high (thus between low risk (group 4) and very high risk (group 5), were further randomized to groups in an interactive web based randomization system created within the electronic program to group **1, 2 or 3.**
The randomization process was as follows; With an estimated maximum number of 30 randomized participants per pharmacy, participants with the intermediate risk score were block-randomized using block size 9 and stratified by gender and pharmacy, to either group 1, 2 or 3. Simultaneous with the randomization, participants received a five-digit-identification (ID)-number, with the first two digits as the pharmacy number, and the next three digits as a unique number between 001 and 030. ID-numbers were assigned consequently in ascending order. Each ID-number was linked to a corresponding ID-envelope that included:

- CVD risk-lowering advice material (two "know your risk factors-cards" one for V1 and one for V2 and one interpret brochure for CVD prevention).
- Two four-page food frequency questionnaires (VISA-FFQ) titled "Questionnaire diet and physical activity" that was optically readable and pre-coded with participant's ID-number and visit-number (V1 and V2). The questionnaire was modified from the Henriksen *et al.[5]* designed to capture intake of major food groups the prior 8 weeks.

All participants were requested to complete- and return the VISA-FFQ before leaving the pharmacy.

Group 1: Participants assigned to group 1 were the Alert/advice group. In this group, participants were immediately alerted of their CVD risk communicated as risk factors compared to the general recommendations. The risk alert was followed with risk modifying advice including the motivational statement that they had 8 weeks to reduce highly modifiable elevated risk factors and that even small changes in each risk factor would have a huge impact on their risk of CVD. Participants in group 1 received all the CVD risk-lowering advice material to help in the process of lowering their elevated levels.

Group 2: Participants assigned to group 2 were the *Advice-only group* (intervention group). Participants in group 2 received the brochure from the CVD risk-lowering advice material but without telling them their measured risk values until after 8 weeks at V2 (thus did not receive the "know your risk factors-card").

Group 3: Participants assigned to group 3 were the *Control group or the un-intervened group.* Participants in this group received neither CVD risk-lowering advice material, nor received risk value information until after 8 weeks at V2.

Subsequently, participants in all three groups were given an appointment in the same pharmacy after 8 weeks and they were informed that they would be informed about their risk factor levels and possible change after 8 weeks when they returned to pharmacies.

After finishing the consultation with the participant, health care professionals combined the participants ID-number with personal information obtained from the informed consent into a coupling list. The participant's group number and ID-number were recorded to the participant's questionnaire that subsequently put back in the participant's ID-envelope. The ID-envelope with the reaming material not handed out at V1 was kept at the pharmacy for 8 weeks until V2.

The screening took on average 30-45 minutes per participant; consequently each pharmacy provided extra staffing for the intervention week.

Power calculation

Sample size calculation for the RCT was estimated assuming a 10% reduction in ad hoc risk score after 8 weeks in group 1 compared to group 3 following the convention of Laake et al.[6] With significance level set to 5% (two-sided) and power 80%, the sample size needed in each group was estimated to be 200.

Intermediate between V1 and visit 2 (V2)

Participants in group 1 and 2 (whose email addresses were readable) received in total four email alerts with written risk factors-specific material between V1 (the randomization visit) and V2 (after 8 weeks). Examples of advice were one letter focusing on the importance of physical activity and salt intake to reduce blood pressure level with concrete tips on how to reduce salt intake.

Approximately one week before the 8-week follow-up visit (V2) in pharmacies all participants received a reminder of their appointment date and time.

Part 2, Visit 2 (V2) (week 8)

Health care professionals that were performing V2 had to read and understand the procedure for V2 prior to the visit. V2 was conducted 8 weeks after V1 among those who completed part 1 in the same pharmacy. Following the same procedure as in V1 (for the Alert/advice group), TC, LDL-C, HDL-C, triglycerides, HbA1c, blood pressure, weight and BMI were measured/calculated by pharmacy staff (height was not measured again). VISA-FFQ (this time labeled "Visit 2" and found in the ID-envelope) was self-completed by participants. The measured values of the CVD risk factors were recorded on the screening questionnaire that was kept in pharmacies after V1. Participants in all three groups were informed immediately after the measurements about their CVD risk communicated as risk factors compared to the general recommendations. They also received the CVD risk-lowering advice material that was remaining in their ID-envelope to help in the process of reducing elevated levels.Lastly, participants were informed that the investigators of the study would contact them again after a year and invite them back to pharmacies for the third and last visit 3 (V3).

Between V2 and V3

There was no further contact with participants until approximately 49 weeks after V1. Appointment time at V2 and availability of each pharmacy formed the basis for appointment times for V3, 52 weeks after V1. Hence, appointment time for V3 was selected by the investigators without asking the participant about suitability of timing and place. Participants were informed about their appointment time and date by text message, email or by phone call approximately three weeks prior to the anticipated appointment.

A final reminder with date, time and place described as "the same pharmacy as you visited last year", was sent about one week before the scheduled appointment. If the participant was not able to attend the appointed time, or if the participant did not show up for V3, a new appointment within two weeks of their original appointment was attempted re-scheduled.

Part 2, visit 3 (V3) (week 52)

To perform V3, health care professionals in pharmacies had to familiarize themselves with the procedure for each activity for V3 in addition to self-training with the blood collection method called dried blood spots (DBS) provided by VITAS^{TM} Analytical Services. Pharmacy staff in 23 of the pharmacies were randomized to intervention-pharmacies at V3 and received an additional one-hour of in-person training on how to provide the intervention.
Of the 49 pharmacies from V2, 48 pharmacies were scheduled to perform V3, 52 weeks after V1 among those who completed V2. At V3, participants measured, for the last time, multiple CVD risk factors and completed the VISA-FFQ following the same procedure as V2.

Overall aims of the 52-week follow-up visit were to:

- Study the effect of communicating the concept of Heart Age and tailored risk factor messages to enhance risk reduction after four weeks.
- Study possible change in risk factors from V2 and possible initiation of medication.

- Evaluate intake of low fat, fat-reduced or whole fat milk and other dairy products, meat and meat products, egg consumption, use of cholesterol-lowering margarine and smoking habits assessed with the VISA-FFQ.

Randomization of pharmacies

At V3, pharmacy was the unit of randomization and 48 pharmacies were randomized into two arms. The randomization process was as follows: Pharmacies were first sorted by sample size (participant numbers in the earlier phases of the VISA-study (V2)), 1 record per line in Microsoft Excel 2010. Paired cluster randomization was used (pair the two biggest pharmacies and randomize one member of each pair to group 1 and the other to group 2), leading to 24 intervention and 24 control/ usual care pharmacies. The distribution of gender, age and geography was considered satisfactory. One of the intervention pharmacies had only one participant returning to V3, thus upon request from this pharmacy, their status was changed to control pharmacy, leading to a final distribution of 23 intervention pharmacies and 25 control pharmacies.

One arm, the 23 randomly selected intervention pharmacies, provided an innovative Heart Age messaging tool plus more individual, tailored information to enhance risk reduction. The latter consisted of one card with information on diet and lifestyle for lowering blood pressure, one on glucose/diabetes and one on cholesterol particles. Heart age is a risk calculator and communication tool developed by joint British Societies for the prevention of CVD, aiming to empower patients to make appropriate decisions about their lifestyle and drug treatment to better understand CVD risk [7]. In the intervention pharmacies, participant's age, and assessed values of BMI, TC, HDL-C, systolic blood pressure and smoking status were recorded in the online risk calculator and heart age was calculated for those between 30 and 70 years. Heart age was then compared to the individual's biological age, and there were more tools to visually show how one could decrease one's heart age if it was higher than his or her biological age. The 25 control pharmacies provided usual care, following the same procedures at V2.

All participants completed the VISA-FFQ. And an additional follow-up questionnaire that included questions regarding various health related issues the previous year (e.g. if they had seen a doctor, started using any medication etc.)

Dried blood spot tests

In line with the intervention provided at V3, pharmacies presented participants with the choice to provide an additional finger-prick blood sample on a dried blood spot (DBS) card. They could choose one or more of the following activities presented on a short-consent form;

a) If they were willing to give blood for an additional blood sample that day, by using DBS from which cholesterol, plasma fatty acid profile were eventually analyzed

b) If they are willing to bring the equipment home (DBS collection kit) and perform a DBS test at home after 4 weeks

c) If they were willing to complete the short FFQ labeled V4

There was one criterion for DBS measurement: No intake of fish and/or supplements rich in omega-3 fatty acids the previous 12 hours. DBS testing was performed by taking a small amount of blood collected from the fingertip and spot it onto five available spots on the DBS card, following the instruction provided at Vitas.no [8]. In the present study, it was required that two, out of five spots (~60µ) had to be completely filled with blood.
The participant's ID-number was attached as a barcode to the DBS card after the measurement. The DBS card was then air-dried, stored (until all participants within that week had completed V3), and then shipped in a special bag at room temperature to the VITAS-laboratory for analyses.

If participants consented to self-sample DBS at home four weeks later, the participants received a DBS collection kit along with instruction of how to perform the blood sample, in addition to an information letter containing information on criteria for DBS testing and tips for performance. Participants were also provided with the VISA-FFQ labeled V4 and were requested to complete it the same day as they completed the DBS (of course only if consent was given). Lastly, participants received a return envelope for the DBS and/or VISA-FFQ that were pre-addressed to the University of Oslo. DBS card and the short FFQ were both labeled with the participant's ID-number.

Part 2, visit 4 (V4) (week 56)

Participants who consented to self-sample DBS at home received a text message (preferable), or an email or phone call four weeks after V3 with information to take DBS the following day or at their first availability. Consequently, as reported in the text message, they should abstain from eating foods or take supplements rich in omega-3 fatty acids the same - and following days. It was also recommended to self-sample DBS after an overnight fasting. Participants returned the DBS card and/or the VISA-FFQ in the return envelope. At the University of Oslo, the test was immediately put in a fridge until delivered to VITAS , who subsequently stored the test in a -20 Celsius freezer until all test were gathered and ready to be analyzed.

From the DBS we analyzed cholesterol and plasma fatty acid profile. Omega-3 index, a marker of low intake of omega-3 that may have a possible association to CVD risk perception [9] was also measured, and the result was sent to the participants after the study was ended.

Change in cholesterol and fatty acids between V3 and V4 measured by DBS and VISA-FFQ will be used to study:

- If the intervention including Heart age and tailored CVD risk lowering advice was more effective than usual care
- To evaluate the VISA-FFQ on a group level
- Association between fatty acid profile, CVD risk factors and diet

Part 2, link to central registry

No coupling to Central Health registers death registry, patient registry or Norwegian Prescription Database was performed after 2 years (2016). It might be performed after 5 years (year 2019) as approved by The Norwegian Data Protection Authority.

The aim of the central registry coupling is to follow-up participants in the intervention study to assess the long-term effects of intervening on participants with elevated risk of CVD. We will study:

- The effect of detecting elevated CVD risk on medication use and incidence of CVD morbidity and mortality after 2 and 5 years will be compared to a random gender- and age-matching control group.

Funding
The VISA-study was supported by the University of Oslo, Mills AS, Boots Norge AS and from various grants for UNIFOR. Funding from Mills was used for optical reading of questionnaires. Mills and Boots contributed financially to advertisement of the screening. Boots pharmacies contributed with expenses related to staff, advertisement and all equipment needed for the TC tests.

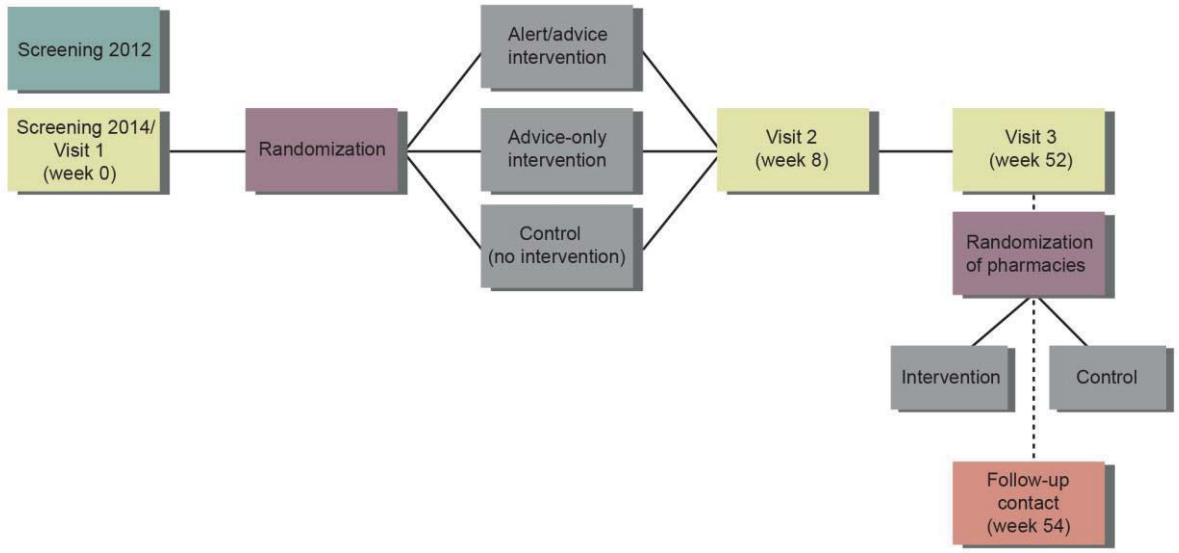


Figure 1. The complete study design of the VISA-study.

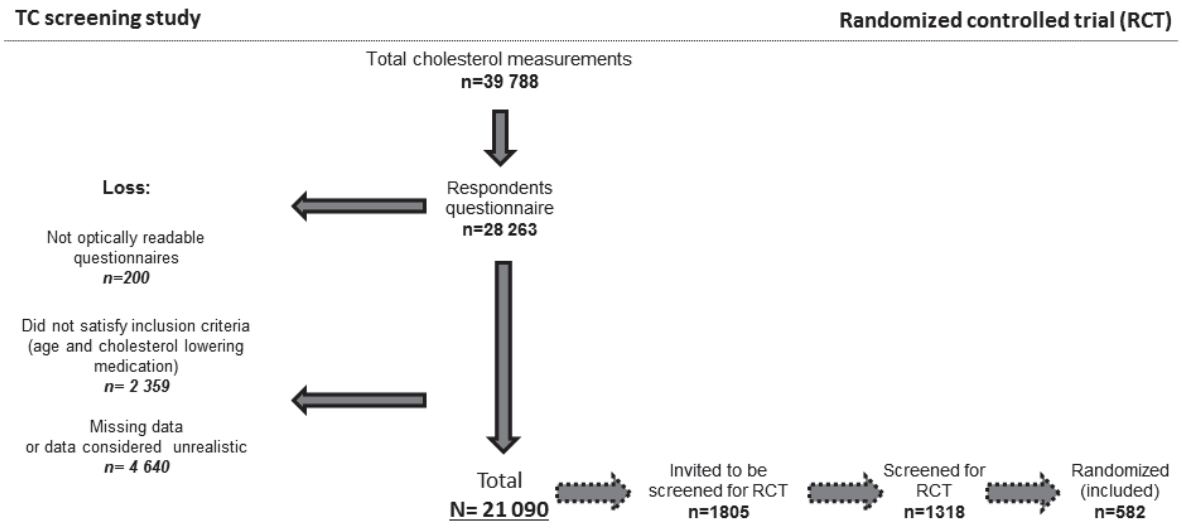


Figure 2. Description of participants in a cholesterol (chol.) screening and inclusion to intervention study (V1 and V2).

Table 1. Individual scores for each risk factor used to calculate ad hoc risk score.

	Score			
	0	**1**	**2**	**4**
Systolic and diastolic blood pressure[1]	< 131 sys and/or < 86 DIA mmHg	SYS BP ≥ 131 and/or DIA ≥ 86 mmHg	SYS BP ≥140 and/or DIA ≥90 mmHg	SYS BP ≥ 160 and/or DIA ≥ 100 mmHg
Total cholesterol	< 5 mmol/L	≥ 5.00 mmol/L	≥ 6.00 mmol/L	≥ 7.00 mmol/L
HDL-cholesterol[2]	> 1.0 mmol/L	< 1.0 mmol/L		
HbA1c	< 5.6 %	≥ 5.6 %	≥ 5.8 %	≥ 6.4 %
Body mass index	< 30 kg/m2	> 30 kg/m2		
Age	> 50 years	< 50 years	≤ 40 years	

HDL, high density lipoprotein. HbA1c, hemoglobin A1c. BMI, Body mass index.

[1]Mean of two measurements was recorded. Only the highest value of Systolic and diastolic blood pressure was included in risk score calculation.

[2] If HDL was not calculated (triglycerides were>7.34 mmol/L), score 0 was assigned HDL.

Table 2. Key principle investigators, the VISA study.

Primary and co-investigators/organizations	**Affiliation and position**
Kjetil Retterstøl (Prinsipal Investigator and supervisor PhD candidate)	Professor, M.D., PhD University of Oslo, Department of Nutrition
Karianne Svendsen (PhD Candidate)	Master in Nutrition, PhD Candidate in Nutrition, Department of Nutrition, University of Oslo
Vibeke H. Telle-Hansen (Supervisor PhD candidate)	Associate Professor, PhD, Faculty of Health, Oslo and Akershus University College of Applied Sciences
David R. Jacobs Jr. (Supervisor PhD candidate)	Professor, PhD, Epidemiology & Community Health, University of Minnesota
Marte Gjeitung Byfuglien	Clinical nutritionist, Nutrition Manager, Mills DA
Kjersti Wilhelmsen Garstad (Major collaborator)	Master in Pharmacy, Professional Services Manager, Boots Norge AS Manager Professional Service Boots Norge AS
Lisa, Lisa T. Mørch-Reiersen (Major collaborator)	Master in Pharmacy, Training Manager, Boots Norge AS
Ida Tonning Røyseth (Master student)	Master in Public Nutrition
Beate Østengen (Master student)	Master in Public Nutrition
Tove Caroline Nordstrand Rusvik (Master student)	Master in Clinical Nutrition
Maren Hoff	Quality adviser, Boots Norge AS
Kari Thyholt	Previous Mills DA employee
Linda Granlund	Previous Mills DA employee
Ivar Sønby Kristiansen	Professor at the Department of Management and Health Economic, University of Oslo
John Bjarne Hansen	Professor in hematology, Department of Clinical Medicine, University of Tromsø
Norwegian Health Association	Organization included
Grete Roede™	Organization included

References:

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C *et al*: **2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)**. *Atherosclerosis* 2016, **252**:207-274.
2. Jain A, Rao N, Sharifi M, Bhatt N, Patel P, Nirmal D, Persaud JW, Nair DR: **Evaluation of the point of care Afinion AS100 analyser in a community setting**. *Annals of clinical biochemistry* 2016.
3. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A *et al*: **2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)**. *Eur Heart J* 2013, **34**(28):2159-2219.
4. National Health and Nutrition Examination Survey: **ANTHROPOMETRY PROCEDURES MANUAL** In.; 2004: 65.
5. Henriksen HB, Carlsen MH, Paur I, Berntsen S, Bøhn SK, Skjetne AJ, Kværner AS, Henriksen C, Andersen LF, Smeland S *et al*: **Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients**. *Food and nutrition Research* 2018, **62**(1306):1306.
6. Laake P, Hjartåker A, Thelle DS, Veierød MB: **Epidemiologiske og kliniske forskningsmetoder**, 1. edn. Oslo: Gyldendal akademisk; 2007.
7. **Risk calculator** [http://www.jbs3risk.com/pages/risk_calculator.htm]
8. **Vitas Bioindex Dried Blood spot sampling video English HD** [https://www.youtube.com/watch?v=qFwV24p-fNQ]
9. Harris WS, Von Schacky C: **The Omega-3 Index: a new risk factor for death from coronary heart disease?** *Preventive medicine* 2004, **39**(1):212-220.

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Questionnaire (2012-edition)

Please complete this anonymous questionnaire prior to the cholesterol measurement. Information provided will be used in statistical analysis in the project "Cholesterol level in different groups of the Norwegian population"

1. **Have you previously measured your total cholesterol?**

   Yes: No:

2. **If yes, was your value:** (*Check the correct response):*

   Under 5: 5-6: 6-7: 7-8: Above 8:
   Do not remember: Were not told:

3. **In your experience, was this:**

   Normal: Slightly elevated: Elevated: Severely elevated:
   Were not told: Never measured: Do not remember:

4. **Have you previously measured your blood pressure?**

   Yes: No:

5. **If yes, was your value:**

   Low: Normal: Slightly elevated: Severely elevated:
   Were not told: Do not remember Never measured:

6. **Have you previously measured your blood sugar?**

   Yes: No:

7. **If yes, was the value:** (*Check the correct response:*

   Low: Normal: Slightly elevated: Severely elevated:
   Were not told: Do not remember Never measured:

8. **Are you currently taking any of the medications mentioned below** (Check all that apply):

   Blood pressure lowering: Cholesterol lowering:
   For diabetes: Blood thinners:

9. **What alternative fits best with your physical activity habits:**
   None: 1 hour/week: 1-3 hours/week: 3-6 hours/week:
   More than 6 hours/week:

10. **Do you smoke? about how many per day:**

11. **Have you smoked before? When did you quit?** (month, year)

12. **Have you ever experienced these diseases?** *(Check all that apply):*

Stenting in the heart: By-pass operation: Heart Attack:
Stroke: Heart catheterization Chest pain /angina pectoris:

13. **Education level** (*Check the correct response):*

Primary school: High school: University/college 1-3 years:
University/college 4 years or more:

14. **Your height:**
    Your weight:

15. **To what extent do you agree or disagree with the following statement:**
    "I think a simple health checkup should be offered so that everyone over 40 years of age can measure their risk factors for cardiovascular disease" (*Check most suitable response):*

Strongly agree: Agree: do not know: Slightly disagree: Disagree:

16. **Age:**

17. **Postal number:**

18. **Are you** (*Check the correct response):*
    Male: Female:

19. **Date:**

20. **Your total cholesterol today was:**

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Questionnaire (2014-edition)

Please check the most suitable response. Please provide only one response per. question unless otherwise stated. The questionnaire will take 3-5 minutes to complete

1. **Check:** Male: Female:
2. **Age:**
3. **Which county do you live in:**

Oppland: Hedmark: Akershus: Oslo: Østfold: Buskerud: Rogaland: Vestfold: Telemark: Aust Agder: Vest Agder: Hordaland: Sogn og Fjordane: Møre og Romsdal: Sør-Trøndelag: Nord- Trøndelag: Nordland: Troms: Finnmark:

4. **Which country/ continent were your parents born in?** (*Check all that apply):*

Norway:
Nordic countries except Norway:
Western-Europe:
EU-countries in East-Europe:
East-Europe or Russia:
Africa:
Asia and Turkey:
South/Middle-America:
North America and Oceania:

5. **Height:**

6. **Weight:**

7. **Have you previously measured your cholesterol?**

Yes: No: Do not know/do not remember:

8. **Where did you measure your cholesterol?** *(Check all that apply):*

Pharmacy: Physician: Occupational health: Hospital: Elsewhere:

9. **Were you told that your *last* cholesterol measurement was:**

Under 5: 5-6: 6-7: 7-8: Above 8:
Do not remember: Were not told:

10. **Have you previously measured your blood pressure?**

Yes: No: Do not know:

11. Were you told that your *last* blood pressure measurement was:

Low: Normal: Slightly elevated: Elevated:
Do not remember: Were not told:

12. Have you previously measured your <u>blood sugar</u>?

Yes: No: Do not know:

13. Were you told that your *last* blood sugar measurement was:

Low: Normal: Slightly elevated: Elevated:
Do not remember: Were not told:

14. What is your highest attained education level?

Primary school:
High school :
University/college 1-3 years:
University/college 4 years or more:

15. On average, how often do you engage in activity lasting a minimum of 30 minutes, so that you at least a little out of breath or sweaty? *(Brisk walk, running, skiing, cycling, swimming etc.)*

Never: Less than 1 time per week:
1-2 times per week: 3-4 times per week: 5 times or more per week:

16. What was the total income for household last year?
(Include income from occupation, social assistance and similar. Check the correct response):

Below 150 000 NOK: 151 000 – 300 000 NOK:
301 000 – 450 000 NOK: 451 000 – 600 000 NOK:
601 000 – 750 000 NOK: 751 000 – 900 000 NOK:
over 900 000 NOK: Refuse to respond:

17. Do you smoke:

No, I have never smoked: Yes, daily:
No, I quit smoking: Yes, sometimes (party, vacation, irregularly):

18. What is your marital status:

Married/registered partner:
Significant other:
Not married/no significant other:
Widow / widower/divorced :

19. Have any of your relatives experienced heart attack/angina/chest pain or stroke at a young age?

(Young is below 55 years for men and below 65 years for women.Check all categories that apply):
Yes, mother/father/siblings: Yes, uncle/aunt/grandparents: No:
Do not know:

20. Have you ever experienced these diseases/treatments? *(Check all that apply):*

No, none: Stenting in the heart: By-pass operation: Heart Attack:
Stroke: Heart catheterization Chest pain /angina pectoris:

21. Are you currently taking any of the medications mentioned below: (*Check all that apply):*

No, none: Yes, blood pressure lowering: Yes, cholesterol lowering:
Yes, for diabetes: Yes, blood thinners:

Your total cholesterol level today *(recorded by health care providers):*

		,			**mmol/L**

ERRATA

- Cor = correction

Page	Line	Original text	Type of correction*	Corrected to
3	50	"…screening in terms of identifying undetected high TC.."	Cor	"..screening for undetected high TC…"
10	210	"…were 15% more likely…"	Cor	"…were more likely…"
10	217	"..11% of screenees being altered..."	Cor	"..11% of screenees being alerted.."
14	309	"We present a screening…"	Cor	"We present a pharmacy-based screening…"

II

A randomized controlled trial in Norwegian pharmacies on effects of risk alert and advice in people with elevated cardiovascular risk

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Abstract

We investigated if alerting subjects to elevated total cholesterol (TC), blood pressure (BP) and hemoglobin A1c (HbA1c) (cardiovascular disease (CVD) risk factors that are usually asymptomatic) and if providing advice, would result in reduced risk. We conducted a multicenter (50 pharmacies) parallel three-arm 8-week randomized controlled trial (RCT) with 52 weeks follow-up visit. During six days, screening for TC, HDL- and LDL-cholesterol, triglycerides, HbA1c, BP and body mass index (BMI) were assessed in 1318 individuals. Of these, 582 with a measured and predefined elevated ad hoc CVD risk score were randomized to either Alert/advice (n=198) (immediately alerted of their screening result and received healthy lifestyle-advice), Advice-only (n=185) (received only advice) or Control (n=199) (no advice, not alert). Changes in risk score and self-reported health-related behaviors (diet, alcohol, physical activity) were assessed in pharmacies after 8 weeks. N=543 (93%) completed the RCT. Although the primary analysis showed no significant difference between groups, it seems as if the Control group had the largest reduction in risk score of 14%. The total (uncontrolled) sample reduced risk score 3.2% beyond estimated regression towards the mean and improved their health-related behaviors. Among the 65% (n=377) who returned 52 weeks after baseline, 14% reported started using CVD preventive medication after the screening. The study demonstrated that while assessing risk factors and behaviors in pharmacies proved efficient and possibly led to a small risk decrease, altering people to their screening result did not seem to be more effective than a self-directed approach. ClinicalTrials.gov identifier: NCT02223793.

Highlights:

- Pharmacy-screening reduced CVD risk score more than regression towards the mean
- A self-directed approach could be risk reducing in a pharmacy-based setting
- Recruiting and retaining subjects proved efficient in a pharmacy-RCT
- Pharmacies are accessible sources to health care and can identify high risk of CVD

Figure legends:

Figure 1. Study design of an 8-week randomized controlled trial with 52-week follow-up in Norwegian pharmacies.

Figure 2. Overview of the baseline procedure for each of the intervention and control groups in a pharmacy-based randomized controlled trial.

Figure 3. CONSORT (2010) flow chart of participants in a pharmacy-based randomized controlled trial.

Introduction

Important risk factors for cardiovascular diseases (CVD) are high LDL-cholesterol (LDL-C), blood pressure, body mass index (BMI) and blood glucose and/or type 2 diabetes (T2D).[1] All of these risk factors are modifiable through health-related behavior changes in diet, physical activity and smoking cessation.[2, 3] Even small changes in dietary factors affecting the CVD risk factors are associated with clinically meaningful reductions in CVD events.[2, 4] High levels of cholesterol, blood glucose and blood pressure are however usually asymptomatic, which can be exemplified by the estimation that over 50% of individuals with T2D are undiagnosed.[5] Without knowing one's risk factor levels, targeted decisions on how to lower risk are not probable.[6]

Randomized controlled trials (RCT) have demonstrated that intensive diet and lifestyle interventions can reduce risk factors of T2D and CVD both in primary- [7-9] and secondary prevention.[10] A common feature of such intervention studies is structured counseling by dietitians and physicians, usually in health care clinics, [9] research clinics or in hospitals.[11] However, specialized clinics suffer from high costs and limited capacity. Alternatively, intervention strategies involving community health workers and pharmacists are still developing.[12] We have previously demonstrated the potential of pharmacies as a source to identify individuals who are unaware of their high total cholesterol (TC) concentration.[13] Conversely, we do not know the effects of alerting individuals to their elevated CVD risk factors. The concept is, however, not new. Waldron *et al* stated that people's awareness of their own risk could encourage them to take actions that reduce that risk, especially if risk was high.[14] Our overall aim was to study if alerting subjects to their elevated symptom-free CVD risk factors and providing simple advice could lead to changes in CVD risk score, risk factors and health-related behaviors (composite foods, physical activity, smoking and alcohol) when performed in pharmacies. The a priori primary hypothesis was that CVD risk factor alert and/or health-related behavior would lead to changes in CVD risk score over an 8 weeks period compared with a control group that received neither alert nor advice.

Methods

Study design

This study was a parallel three-group 8-week RCT implemented within the Vascular lifestyle-Intervention and Screening in pharmacies (VISA) study.[13] Pharmacy staff screened volunteers for eligibility during September 8-13, 2014 in 50 pharmacies (Boots Norge AS) in Norway. The protocol included biochemical and anthropometric measures and questionnaires that resulted in calculation of an ad hoc CVD risk score (CVD risk score). The CVD risk score was used as inclusion criteria for randomization to either one of two interventions or the Control group (Table 1). Changes in the CVD risk score, risk factors and health-related behaviors were measured and compared after 8 weeks (end of intervention) and after 52 weeks (follow-up) (Figure 1). All participants provided verbal and written informed consent. The study received ethical approval from the Norwegian Regional Ethical Committee Health South –East (reference number 2013/1660). The study was conducted in accordance with The Helsinki Declaration. National Institutes of Health, ClinicalTrials.gov identifier: NCT02223793. Reporting of the present paper is aligned with CONSORT standards.[15]

Biochemical and anthropometric measures

The protocol included biochemical and anthropometric screening of; lipids (TC, HDL-C, LDL-C, triglycerides), hemoglobin A1c (HbA1c), blood pressure, height, and weight performed by pharmacy staff (pharmacists, technicians or nurses) in a private room within each pharmacy. The initial step was finger-prick measurements of lipids and HbA1c both by using the measurement device Alere Afinion^{TM}AS100. The device calculated LDL-C using Friedewald's formula. At triglycerides >4.52 mmol/L, LDL-C was not calculated, and at triglycerides >7.34 mmol/L, HDL-C could not be measured. After waiting for about five minutes, two consecutive measurements of blood pressure were performed seated by A&D Medical blood pressure Monitor^{TM} Model UA-767Plus30. Average of the measurements was recorded. Standing height was measured using a wall mounted height board with erect posture and feet against the baseboard. Participants were weighed on a digital scale without shoes and in light clothing[16]. To ensure that the protocol was similar in all pharmacies, standardized operating procedures were prepared for each study visit. At baseline, a common procedure was prepared for each of the groups (Figure 2). Pharmacy staff completed practical training and an online e-learning course prior to each research visit.

Eligibility criteria screening

Volunteers could only attend the screening if they fulfilled the inclusion criteria: Age ≥18 years, not pregnant/lactating and not taking lipid lowering-, blood pressure lowering-, or anti-diabetic-medication. Furthermore, no history of CVDs, T2D or type 1 diabetes mellitus was allowed. Participants also had to understand Norwegian.

Randomization (baseline)

Screening-results were recorded in an electronic program created by programmers in LINK medical Research AS Oslo, Norway (not otherwise involved in the study). The program calculated a predefined CVD risk score that was used to assign participants to the RCT.
The CVD risk score was a summarization of scores ranging from zero (favorable measures) to four (very unfavorable measures),[17] assigned for each of HbA1c, blood pressure, TC, HDL-C, BMI and age following the convention of Table 1. Age was included because presence of elevated CVD risk factors are more alarming in younger age.[1] A CVD risk score of ≥4 was inclusion criteria for the RCT as it was intended to resemble moderately elevated risk of CVD.[2] The exceptions were if HbA1c ≥7.0%, TC ≥12.00 mmol/L, systolic blood pressure ≥170mmHg and/or diastolic blood pressure ≥100mmHg; these participants were given advice and excluded from further study participation. Participants were randomized using block size 9, stratified by sex and pharmacy to: Alert/advice, Advice-only or Control, in the ratio 1:1:1.

Alert/advice intervention group

Participants in the Alert/advice group received advice on health-related behaviors to reduce CVD risk verbally and in the form of an intervention brochure. To circumvent that individuals may struggled to understand numeric risk factors,[18] participants were altered to their CVD risk factors using the "know your risk factors- card" (supplementary Figure A.1).
Here, level of each risk factor was categorized into predefined color-zones according to general recommendations; [17] green (favorable), yellow (slightly unfavorable) and orange (unfavorable) and red (clearly unfavorable). Pharmacy staff were requested to give advice on risk factors corresponding to ≥ yellow color-zone. The VISA-study investigators developed the intervention material.

Advice-only intervention group

At baseline, the Advice-only group received the intervention brochure, of which pharmacy staff addressed advice on health-related behaviors, but no risk alert. They were told their result would be available at the 8-week visit.

Control group

The Control group received neither risk alert nor intervention brochure at baseline, but were told that their result would be available at the 8-week visit.

8-week visit (end of intervention)

The 8-week visit included an in-pharmacy screening for the CVD risk factors and alerting participants to their screening result (same as Alert/Advice at baseline) and possible changes from baseline. Those in the Control group also received the intervention brochure. Participants were informed that they would be invited back for a follow-up visit, 52 weeks after baseline.

52-week follow-up visit

Prior to the 52-week follow-up visit, participants who had completed the RCT were given an appointment at the same place, weekday and time as at the 8-week visit if possible. The procedure for the 52-week follow-up visit was similar to the 8-week visit.

Questionnaires

The protocol included three questionnaires: screening questionnaire, food frequency questionnaire (VISA-FFQ) and a follow-up questionnaire.

Screening questionnaire

Prior to the screening, participants filled out a screening questionnaire (developed by the VISA-study investigators) which had been pretested and described previously.[13] Data obtained from the questionnaire included age, sex, highest attained educational level, smoking status and prevalence of CVD in first-degree relatives.

VISA-FFQ

Participants self-reported their health-related behaviors through the validated four-page 62-item VISA-FFQ, at all visits.[19, 20] The FFQ covers habitual dietary intake (grams per day) of foods eaten the last 1-2 months, including both frequency and amount of food item. For the purpose of this paper, foods were combined into composite food groups. For example, SFA dairy consisted of whole/high fat milk, milk products and cheese. VISA-FFQ also assesses number of cigarettes /day and length of moderate intensity- and vigorous intensity- physical activity.[21]

Follow up- questionnaire

At the 52-week follow-up visit, a four-page follow-up questionnaire developed by the VISA-study investigators was completed by participants. The questionnaire was intended to tell how participants perceived the screening result and to study one-year effects of the RCT. For the purpose of this paper, we used data from the question (translated): "To the best of your recollection, did you experience during the examination last year that; TC, HbA1c and/or blood pressure were higher than expected, lower than expected, as expected or do not know/do not remember". Moreover, we used self-reported information on physician-control for measures of TC, blood glucose and blood pressure and medication initiation the previous year.

Outcomes

Primary outcome was change in CVD risk score from baseline to the 8-week visit between intervention and control groups. Secondary outcomes were change in CVD risk factors and health-related behaviors between baseline, 8- and 52-week visits both between- and within groups. Other secondary outcomes included observing the uncontrolled trends for the total sample in CVD risk score from baseline to the 8-week visit, to describe how the screening result was perceived at baseline, and to assess the frequency of physician control and medication use reported at the 52-week visit.

Statistics

Continuous variables are presented with mean and standard deviation (SD) and with mean difference and 95 percentage confidence intervals (95% CI) when approximately normally distributed. Median and quartiles (Q) are given for non-normally distributed data, while categorical variables are described by frequencies (n/N) and percentages. Statistical description and analyses of data are performed using SAS software version 9.4 for Windows if not otherwise specified. Significance level was set to 5% (two-sided).

The primary outcome, change in CVD risk score between groups, was assessed using linear regression (LR) of which 2 degrees of freedom F-test was the primary analysis. Only complete cases were included. We ran unadjusted and analyses adjusted for age and sex, and included pharmacy as random effect in a linear mixed model. As a secondary approach, we used multiple imputations to test the sensitivity for missing observations (the 39 participants who did not return at the 8-week visit).[22] Findings were very similar to complete case analysis and are therefore not presented. Secondary outcomes (change in CVD risk factors) were

analyzed using unadjusted and age and sex adjusted LR between baseline and 8-week visit and between 8- and 52-week visits adjusted for baseline. Secondary outcomes (health-related behaviors) were analyzed by Wilcoxon Signed rank test for repeated measures within groups and Kruskal Wallis test of differences between groups.

Other secondary outcomes were analyzed for the total (uncontrolled) sample. Due to the study's high cut-off inclusion criteria and repeated measurements, effects of regression towards the mean (RTM) was estimated and accounted for in the total change in CVD risk score.[23] RTM was calculated using the fixed cut-point censoring (CVD risk score ≥4 points), following the method proposed by Hannan and colleagues.[23] RTM with 95% CI was calculated based on 10000 bootstrap samples using the statistical software R.

Power calculation

Sample size was estimated assuming a 10% 8-week reduction in CVD risk score in the Alert/advice group compared with the Control group following the convention of Laake *et al.* [24] With significance level 5% (two-sided) and power 80%, the estimated sample size needed in each group was ~200. We assumed ≤ 10% drop out rate in each group, and were aiming to recruit 220 participants in each group.

Study participants

As shown in Figure 3, 1318 consented were screened for CVD risk factors. Of them, one participant withdrew consent, 656 (49.8%) were excluded due to CVD risk score ≤ 4, and 79 (6.0%) were excluded due to systolic blood pressure ≥170mmHg (n=35) and/or diastolic blood pressure ≥ 100mmHg (n=57), HbA1c ≥ 7.0% (N=5), TC ≥12.00 mmol/L (n=1).

In total 582 (44.2%) satisfied the inclusion criteria for the RCT and were randomized as follows; 198 in Alert/advice group, 185 in Advice-only group and 199 in the Control group. After 8 weeks, 543 (93.3%) participants from 48 pharmacies completed the RCT by returning to pharmacies to the 8-week visit (Figure 3). 52 weeks after baseline, 377 (65%) participated in the 52-week follow-up visit.

Results

Baseline characteristics

We included 582 individuals of whom 28% (n=165) were men and 72% (n=417) were women with mean age 56.5 years ±14.6. There were no significant differences between groups in any baseline characteristics (Table 2).

Primary outcome

In primary unadjusted analysis, we found that the 8-week RCT was not significant related to changes in CVD risk score reduction between groups (F-value = 2.78, p=0.06). Adjustment for age and sex did not substantial alter the result. In secondary unadjusted analysis we observed that the Control group reduced CVD risk score by 14.1% (-0.76 (95% CI: -1.02 to -0.50)) compared to 6.7% reduction in the Alert/advice group (primary intervention) (-0.36 (95% CI: -0.62 to -0.09)), p=0.03. Findings for the less intense intervention group (Alert-only) were close to those for the control group, with 13.7% risk score reduction (-0.71 (95% CI: -0.99 to -0.44) (versus control p= 0.8, versus Alert/advice p=0.06).
This pattern of findings persisted even when the 48 level pharmacy variable was added as a random effect (Table 3).

Secondary outcomes

We observed significant but small 8-week reductions within one or more groups for HbA1c, TC, LDL-C, systolic- and diastolic blood pressure, but no significant differences between groups (Table 3). These within- group changes were accompanied by changes in health-related behaviors. Alert/advice and Advice-only groups both significantly reduced their intake of foods high in sugar (soda, sweets etc.) (p=0.01 and 0.003, respectively), and non-significantly increased their intake of whole grains. Contradictorily, fruit and vegetable intake decreased significantly for Advice-only group and the Control group (Table 4). Beneficial, but minor changes within groups for CVD risk factors and health-related behaviors persisted after 52 weeks, except for increased BMI in the Alert/advice group (as opposed to reductions in the Control and Advice-only groups) (Supplementary Tables A.1 and A.2). The sample at the 52-week follow-up visit (n=377) had similar baseline- age, BMI, CVD risk score, TC level, and share of male participants, low educated and smokers as the baseline sample (n=582).

Other secondary outcomes

The total (uncontrolled) sample reduced 8-week CVD risk score -11.5 % (-0.61 (95% CI: -0.76 to -0.45) from 5.3±1.4 at baseline. After correction for expected RTM of -0.44 (95% CI: - 0.38 to -0.50) using the calculation of Hannan *et al.*[23], the remaining CVD risk score reduction was -3.2% (-0.17 (95% CI: - 0.01 to -0.33)). CVD risk score change was highest correlated with change in TC calculated with Pearson correlation coefficient r=0.6 ($p<0.01$).

Of the 363 participants that completed the 52-week follow-up questionnaire, 50% (n=188), 83% (n=309) and 78% (n=289) reported that measured TC, blood glucose and blood pressure at baseline, respectively were in accordance with their expectation. There was no significant trend between change in CVD risk score and categories of expectations towards the measured value. On private initiative 31.4% (n=114), 14.3% (n=52) and 39.1% (n=142) had controlled their TC, blood glucose or blood pressure respectively after the 8-week visit. Only acetylsalicylic/other anticoagulants were allowed to use at baseline. 52 weeks after baseline, use of preventive medicine had increased to 14.1% (n=53). Statins and acetylsalicylic/other anticoagulants were both used by 4.5% (n=18), anti-hypertensive medication was used by 3.2% (n=12) and 2.3% used anti-diabetic medication (N=5).

Discussion

The formal analysis of the RCT found no significant difference in the primary a priori outcome variable, namely CVD risk score change. Nevertheless, we observed reduced CVD risk score in all participants combined, beyond what would have been expected with RTM. Separate important outcomes of the pharmacy-based screening were identification of 79 subjects with either severe hypertension (blood pressure ≥ 170/100 mmHg), T2D (HbA1c >7.0 %) or severe hypercholesterolemia (TC > 12 mmol/L) who were referred to treatment, and that CVD risk lowering medication was initiated in 53 subjects.

In an attempt to reconcile the two interpretations of findings within the RCT, we performed a series of secondary analyses. These provided suggestive evidence of a finding opposite to the a priori hypothesis: That the Control group that received neither risk alert nor advice had the highest amount of risk reduction in the RCT after 8 weeks. The Control group's change in CVD risk score was similar for those in the Alert-only group. Hence, the Alert/advice group appeared to have had the least risk reduction, as opposed to what have been suggested by others.[14] This finding of difference in CVD risk score between groups is consistent with self-reported non-significant greater increase in physical activity level for the Control and Advice-

only groups than in the Alert/advice group. However, it does not correspond to dietary changes between groups; those appeared to be similar across groups. Furthermore, overall considerable increase in physical activity level and reductions in intake of SFA dairy and sugar suggest compliance with the intervention material emphasizing more exercise, eat healthy fats and less sugar. Hence, we keep the conclusion that a completely self-directed effort is superior to risk alert followed by advice, tentative, given that the formal analysis of the RCT did not find a clear difference in response among the interventions and control. Moreover, several others have observed that a brief intervention- interaction may not be sufficient to affect health behaviors.[25] [14]

We observed health enhancing behavior changes and favorable changes in the CVD risk factors for the total sample after both 8 and 52 weeks. Consequently, we observed a reduced CVD risk score and found that the reduction was beyond what would be expected due to RTM. These findings of risk reduction after a pharmacy-based screening is comparable to a systematic review of RCTs of pharmacists care.[26] The initial screening for the RCT resulted in 6% being referred to physician before randomization due to very high risk factor levels. Fifty-two weeks after baseline, 14% were using CVD preventive medicines. These results are likely to be benefits of the pharmacy-based screening, revealing possible underdiagnoses, as supported by a similar study in Austria.[27]

Strengths and limitations

Strengths of the study include a loss to follow-up rate of only 7% after 8 weeks with similar losses across randomized groups. At the 52-week follow-up visit, ~35% were lost to follow-up, which affects the representativeness of these results. However, we did not strive to get participants who did not complete the RCT to attend the follow-up visit due to restricted resources. Nevertheless, the sample was similar to the baseline-sample. This study has several limitations. We did not use a validated score as the primary outcome and inclusion criteria. Mostly because relevant risk score calculators such as NORRISK[28] and the atherosclerotic CVD (ASCVD) algorithm[29] could not be used in persons younger than 40 years. Bearing in mind the nature of atherosclerosis with initiation early in life and a slowly progression toward disease[30], we were particularly interested in including youngsters.

There were 48 pharmacies/study centers, an unequal number of participants within each pharmacy (although the randomization would ensure that the groups are equally represented across pharmacies), and three repeated observations for each individual. Thus, we

acknowledge that despite efforts to standardize the training, there might be variations in compliance to the procedures. Participants were included from all across Norway. This contributes to variations in sample characteristics, but on the other hand increases the external generalizability of results.[31] Another limitation was that the intervention intensity was low.[7] It was however an aim of the VISA-study that the protocol should be feasible and easily translated into the daily pharmacy-practice. Measuring CVD risk factors is one of many preventive services provided by pharmacies today.[32] Detecting and evaluating new ways to deliver health-related services such as CVD risk screening is necessary to deal with an aging world population,[33] and to make health care convenient and accessible. Therefore, pharmacy's role as a health care provider needs to be further studied, which may be particular advantageous in rural areas and areas with low population density, where physicians and centralized hospitals are less easily accessible for all.[34]

Conclusion

We performed a RCT to test whether alerting and advising participants to their risk status with a minimalistic intervention strategy could help to mitigate risk. We found that participants did not seem to make differential changes in relation to the level of advice or risk factor alerting that they received. There appears to have been a risk score response to the screening, given that the overall risk status of the screening participants in all groups was improved after both 8 and 52 weeks. Furthermore, participants listed several specific health-related behavior changes that they made. We also demonstrated with this study that pharmacies were efficient in finding, and referring high risk individuals to proper treatment, and in recruiting and retaining participants.

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Authors contributions

LTMR, KWG, KS, VTH, KR, DRJ, KT and LG contributed to the conceptual design and implementation of the VISA-study. LTMR and KWG were responsible for management of pharmacy staff and their executing of the study. DRJ KS VTH JMG HBH and KR contributed to analyzing and interpretation of data. KS KR VTH DRJ had the responsibility for the final review of the study and input on revisions. All authors read and approved the final manuscript.

Declaration of conflicting interests

VTH, KT, LG were employees in Mills AS, and KWG and LTMR were employees in Boots Norge AS, at time of study initiation.

Conflicts of interest

KS, VTH and KR have received research grants from Mills AS. KS has also received grant from Visa hjertego' (MILLS AS brand). DRJ is consultants for California Walnut Commission. KR has received honoraria for meeting in advisory boards and lectures for Amgen, Chiesi, Sanofi, Mills DA, MSD (Norway) and for participation in meetings for Norwegian Directorate of Health and the Norwegian Medical Association.

References

1. Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* 2017 2017/03/23. DOI: 10.1016/s0140-6736(17)30752-3.
2. World Health Organization. *Global status report on noncommunicable diseases 2010: Description of the global burden of NCDs, their risk factors and determinants*. 2010. Genevé.
3. Global Burden of Disease Mortality Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459-1544. 2016/10/14. DOI: 10.1016/s0140-6736(16)31012-1.
4. Law MR, Wald NJ and Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994; 308: 367-372. DOI: 10.1136/bmj.308.6925.367.
5. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes research and clinical practice* 2011; 94: 311-321. 2011/11/15. DOI: 10.1016/j.diabres.2011.10.029.
6. Mooney LA and Franks AM. Impact of health screening and education on knowledge of coronary heart disease risk factors. *Journal of American Pharmacy Association* 2011; 51: 713-718. DOI: 10.1331/JAPhA.2011.10127.
7. Hoskin MA, Bray GA, Hattaway K, et al. Prevention of Diabetes Through the Lifestyle Intervention: Lessons Learned from the Diabetes Prevention Program and Outcomes Study and its Translation to Practice. *Current nutrition reports* 2014; 3: 364-378. 2014/11/11. DOI: 10.1007/s13668-014-0094-2.
8. Hjermann I, Velve Byre K, Holme I, et al. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *Lancet* 1981; 2: 1303-1310. 1981/12/12.
9. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *New England Journal of Medicine* 2013; 368: 1279-1290. 2013/02/26. DOI: 10.1056/NEJMoa1200303.
10. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes care* 2007; 30: 1374-1383. 2007/03/17. DOI: 10.2337/dc07-0048.
11. Sialvera TE, Papadopoulou A, Efstathiou SP, et al. Structured advice provided by a dietitian increases adherence of consumers to diet and lifestyle changes and lowers blood low-density lipoprotein (LDL)-cholesterol: the Increasing Adherence of Consumers to Diet & Lifestyle Changes to Lower (LDL) Cholesterol (ACT) randomised controlled trial. *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association* 2017 2017/09/12. DOI: 10.1111/jhn.12508.
12. Jeet G, Thakur JS, Prinja S, et al. Community health workers for non-communicable diseases prevention and control in developing countries: Evidence and implications. *PLoS ONE* 2017; 12: e0180640. 2017/07/14. DOI: 10.1371/journal.pone.0180640.
13. Svendsen K, Jacobs Jr. DR, Røyseth IT, et al. Pharmacies offer a potential high-yield and convenient arena for total cholesterol and CVD risk screening *Unpublished results (submitted to BMC public health)* 2017.
14. Waldron CA, van der Weijden T, Ludt S, et al. What are effective strategies to communicate cardiovascular risk information to patients? A systematic review. *Patient education and counseling* 2011; 82: 169-181. 2010/05/18. DOI: 10.1016/j.pec.2010.04.014.
15. CONSORT. Consort checklist http://www.consort-statement.org/consort-statement/checklist (2010).
16. National Health and Nutrition Examination Survey. Anthropometry procedures manual (2004, accessed 25.1 2018).

17. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207-274. 2016/09/25. DOI: 10.1016/j.atherosclerosis.2016.05.037.
18. Rothman RL, Montori VM, Cherrington A, et al. Perspective: the role of numeracy in health care. *Journal of health communication* 2008; 13: 583-595. 2008/08/30. DOI: 10.1080/10810730802281791.
19. Henriksen HB, Carlsen MH, Paur I, et al. Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients [Manuscript submitted for publication]. *Food and nutrition Research (Accepted)* 2017.
20. Svendsen K, Henriksen HB, Østengen B, et al. Evaluation of Items in a short Food Frequency Questionnaire to assess Cardiovascular Disease-related Diet and Lifestyle factors. *Unpublished results (submitted to Food and Nutrition Research)* 2017.
21. Henriksen HB, et al. Validation of two short questionnaires assessing physical activity in colorectal cancer patients. *BMC Sports Science, Medicine and Rehabilitation (Accepted)* 2017
22. IDRE Statistical Consulting Group. Missing data techniques with SAS https://stats.idre.ucla.edu/wp-content/uploads/2016/09/Missing-Data-Techniques_UCLA_Stata.pdf (2016).
23. Hannan PJ, Jacobs DR, Jr., McGovern P, et al. Estimating the effect of regression toward the mean under stochastic censoring. *American journal of epidemiology* 1994; 139: 422-431. 1994/02/15.
24. Laake P, Hjartåker A, Thelle DS, et al. *Epidemiologiske og kliniske forskningsmetoder*. 1. ed. Oslo: Gyldendal akademisk, 2007, p.551.
25. Helitzer DL, Lanoue M, Wilson B, et al. A randomized controlled trial of communication training with primary care providers to improve patient-centeredness and health risk communication. *Patient education and counseling* 2011; 82: 21-29. 2010/03/12. DOI: 10.1016/j.pec.2010.01.021.
26. Santschi V, Chiolero A, Burnand B, et al. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Archives of internal medicine* 2011; 171: 1441-1453. 2011/09/14. DOI: 10.1001/archinternmed.2011.399.
27. Rohla M, Haberfeld H, Sinzinger H, et al. Systematic screening for cardiovascular risk at pharmacies. *Open heart* 2016; 3: e000497. 2016/10/16. DOI: 10.1136/openhrt-2016-000497.
28. Selmer R, Igland J, Ariansen I, et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. *European journal of preventive cardiology* 2017; 24: 773-782. 2017/02/17. DOI: 10.1177/2047487317693949.
29. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2014; 63: 2935-2959. 2013/11/19. DOI: 10.1016/j.jacc.2013.11.005.
30. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *European heart journal* 2017; 38: 2459-2472. 2017/04/27. DOI: 10.1093/eurheartj/ehx144.
31. Kahan BC and Morris TP. Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? *Statistics in Medicine* 2013; 32: 1136-1149. 2012/11/01. DOI: 10.1002/sim.5667.
32. Brown TJ, Todd A, O'Malley CL, et al. *Community pharmacy interventions for public health priorities: a systematic review of community pharmacy-delivered smoking, alcohol and weight management interventions* Southampton (UK): NIHR Journals Library, 2016.
33. World Health Organization. World report on Ageing and Health. 2015.

34. Midttun L and Martinussen PE. Hospital waiting time in Norway: what is the role of organizational change? *Scandinavian journal of public health* 2005; 33: 6.

Table 1. Individual scores for each risk factor used to calculate ad hoc risk score.

	Score			
	0	**1**	**2**	**4**
Systolic and diastolic blood pressure[1]	< 131 sys and/or < 86 DIA mmHg	SYS BP ≥ 131 and/or DIA ≥ 86 mmHg	SYS BP ≥140 and/or DIA ≥90 mmHg	SYS BP ≥ 160 and/or DIA ≥ 100 mmHg
Total cholesterol	< 5 mmol/L	≥ 5.00 mmol/L	≥ 6.00 mmol/L	≥ 7.00 mmol/L
HDL-cholesterol[2]	> 1.0 mmol/L	< 1.0 mmol/L		
HbA1c	< 5.6 %	≥ 5.6 %	≥ 5.8 %	≥ 6.4 %
Body mass index	< 30 kg/m2	> 30 kg/m2		
Age	> 50 years	< 50 years	≤ 40 years	

HDL, high density lipoprotein. HbA1c, hemoglobin A1c. BMI, Body mass index.

[1]Mean of two measurements was recorded. Only the highest value of Systolic and diastolic blood pressure was included in risk score calculation.

[2] If HDL was not calculated (triglycerides were>7.34 mmol/L), score 0 was assigned HDL.

Table 2. Baseline characteristics of the study sample participating in a randomized controlled trial in pharmacies in 2014 (N=582)

	Alert/Advice (N=198)	**Advice-only (N=185)**	**Control (N=199)**
Demographics	% (n/N)	% (n/N)	% (n/N)
Men	28.8 (57/198)	24.3 (45/185)	31.7 (63/199)
≤13 years of schooling	54.7 (104/190)	52.0 (91/175)	57.7 (109/189)
Smokers[1]	14.2 (28/197)	18.7 (34/182)	20.3 (40/197)
CVD in first-degree relatives	31.0 (61/197)	25.3 (46/182)	28.3 (56/198)
Risk factors and age	Mean±SD	Mean±SD	Mean±SD
Ad hoc CVD risk score[2]	5.4±1.5	5.2±1.3	5.4±1.5
Age, years	55.7±14.4	57.4±14.6	56.5±15.0
Hba1c, %	5.6±0.3	5.6±0.3	5.6±0.3
Total cholesterol, mmol/L	6.7±1.1	6.6±1.2	6.5±1.1
LDL-cholesterol, mmol/L	4.0±1.0	3.9±1.1	3.9±0.9
HDL-cholesterol, mmol/L[3]	1.7±0.5	1.7±0.5	1.7±0.5
Triglycerides, mmol/L	2.1±1.3	2.1±1.6	2.1±1.3
BMI, kg/m^2	27.2±5.2	26.8±4.2	27.3±4.6
Systolic blood pressure, mmHg	133.2±16.2	131.7±16.6	134.3±15.7
Diastolic blood pressure, mmHg	81.9±9.8	81.8±9.6	82.1±9.4

CVD, cardiovascular disease. HbA1c, hemoglobin A1c (HbA1c). BMI, Body mass index.

[1] Daily or occasional smoking.

[2] Scores from values of HDL, cholesterol, blood pressure, Hba1c, BMI >30 kg/m^2 and age at baseline were summarized to an ad hoc CVD risk score.

[3] N (HDL) n=195 for Alert/advice, n=184 for Advice-only n=198 for Control.

There were no significant trend (p>0.05) in any variable across groups using unadjusted linear regression model for numeric variables, and chi square for relationship between categorical variables.

Table 3. Mean change in cardiovascular risk factors after an 8-week randomized controlled trial (n=543).

	Alert/advice (N=185)		**Advice-only (N=168)**		**Control (N=190)**				
	N	Change, mean (95% CI)	N	Change, mean (95% CI)	N	Change, mean (95% CI)	p^2	p^3	F-value model	(p>F)
Ad hoc CVD risk score[3]	180	***-0.36 (-0.62 to -0.09)***	161	***-0.71 (-0.99 to -0.44)***	182	***-0.76 (-1.02 to -0.50)***	0.03	0.8	2.78	0.06
Hba1c, %	184	***-0.07 (-0.10 to -0.03)***	165	***-0.09 (-0.12 to -0.05)***	189	***-0.09 (-0.12 to -0.06)***	0.4	1.0	0.54	0.58
Total cholesterol, mmol/L	184	-0.08 (-0.23 to 0.06)	165	-0.12 (-0.27 to 0.04)	185	***-0.16 (-0.31 to -0.02)***	0.4	0.7	0.31	0.74
LDL-Cholesterol, mmol/L	168	-0.02 (-0.15 to 0.10)	157	-0.02 (-0.15 to 0.11)	168	***-0.16 (-0.29 to -0.03)***	0.1	0.1	1.48	0.23
HDL-Cholesterol, mmol/L	180	0.01 (-0.04 to 0.05)	164	0.02 (-0.03 to 0.07)	182	0.02 (-0.02 to 0.07)	0.6	0.9	0.12	0.89
Triglycerides, mmol/L	182	-0.14 (-0.30 to 0.03)	163	0.01 (-0.16 to 0.19)	184	-0.06 (-0.23 to 0.10)	0.5	0.5	0.77	0.46
BMI, kg/m^2	183	0.06 (-0.08 to 0.19)	168	0.04 (-0.10 to 0.19)	190	0.05 (-0.08 to 0.19)	0.9	0.9	0.01	0.99
Systolic blood pressure, mmHg	185	-1.21 (-3.12 to 0.69)	168	-0.79 (-2.79 to 1.20)	190	***-1.89 (-3.77 to -0.02)***	0.6	0.4	0.32	0.73
Diastolic blood pressure, mmHg	185	-0.20 (-1.31 to 0.91)	168	***-1.56 (-2.72 to -0.40)***	190	***-1.56 (-2.65 to -0.47)***	0.1	0.1	1.92	0.15

CVD, cardiovascular disease
HbA1c, hemoglobin A1c (HbA1c)
BMI, Body mass index
Bold italics = difference significant within group (Paired sample t-test).
[1]Scores from values of HDL, cholesterol, blood pressure, Hba1c, BMI >30 kg/m2 and age at baseline were summarized to an ad hoc CVD risk score.
p^2= Alert/advice vs. Control, p^3 = Advice-only vs. Control. All data analysed with linear regression model (unadjusted).

Table 4. Composite food groups and lifestyle factors assessed in a randomized controlled trial in pharmacies in 2014 at baseline and at week-8 (end of intervention).

	Advice/alert			Advice-only			Control		
	Baseline (N=190)	**8-week (N=167)**	**p[5]**	**Baseline (N=175)**	**8-week (N=149)**	**p[5]**	**Baseline (N=195)**	**8-week (N=167)**	**p[5]**
	Median (Q1-Q3)	**Median (Q1-Q3)**		**Median (Q1-Q3)**	**Median (Q1-Q3)**		**Median (Q1-Q3)**	**Median (Q1-Q3)**	
Whole grains, grams/day[1]	84.4 (50.0-135.0)	86.9 (52.7-129.2)	0.19	88.8 (57.5-134.6)	94.9 (56.0-137.3)	0.58	93.7 (52.8-136.0)	86.3 (50-133.3)	0.94
Sugar foods/drinks, grams/day[2]	74.8 (35.0-127.3)	58.0 (27.0-120.2)	**0.01**	61.7 (31.4-132.2)	54.6 (22.1-101.2)	0.003	74.0 (29-126.7)	64.6 (23.3-108.7)	0.11
SFA dairy, grams/day[3]	38.0 (14.3-79.1)	25.6 (10.8-63.7)	0.08	35.4 (13.7-77.2)	27.0 (10.6-63.9)	0.11	36.6 (12.8-78.4)	26.8 (10.6-72.1)	0.77
Lean and fatty fish, grams/day	73.2 (42.1-116.1)	67.5 (42.1-119.6)	0.86	75.0 (53.5-105.9)	75.2 (50.7-104.4)	0.94	75.2 (44.0-105.6)	72.4 (43.2-102.1)	0.81
Fruit and vegetables, grams/day	283.2 (190.1-433.1)	280.3 (187.7-429.6)	0.94	297.3 (201.4-430.5)	292.2 (192.2-392.6)	0.001	291.5 (193.7-421.7)	277.3 (185.3-398.2)	0.02
Alcoholic drinks, grams/day[4]	45.0 (0-156.2)	31.9 (0-129.0)	0.32	59.8 (0-140.0)	31.9 (0-140.0)	0.08	31.9 (0-155.4)	42.7 (0-117.7)	0.53
MVPA, minutes/day	151.6 (0-319.1)	166.0 (0-364.4)	0.28	154.3 (71.8-364.4)	211.5 (0-357.8)	0.53	159.5 (0-345.0)	188.9 (76.8-369.1)	0.26
Number of cigarettes/day	7.0 (2.0-12.0) N=25	5.0 (2.0-10.0) N=29	0.43	8.00 (1.0-12.0) (N=39)	10.0 (4.0-13.0) (N=25)	0.08	9.0 (4.0-15.0) N=34	10.0 (5.0-11.0) N=29	0.68
High fat meat products, grams/day	21.0 (0-35.3)	11.9 (0-27.4)	0.18	14.3 (1.4- 24.8)	21.0 (1.4-24.6)	0.56	21.0 (1.4-43.5)	21.0 (1.4-43.5)	0.91
Lean meat products, grams/day	47.1 (21.0-87.0)	43.5 (21-73.8)	0.06	47.1 (22.4-85.5)	43.5 (21.8-65.9)	0.03	38.7 (21.0-64.5)	43.5 (21.8-64.5)	0.89

SFA, Saturated fatty acids. MVPA, moderate -to- vigorous intensity physical activity. Q1, quartile 1 (25th percentile). Q3, quartile 3 (75th percentile).

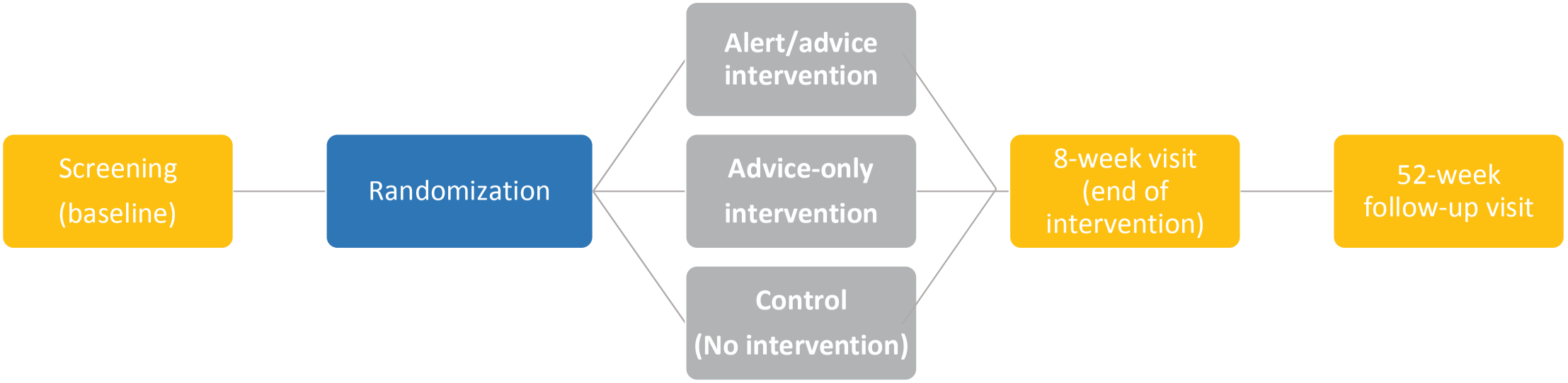
[1] Whole grains factor used in calculation of whole grains intake (bread contains 60% flour): bread with 0-25 % wholemeal flour: (60*0)/10000=0, bread with 25-50% wholemeal flour: (60*25)/10000= 0.15, bread with 50-75 wholemeal flour: (60*50)/10000=0.30, bread with 75-100% wholemeal flour: (60*75)/10000=0.45. Hence crisp bread= 0, whole grains crisp bread =1, sweetened cereals = 0.25, unsweetened cereals = 0.75. Boiled rice and pasta contains 70% water and 30% cereals. Whole grains factor used in calculation of whole grains intake from rice and pasta: Brown rice=0.30, white rice=0, whole grains pasta=0.30, white pasta=0.

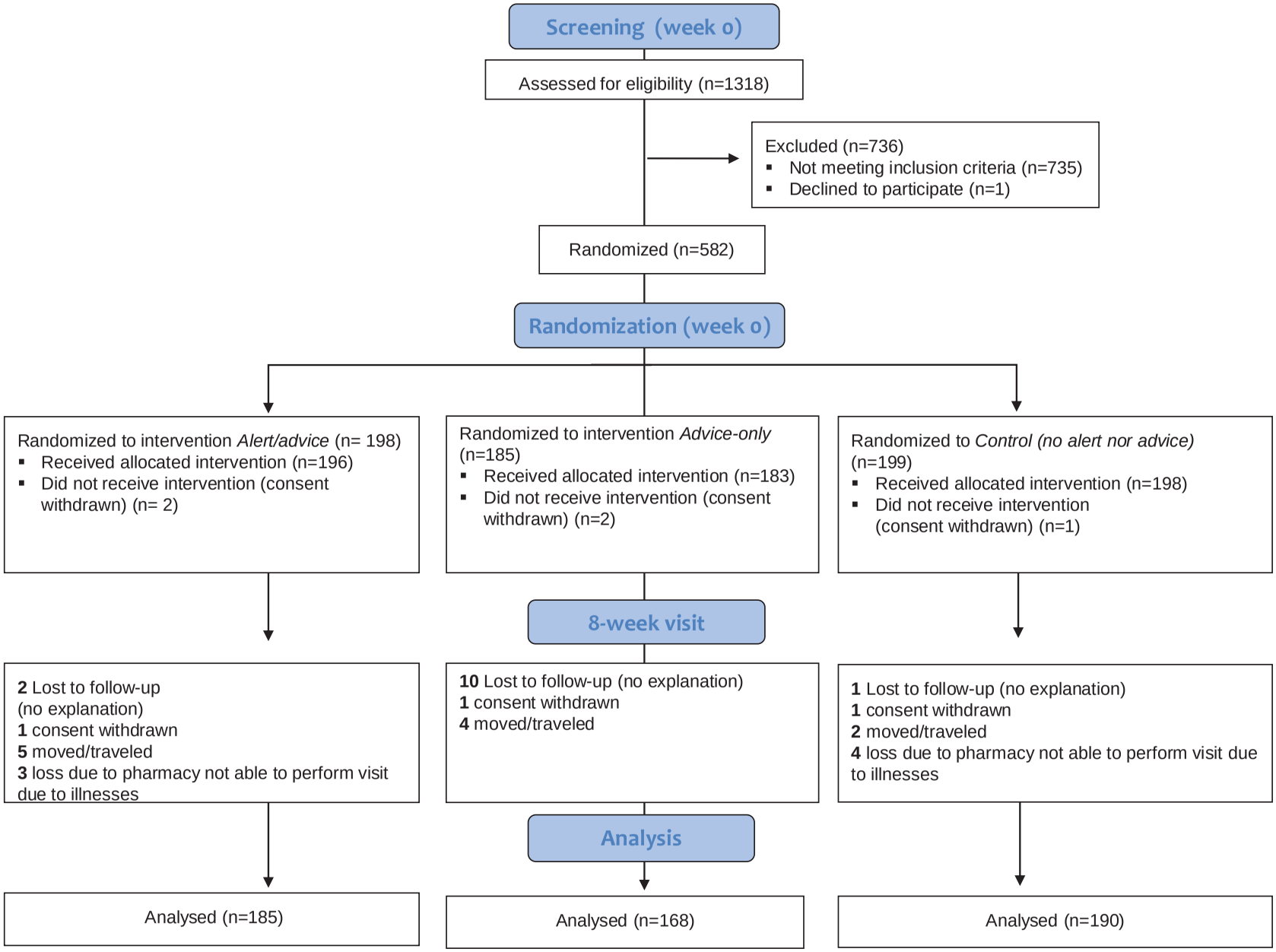
[2] Sugar foods/drinks: Sweet drinks (1 glass = 200 grams), sweetened cereals (e.g. Corn Flakes), cakes, buns, waffles, sweet biscuit.

[3] Dairy SFA = (whole fat milk- high- and medium fat milk products and cheese).

[4] Alcoholic drinks = wine, beer and spirits.

[5] p value = Wilcoxon Signed rank test p value for within group difference. There were no significant differences between groups.


Screening (baseline)
Randomization
Alert/advice intervention
Advice-only intervention
Control (No intervention)
8-week visit (end of intervention)
52-week follow-up visit


Screening (week 0)
Assessed for eligibility (n=1318)
Excluded (n=736)
Not meeting inclusion criteria (n=735)
Declined to participate (n=1)
Randomized (n=582)
Randomization (week 0)
Randomized to intervention Alert/advice (n= 198)
Received allocated intervention (n=196)
Did not receive intervention (consent withdrawn) (n= 2)
Randomized to intervention Advice-only (n=185)
Received allocated intervention (n=183)
Did not receive intervention (consent withdrawn) (n=2)
Randomized to Control (no alert nor advice) (n=199)
Received allocated intervention (n=198)
Did not receive intervention (consent withdrawn) (n=1)
8-week visit
2 Lost to follow-up (no explanation)
1 consent withdrawn
5 moved/traveled
3 loss due to pharmacy not able to perform visit due to illnesses
10 Lost to follow-up (no explanation)
1 consent withdrawn
4 moved/traveled
1 Lost to follow-up (no explanation)
1 consent withdrawn
2 moved/traveled
4 loss due to pharmacy not able to perform visit due to illnesses
Analysis
Analysed (n=185)
Analysed (n=168)
Analysed (n=190)

Alert/advice

- *Duration: 30-40 minutes*
- Measures of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HbA1c, height, weight
- **Questionnaires:**
  - Screening questionnaire
  - VISA-FFQ
- **Risk alert + advice intervention:**
  - Numeric information and interpretation of measurements verbally and through the *know your risk factors-card*
  - General diet and lifestyle advice advice (brochure)
  - New appointment after 8 weeks

Advice-only

- *Duration: 30-40 minutes*
- Measures of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HbA1c, height, weight
- **Questionnaires:**
  - Screening questionnaire
  - VISA-FFQ
  - **Advice intervention**
  - General diet and lifestyle advice on how to reduce CVD risk (brochure)
  - New appointment after 8 weeks

Control

- *Duration: 30-40 minutes*
- Measures of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceridess, HbA1c, height, weight
- **Questionnaires:**
  - Screening questionnaire
  - VISA-FFQ
- **No intervention (control)**
  - No information on risk status or any advice until after 8 weeks
  - New appointment after 8 weeks

Supplementary table A.1 Mean change in cardiovascular risk factors assessed between end of an 8-week randomized controlled trial and a 52-week follow-up visit in pharmacies (n=377).

	N	Advice/alert (N=121)	N	Advice-only (N=124)	N	Control (N=132)	F-value model	(p>F)
		Change, mean (95% CI)		Change, mean (95% CI)		Change, mean (95% CI)		
Ad hoc CVD risk score[1]	116	***-0.39 (-0.72 to -0.05)***	119	-0.05 (-0.38 to 0.28)	129	***-0.35 (-0.67 to -0.03)***	2.36	0.07
HbA1c, %	120	0.02 (-0.02 to 0.05)	122	0.02 (-0.01 to 0.06)	132	-0.01 (-0.17 to 0.20)	2.55	0.06
Total cholesterol, mmol/L	120	-0.15 (-0.34 to 0.04)	122	-0.07 (-0.12 to 0.26)	130	-0.01 (-0.16 to 0.18)	1.37	0.25
LDL-Cholesterol, mmol/L	107	-0.10 (-0.27 to 0.07)	114	0.02 (-0.14 to 0.19)	116	-0.003 (-0.17 to 0.16)	0.50	0.68
HDL-Cholesterol, mmol/L	116	0.04 (-0.03 to 0.10)	121	0.003 (-0.06 to 0.06)	128	0.04 (-0.02 to 0.10)	0.30	0.83
Triglycerides, mmol/L	118	-0.13 (-0.33 to 0.07)	121	0.03 (-0.17 to 0.23)	129	-0.12 (-0.31 to 0.08)	1.67	0.17
BMI, kg/m^2	119	0.08* (-0.14 to 0.30)	124	-0.09 (-0.30 to 0.13)	132	***-0.23**** ***(-0.43 to -0.02)***	2.75	0.04
Systolic blood pressure, mmHg	121	***-3.15 (-5.72 to -0.59)***	124	***-3.11 (-5.65 to -0.58)***	132	***-4.66 (-7.11 to -2.20)***	0.74	0.53
Diastolic blood pressure, mmHg	121	-1.11 (-2.48 to 0.26)	124	0.34 (-1.02 to 1.69)	132	-0.08 (-1.39 to 1.23)	0.83	0.48

CVD, Cardiovascular disease. BMI, body mass index.

[1]Scores from values of HDL, cholesterol, blood pressure, Hba1c, BMI >30 kg/m2 and age at baseline were summarized to ad hoc risk score.

*p value <0.05 (Alert/advice versus control). All data are analysed with linear regression model, adjusted for baseline.

Bold italics = significant difference within group.

Supplementary table A.2 Composite foods and lifestyle factors assessed at the 8- week visit and at the 52-week follow-up visit of a randomized controlled trial in pharmacies.

	Advice/alert			**Advice-only**			**Control**		
	8-week (N=167)	**52-week (N=127)**		**8-week (N=149)**	**52-week (N=117)**		**8-week (N=167)**	**52-week (N=126)**	
	Median (Q1-Q3)	Median (Q1-Q3)	p_1	Median (Q1-Q3)	Median (Q1-Q3)	p_2	Median (Q1-Q3)	Median (Q1-Q3)	p_3
Whole grains, grams/day[4]	86.9 (52.7-129.2)	90.0 (48.5-130.0)	0.81	94.9 (56.0-137.3)	92.8 (52.8-128.5)	0.30	86.3 (50-133.3)	97.1 (54.0-140.4)	0.87
Sugar foods/drinks, grams/day[5]	58.0 (27.0-120.2)	49.9 (23.9-80.5)	0.13	54.6 (22.1-101.2)	60.2 (27.7-97.7)	0.48	64.6 (23.3-108.7)	43.1 (25.9-83.9)	0.78
SFA dairy, grams/day[6]	25.6 (10.8-63.7)	39.3 (17.2-82.1)	0.29	27.0 (10.6-63.9)	27.1 (10.6-49.8)	0.62	26.8 (10.6-72.1)	22.5 (10.8-44.3)	0.05
Lean and fatty fish, grams/day	67.5 (42.1-119.6)	81.1 (47.2-117.5)	0.56	75.2 (50.7-104.4)	77.6 (46.3-124.7)	0.12	72.4 (43.2-102.1)	77.6 (53.5-117.5)	0.91
Fruit and vegetables, grams/day	280.3 (187.7-429.6)	294.3 (206.8-409.1)	0.49	292.2 (192.2-392.6)	269.4 (197.3-397.7)	0.29	277.3 (185.3-398.2)	288.3 (169.3-416.4)	0.80
Alcoholic drinks, grams/day[7]	31.9 (0-129.0)	39.1 (0-111.7)	NA	31.9 (0-140.0)	42.7 (0-155.4)	NA	42.7 (0-117.7)	61.1 (0-204.6)	NA
MVPA, min/day	166.0 (0-364.4)	211.5 (0-357.8)	0.50	211.5 (0-357.8)	188.9 (77.1-419.5)	0.94	188.9 (76.8-369.1)	166.0 (89.5-365.0)	0.91
Number of cigarettes/day	5.0 (2.0-10.00) N=29	10.0 (2-15.0) (N=14)	0.63	10.0 (4.0-13.0) (N=25)	10.0 (3.0-15.0) (N=11)	NA	10.0 (5.0-11.0) N=29	9.0 (3.0-15.0) N=19	0.75
High fat meat products, grams/day	11.9 (0-27.4)	21.0 (0 to 30.7)	0.19	21 (1.4-24.6)	21.0 (3.6-43.5)	0.11	21.0 (1.4-43.5)	21.0 (0-24.6)	0.71
Lean meat products, grams/day	43.5 (21-73.8)	47.1 (24.6-64.5)	0.80	43.5 (21.8-65.9)	43.5 (22.4-68.1)	0.98	43.5 (21.8-64.5)	43.5 (22.4-65.6)	0.56

Q1 = quartile 1 (25th percentile), Q3 = quartile 3 (75th percentile). MVPA = moderate -to- vigorous intensity physical activity.

[1, 2, 3] p value = Wilcoxon Signed rank test p value for within group difference. (There were no significant differences between groups).

[4]Whole grains factor used in calculation of whole grains intake (bread contains 60% flour): bread with 0-25 % wholemeal flour: (60*0)/10000=0, bread with 25-50% wholemeal flour: (60*25)/10000= 0.15, bread with 50-75 wholemeal flour: (60*50)/10000=0.30, bread with 75-100% wholemeal flour: (60*75)/10000=0.45. Hence crisp bread= 0, whole grains crisp bread =1, sweetened cereals = 0.25, unsweetened cereals = 0.75. Boiled rice and pasta contains 70% water and 30% cereals. Whole grains factor used in calculation of whole grains intake from rice and pasta: Brown rice=0.30, white rice=0, whole grains pasta=0.30, white pasta=0.

[5] Sugar foods/drinks: Sweet drinks (1 glass = 200 grams), sweetened cereals (e.g. Corn Flakes), cakes, buns, waffles, sweet biscuit.

[6] Dairy SFA = (whole fat milk- high- and medium fat milk products and cheese).

[7] Alcoholic drinks = wine, beer and spirits.

Know your values

- *To know your cardiovascular risk*

Did you know that you cannot physically notice your risk of cardiovascular disease?
It can therefore be smart to familiarize yourself with
your values of cardiovascular risk factors.

Being active and having a healthy diet can positively affect your values.
Reduce your intake of sugar and unfavorable (saturated) fat and eat more fruit and vegetables.
A tip can be to switch from unfavorable fats to favorable fats (unsaturated);
see list on www.suntfett.no

If you smoke, quitting would considerably reduce your risk of cardiovascular disease.

Research have shown that an 8-week effort, with small health-beneficial changes, can considerable lower your risk factor numbers and
thus reduce your risk of cardiovascular disease.

How can I improve my values?

Blood pressure

High blood pressure can be prevented and reduced by limiting your exposure to stress, salt, saturated fat and sugar and by exercising more.

Long-term blood sugar (HbA1c)

A healthy diet with a limited amount of sugar in combination with more frequent and regular exercise will improve your long-term blood sugar considerably.

Blood fats

The «good» HDL-cholesterol should not be too low. However, your “bad cholesterol” LDL-cholesterol should indeed be low. You can reduce the bad cholesterol considerably by choosing foods with unsaturated fats and exercising regularly.

It is worth noticing that your triglycerides increases after a meal. If you have had anything to eat during the past 12 hours you might experience misleading triglyceride levels. Low values are favorable. Less sugar and alcohol are beneficial for your triglycerides.

Body mass index (BMI)

BMI is a relationship between weight and height. It is particularly the fat around your belly that should be avoided. A small weight reduction can have a large impact on all risk factor values.

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Boots apotek

Mills

	Favorable	Slightly Unfavorable	Unfavorable	Clearly unfavorable
Blood pressure (mmHg)	**120-139/ 80-89**	**140–159/ 90–99**	**160–179/100-109**	**>180/>110**
Your value:				
HbA1c (%)	**<5.7**	**5.7-6.0**	**6.1-6.4**	**6.5-7.5**
Your value:				
Total cholesterol (mmol/L)	**<5.0 mmol/L**	**5.0-6.5**	**6.6-7.9**	**≥8**
Your value:				
LDL (mmol/L) *«Bad» cholesterol*	**<2.5-3.3**	**3.4-4.1**	**4.2-4.8**	**≥4.9**
Your value:				
HDL (mmol/L) *«Good» cholesterol*	**Women ≥1.2 Men ≥1.0**	**Women <1.2 Men <1**		
Your value:				
Triglycerides (mmol/L)	**0.5-2.6**	**>2.6**		
Your value:				
BMI (kg/m^2)	**18.5-24.9 Normalweight**	**25.0-29.9 Overweight**		**>30,0 Obese**
Your value:				

More information in the brochure and www.suntfett.no
Questions? Contact Nutritionist Karianne Svendsen:
E-mail: karianne.svendsen@medisin.uio.no
phone: 22 85 12 10

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Mills

III

food & nutrition research

ORIGINAL ARTICLE

Evaluation of a short Food Frequency Questionnaire to assess cardiovascular disease-related diet and lifestyle factors

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Abstract

Background: The Vascular lifestyle-Intervention and Screening in phArmacies (VISA) study investigates diet and lifestyle factors associated with risk of cardiovascular disease (CVD). As part of the study methodology, a short Food Frequency Questionnaire (FFQ), the VISA-FFQ, was adapted from the Norwegian NORDIET-FFQ.

Objective: The aim of this study was to evaluate the VISA-FFQ and its ability to estimate intakes of foods and lifestyle factors in screening for elevated risk of CVD. The evaluation included assessment of relative validity of intake of milk fat and assessment of reproducibility of several foods and lifestyle factors.

Design: Relative validity of milk fat estimated from the VISA-FFQ was assessed in 307 participants by comparing estimated dietary intake of the fatty acids pentadecanoic acid (15:0) and heptadecanoic acid (17:0), from milk fat with whole blood biomarkers 15:0 and 17:0. Reproducibility was evaluated in 122 participants by comparing consistency in intakes of different foods and lifestyle factors reported by the VISA-FFQ and administered twice with a 4-week interval.

Results: Dietary 15:0 milk fat estimated from the VISA-FFQ correlated positively with whole blood 15:0 ($r = 0.32$, $P < 0.05$). Men presented higher correlations than women did. Acceptable and consistent reproducibility ($r = 0.44$–0.94 and no large difference between test and retest) was observed for most beverages, milk products, spreads on bread and meat (all of which included food items categorised into at least two fat categories) and also for eggs, fruits and vegetables, nuts, pasta and rice, dessert/sweets, smoking and physical activity. Reproducibility did not consistently meet a satisfactory standard ($r \leq 0.41$ or large difference between test and retest) for unsweetened cereals, fatty fish, cakes, oils, white-, bread, crispbread and rice.

Conclusion: The validity of the VISA-FFQ was acceptable for intake of milk fat, and there was an overall satisfactory, though variable, reproducibility for intake of several foods and lifestyle factors in the VISA-FFQ.

Keywords: *Food Frequency Questionnaire; validity; biomarkers; fatty acids; dietary assessment; short-FFQ; milk-fat; saturated fat*

To access the supplementary material, please visit the article landing page

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It has been calculated that an unhealthy diet contributes to the largest proportion of disability-adjusted life years globally (1) and is associated with about 45% of all deaths from cardiovascular diseases (CVD) and type 2 diabetes (T2D) in America (2, 3). It is therefore important to assess food and lifestyle factors that can modulate the risk of disease and to use the assessment to recognise individuals and groups who would benefit from dietary changes (4). The Food Frequency Questionnaire (FFQ) is the most common tool in epidemiological studies to assess diet in relation to health outcomes. FFQs are designed to assess usual diet in retrospect, but are often time-consuming to complete (5). Short FFQs are considered less time-consuming (6), which may be of particular importance in any clinical setting where limited time may be an issue (7).

The validated short FFQ, NORDIET-FFQ (8), was developed in an ongoing study of colorectal cancer patients (9). The NORDIET-FFQ was designed to assess adherence to the Norwegian food-based dietary guidelines (10), including estimation of food quantities for the previous 1–2 months (9). Convenient, quantitative assessment of foods and lifestyle associated with CVD was desired in the Vascular lifestyle-Intervention and Screening in phArmacies (VISA) study (11). The Norwegian screener 'SmartDiet' offered such assessment (12), however without estimation of food quantities. Consequently, a study-specific FFQ, the VISA-FFQ, was adapted from the NORDIET-FFQ in order to include assessment of intake of foods and lifestyle factors associated with CVD risk.

The aim was to evaluate the VISA-FFQ's relative validity of estimated intake of milk fat (using biomarker fatty acids pentadecanoic acid [15:0] and heptadecanoic acid [17:0] as references) and reproducibility of intake of foods and lifestyle factors among a group of individuals with moderately high risk of CVD.

Methods

Study design

The study population was pharmacy customers in 48 pharmacies that were enrolled in the VISA study. The VISA study subsample included 558 participants with moderately elevated risk of CVD who had been screened in the previous year. Of them, 375 participants participated in a 4-week intervention randomised by pharmacy (23 intervention pharmacies and 25 usual care pharmacies) in September 2015 and were for that eligible for this evaluation (Table 1).

During the pharmacy visit (time 1, the beginning of the intervention), participants were asked for consent to obtain extra blood for dried blood spots (DBS) sampling and to complete the VISA-FFQ. If consent was given, participants were also asked to self-sample DBS and complete the VISA-FFQ at home 4 weeks later, at designated time 2 (end of intervention).

The VISA-FFQ and DBS were completed on the same or the next day. For the purpose of this study, data from the VISA-FFQ and fatty acid 15:0 and 17:0 % of Fatty Acid Methyl Ester (FAME) assayed from DBS obtained at time 1 and 2 were utilized to evaluate the VISA-FFQ for relative validity of milk fat and overall reproducibility.

DBS sampling

The DBS is a form of bio-sampling where blood obtained by a finger-prick lancet is blotted on spots on filter paper (DBS-card) (13). DBS sampling was performed by health care providers in pharmacies at time 1 and by each participant (self-sampling) at time 2. Fasting samples were desired but not required. Participants with appointments late in the day, and those who had taken

Table 1. Retrospective background characteristics of completers- and non-completers of the VISA-FFQ at study inclusion.

	Completers (*N* = 368)	Non-completers (*N* = 190)[a]	*p*[b]
Men, % (*N*)	26.1 (96/368)	32.6 (62/190)	0.11
Living alone, % (*N*)[c]	37.8 (139/368)	36.8 (70/190)	1.00
Smokers, % (*N*)[d]	17.2 (54/368)	22.9 (43/188)	0.02
Ethnicity outside Nordic countries, % (*N*)[e]	11.8 (43/365)	15.7 (29/185)	0.23
Low education, % (*N*)[f]	52.4 (184/351)	59.2 (106/179)	0.14
Age (years), mean (SD)	58.1 ± 13.7	53.7 ± 15.9	0.02
Body mass index (kg/m^2), mean (SD)	27.0 ± 4.4	27.2 ± 5.1	0.64
Hemoglobin A1c (%), mean (SD)	5.5 ± 0.3	5.5 ± 0.3	0.28
Systolic blood pressure (mmHg), mean (SD)	131.1 ± 16.9	131.7 ± 17.6	0.72
Diastolic blood pressure (mmHg), mean (SD)	80.3 ± 9.6	81.2 ± 10.5	0.33
Total cholesterol (mmol/L), mean (SD)	6.5 ± 1.2	6.4 ± 1.3	0.18
HDL-cholesterol (mmol/L), mean (SD)	1.7 ± 0.5	1.7 ± 0.5	0.07
LDL-cholesterol (mmol/L), mean (SD)	3.9 ± 1.0	3.9 ± 1.0	0.39
Triglycerides (mmol/L), mean (SD)	2.0 ± 1.1	2.1 ± 1.2	0.57

Data are presented as percentage (%) and numbers (N), or mean and standard deviation (SD). HDL, high density lipoprotein; LDL, low density lipoprotein.
[a]Includes 7 participants that attended the study visit but did not complete the questionnaire.
[b]Chi-square test of independence or independent sample *t*-test.
[c]Not married/no significant other and widow/widower/divorced.
[d]% Yes, daily/Yes, occasionally.
[e]Both or one parent born outside Norway.
[f]Low education ≤13 years of schooling.

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omega-3 supplements or had recently eaten fatty fish were excluded from DBS sampling. After completion, the DBS-card was left to dry for 2–4 h before it was put in an airtight aluminium bag and stored in the refrigerator at 1–4°C (14).

DBS samples were returned either to the University of Oslo or directly to the laboratory responsible for the analyses, VITAS AS (Oslo). From DBS, fatty acids in whole blood (plasma and cells) (15) were separated and determined by extracting FAME that were further analysed with gas chromatography – flame ionisation detector (GC-FID) after direct transmethylation by VITAS. The results were given in % of FAME (16).

VISA-FFQ

The 62-item VISA-FFQ originates from the 66-item NORDIET-FFQ (8). The VISA-FFQ and the NORDIET-FFQ share the features of 15 minutes completion time and of being a semi-quantitative FFQ that covers habitual dietary intake (grams/day) of food and lifestyle factors for the past 1–2 months (8). The questionnaires include both frequency (how often the item was consumed) and amount of the food items. Amounts were expressed as portion sizes, specified according to the food composition and nutrient calculation system (named KBS), version AE-14, developed at the University of Oslo. When different foods were combined into one category (such as high-fat [HF] meat comprising, e.g., hamburger, hot dogs and processed meat, ~17% fats), the average portion size of all the items was estimated from KBS and recorded (8). The VISA-FFQ was optically readable, and the handling of data including missing data followed the same procedure as described earlier by Henriksen et al. (8).

Development of the VISA-FFQ

In the development of the 62-items VISA-FFQ, we altered 14 items, added 4 items, deleted 9 items and kept the remaining 44 items unchanged from the original NORDIET-FFQ (8), as presented in Supplementary file 1.

Altered items

Fourteen items in the categories beverages (milk), milk products, spreads (cheese and meat) and meat (dinner or hot lunch) were revised in order to provide more comprehensive information on intake of foods that are major contributors to dietary saturated fatty acids (SFA) according to the national food database (17). Milk, milk products, cheese and meat products were categorised according to low-fat (LF), medium-fat (MF) and HF content (majority SFA), using KBS and SmartDiet (12) as references (Supplementary file 1). In later data analysis, MF and LF cheese and meat (dinner or hot lunch) were combined into one single medium/LF item each.

Items added, deleted and/or unaltered

Four items associated with the risk of CVD were added to the VISA-FFQ. These were; prevalence of smoking and number of cigarettes per day (18), weekly egg intake (19) and use of cholesterol lowering margarine with added plants sterols (20). Smoking and cholesterol lowering margarine had three fixed response categories: 'no'; 'yes, occasional'; and 'yes, daily' and an additional 'do not know' category for the margarine. Egg intake and number of cigarettes were numeric variables (Supplementary file 1). To preserve the VISA-FFQ as a four-page, 62-item questionnaire, nine items in the NORDIET-FFQ that were considered less relevant for CVD risk, or were redundant with information previously collected in VISA study, were dropped in favour of the new items. These included age, height, weight and gender, and five diet-related items: use of dietary supplements, intake of 'small fruits', 'berries and dried fruit' from the category 'fruit', tomato sauce from the category 'vegetables' and 'tea' from the category 'beverages' (Supplementary file 1).

The VISA-FFQ also includes 44 other items within the categories fruits, nuts, vegetables, cereals, beverages, bread, spreads on bread, fat spreads and oils, fish for dinner, rice and pasta, cakes, dessert and sweets, and physical activity. These were unaltered from the NORDIET-FFQ and have previously been validated in a colorectal cancer sample (8, 21).

Evaluation of VISA-FFQ

Relative validity of milk was assessed at times 1 and 2 in the pooled intervention and usual care pharmacies. Milk fat in the VISA-FFQ comprised the items whole-fat milk, LF milk, HF and MF milk products, and HF and MF cheese. From KBS, we obtained data on average nutritional content of 15:0 and 17:0 from the milk fat items (Supplementary file 2). These data were utilised to calculate total 15:0 and total 17:0 in consumed milk fat estimated from the VISA-FFQ. Hence, to assess relative validity of milk fat, 15:0 and 17:0 in consumed milk fat (grams/day) estimated from the VISA-FFQ were compared with biomarkers 15:0 and 17:0 % of FAME assayed from DBS.

Completed VISA-FFQs obtained from participants in the usual care pharmacies (in which there had not been any intervention) at time 1 (test) and time 2 (retest) were used to evaluate reproducibility. We assessed reproducibility of the 18 items within several categories that were changed relative to the VISA-FFQ: beverages (whole-fat, LF milk and skimmed milk), milk products (HF, MF and LF milk products), spreads on bread (HF, MF and LF cheese, and HF and LF meat), meat for dinner or hot lunch (HF, MF and LF meat), eggs, cigarettes, smoking and use of cholesterol lowering margarine. Next, we assessed reproducibility of the 44 unchanged items within the categories fruits, nuts,

vegetables, cereals, beverages, bread, spreads on bread, fat spreads and oils, fish for dinner, rice and pasta, cakes, dessert and sweets, and physical activity.

Statistical analysis

Power calculation

Sample size was estimated following Hulley's calculation (22, 23). A sample size of 41 participants would be sufficient to observe correlation coefficients (r) of 0.50 or higher, with a significance level of 5 and 80% power.

Statistical methods

All analyses were performed in SAS software 9.4 for Windows, with the exception of the Bland-Altman plots that were computed in SPSS version 23. The level of significance was set to 5%. Continuous variables considered to be non-normally distributed were presented as median and 25th (P_{25}) and 75th (P_{75}) percentiles; otherwise, data were presented as mean and standard deviation (SD). Categorical data were presented with percentages and numbers.

For the evaluation of relative validity of milk fat, Spearman's rank order correlation (RHO) was used to explore the relationship between 15:0 and 17:0 in consumed milk fat (grams/day) and biomarker 15:0 and 17:0% of FAME. Correlation coefficients were stratified by sex and adjusted for total intake of foods and drinks (grams/day) computed from summarising all food items (except tap water) from the VISA-FFQ.

Several measures were used to evaluate reproducibility of items between test and retest completion of the VISA-FFQ. Spearman's RHO was used, and correlation coefficients were considered as follows: $r \geq 0.50$ was defined as 'satisfactory or good', $r = 0.30$–0.49 were defined as 'fair' and $r < 0.30$ was defined as 'poor' (24). Weighted Kappa correlation coefficient was used to explore the strength of relationship between categorical variables. Bland–Altman plots were used to explore the presence of outliers and degree of agreement between test and retest, including the limits of agreement that comprise 95% (mean difference ± 1.96 SD) of the sample (25). Lastly, the non-parametric options, Wilcoxon signed-rank test and Kruskal–Wallis test, were used to test for significant difference in intakes between test and retest, whereas McNemar test was used for categorical variables.

Background characteristics were obtained approximatly 44 weeks prior to the evaluation. Characteristics were presented as the total sample available for the evaluation, completers of the VISA-FFQ compared to non-completers (who either did not complete the VISA-FFQ at time 1 or were lost to follow-up before time 1).

Ethics

Participants gave written informed consent to participate. The VISA study was approved by the National Committee for Research Ethics in Norway (REK) with reference number 2013/1660-/REK South-East and was reported to the Norwegian Center for Research.

Results

In total, 98.1% ($n = 368$) of participants at time 1 completed the VISA-FFQ (completers). Males were on average 55.6 ± 13.8 years old, whereas females were 59.3 ± 13.2 years old. Compared to the non-completers, smoking was less frequent (17.2%, $n = 54$ vs. 22.9%, $n = 43$), and age was higher (58.1 ± 13.7 years vs. 53.7 ± 15.9 years) in completers. Otherwise, samples seemed similar (Table 1).

The sample utilised to evaluate relative validity of milk fat included 307 participants (79 males, 226 females and 2 with missing gender data) at time 1 who had satisfactorily completed both the VISA-FFQ and the DBS. The corresponding number at time 2 was 237 participants (57 males, 173 females and 7 with missing gender data). The sample utilised to evaluate reproducibility (test–retest) consisted of 122 participants (26 males and 96 females) who completed the VISA-FFQ both at times 1 and 2 (Figure 1).

Evaluation of relative validity

At time 1, intake of 15:0 in consumed milk fat (grams/day), adjusted for total intake of foods and drinks, was significantly correlated with biomarker 15:0 (% of FAME), with $r = 0.32$ ($p < 0.05$) for the total sample. Corresponding correlation between 17:0 in consumed milk fat and biomarker 17:0% of FAME was non-significant ($r = 0.10$). Correlations tended to be slightly higher the first time the biomarker fatty acids were measured, and higher for males than females (Table 2). We also stratified the correlations by age groups. Total food and drinks-adjusted correlations between 15:0 in consumed milk fat and biomarker 15:0 appeared highest for the 57 participants in the age group 18–45 years with $r = 0.56$ ($p < 0.05$). Corresponding correlation in the age group 46–55 years ($n = 146$) was $r = 0.18$ ($p < 0.05$) and $r = 0.35$ in the age group 66–88 years ($N = 104$). Overall, Pearson's correlation coefficients were numerically lower than the presented Spearman's RHO coefficients.

Evaluation of reproducibility of the altered items

Measures of reproducibility between the test and retest completion of the VISA-FFQ for the 18 altered or added items are presented in Table 3.

Significant correlations between test and retest results defined as satisfactory or good were observed for 12 out of 18 items (67%). This included eggs ($r = 0.76$) and cigarettes ($r = 0.92$), in addition to LF milk and skimmed milk, HF- and LF-milk products, HF cheese, HF and LF meat (spreads) and HF meat (dinner or hot lunch), smoking and use of cholesterol lowering margarine.

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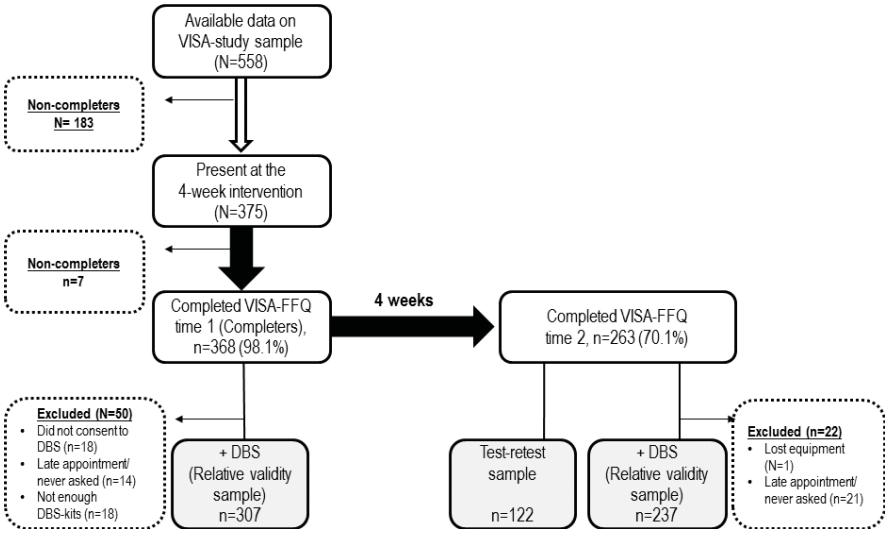

Fig. 1. Study design and flow of participants included in the evaluation of the VISA-FFQ.

Table 2. Correlations (Spearman's rho) between milk fat estimated from the VISA-FFQ and biomarker saturated fatty acids measured in whole blood at time 1 and 2.

	Pentadecanoic acid (15:0) % of FAME						Heptadecanoic acid (17:0) % of FAME					
	Time 1[a]			Time 2[b]			Time 1[a]			Time 2[b]		
	Total[c] (*N* = 307)	Male (*N* = 79)	Female (*N* = 226)	Total (*N* = 237)	Male (*N* = 57)	Female (*N* = 173)	Total[c] (*N* = 307)	Male (*N* = 79)	Female (*N* = 234)	Total (*N* = 237)	Male (*N* = 57)	Female (*N* = 173)
Milk (g/day)												
Whole-fat milk	0.16*	0.17	0.16*	0.14*	-0.08	0.20*	0.06	0.16	0.02	0.10	0.02	0.13
Milk products (g/day)[d]												
High-fat milk products	0.20*	0.24*	0.18*	0.18*	0.29*	0.12	0.05	0.15	0.01	0.05	0.01	0.04
Cheese (g/day)												
High-fat cheese	0.24*	0.36*	0.21*	0.24*	0.52*	0.14	0.11	0.08	0.13*	0.10	0.34*	0.03
Total dietary milk fatty acids[e]	0.32*	0.38*	0.29*	0.30*	0.40*	0.27*	0.10	0.16	0.09	0.07	0.008	0.10

VISA-FFQ, Vascular lifestyle-Intervention and Screening in pharmacies- food frequency questionnaire.
FAME = fatty acids methyl esters.
*Correlation coefficient is significant at the 0.05 level (2-tailed). Adjusted for total food and drink intake (except tap water) in grams/day.
[a]Dried blood spot sampling and VISA-FFQ performed in pharmacy.
[b]Dried blood spot sampling and VISA-FFQ performed at home.
[c]Including missing gender.
[d]Cream and yoghurt.
[e]Total dietary milk fatty acids 15:0 and 17:0 were estimated from intakes of from milk, milk products and cheese except low-fat/fat-free and compared to corresponding biomarker fatty acid.

Significant correlations defined as fair were found for the remaining items. Combining MF and LF items for cheese (spreads) and meat (dinner or hot lunch) into a single item each resulted in correlations considered satisfactory/good (Table 3).

Among these 18 items, only typical intake in grams/day of HF cheese, whole-fat milk and use of cholesterol lowering margarine was significantly different between test and retest (Table 3). The Bland–Altman plots in Figure 2 illustrate that the mean difference in intake of HF cheese between test and retest was −2.00 grams/day. Further, that 95% of the observations were within the range of 15.7–19.7 grams/day (limits of agreements), corresponding to about two slices of cheese (Figure 2a). Mean difference in the intake of whole-fat milk was 9.0 grams/day, with limits of agreements of 148.0–157.0 grams/day, corresponding

Table 3. Measures of reproducibility for 18 food and lifestyle factors[a] in the test-retest sample (N = 122).

	Test (time 1)[b]	Retest (time 2)[c]	*P*-value of difference[d]	Correlation coefficient[e]
	Total (N = 122)	Total (N = 122)	Total (N = 122)	Total (N = 122)
	Median (P_{25}, P_{75})	Median (P_{25}, P_{75})	*p*	*r*
Milk (g/day)				
Whole-fat milk	0 (0,0)/ 23.8±14.9[f]	0 (0,0)/ 14.9±52.1[f]	0.03	0.45*
Low-fat milk	58.0 (0, 142)	50.0 (0, 186)	0.94	0.81*
Skimmed milk	0 (0, 14)	0 (0, 28)	0.92	0.68*
Milk products (g/day)[g]				
High-fat milk products	0 (0, 7)	0 (0, 3.5)	0.67	0.50*
Medium-fat milk products	7.0 (0, 17.8)	7.0 (0, 14.5)	0.34	0.48*
Low-fat milk products	3.5 (0, 14.5)	7.0 (0, 23.3)	0.63	0.53*
Spreads (g/day)				
High-fat cheese	3.6 (1.43, 9.3)	6.4 (1.4, 9.3)	0.02	0.51*
Medium-fat cheese	0 (0, 3.6)	0 (0, 3.6)	0.50	0.40*
Low-fat cheese	0 (0, 1.4)	0 (0, 1.4)	0.77	0.47*
Medium/low-fat cheese[h]	1.4 (0, 6.4)	0 (0, 6.4)	0.47	0.51*
High-fat meat[i]	1.4 (0, 3.6)	0 (0, 3.6)	0.72	0.59*
Low-fat meat[j]	3.6 (0, 6.4)	3.6 (0, 6.4)	0.82	0.59*
Meat dinner or hot lunch (g/day)				
High-fat meat[k]	10.5 (0, 42.0)	10.5 (0, 21.0)	0.14	0.52*
Medium-fat meat[l]	15.8 (0, 43.5)	21.0 (0, 43.5)	0.09	0.44*
Low-fat meat[m]	43.5 (21.0,64.5)	43.5 (21, 64.5)	0.43	0.46*
Medium/low-fat meat[h]	64.5 (32.3, 87.0)	64.5 (43.5, 106.5)	0.06	0.50*
Other				
Eggs per week	4.0 (2, 6)	3.0 (2, 5)	0.29	0.76*
Number of cigarettes	10.0 (7, 20)	8.0 (0, 10)	0.25	0.92*
Smoking[n]	0.08 (10/121)	0.08 (10/122)	1.00	0.94*
Cholesterol lowering Margarine[n]	30.0 (36/120)	36.7 (44/120)	0.03	0.50*

VISA-FFQ, Vascular lifestyle-Intervention and Screening in pharmacies- food frequency questionnaire.
*Spearman's rank order correlation (rho) coefficient is significant at the 0.05 level (2-tailed).
[a]These 18 items in the VISA-FFQ were revised relative to the original questionnaire, NORDDIET-FFQ (8).
[b]VISA-FFQ completed at pharmacy.
[c]VISA-FFQ completed at home.
[d]Tested by Wilcoxon Signed-Rank test, McNemar test for smoking and cholesterol lowering margarine.
[e]r = Spearman's rho coefficient or Weighted Kappa coefficient (smoking and cholesterol lowering margarine).
[f]Mean and standard deviation.
[g]Milk products = cream and yoghurt (whole-fat, medium-fat and low-fat according to approximately SFA content).
[h]Not an original category in the VISA-FFQ. Made by combining low-fat and medium-fat alternatives.
[i]High fat meat spreads = salami, liver paste etc.
[j]Low-fat meat spreads = ham, chicken/turkey etc.
[k]High-fat meat = ground meat, sausage, hamburger.
[l]Medium-fat meat = low-fat ground meat, sausage, hamburger.
[m]Low-fat meat = game, pork, chicken filets.
[n]Yes, daily /Yes, occasionally % (n/N).

to a big glass of milk (Figure 2b). No distinct pattern of outliers was observed for any item.

Evaluation of reproducibility of the unaltered items

Among the unaltered items, significant correlations between test and retest results defined as satisfactory or good were observed for 35 out of 44 items (80%) (Table 4). These included all items in the categories nuts, cereals, beverages, fish for dinner, cakes, dessert and sweets and physical activity. Despite satisfactory correlations, estimated intake of tomato, unsweetened and sweetened cereals, tap water, sodas with no added sugar, fatty fish, cakes and dessert and chips was significantly different in intakes (grams/day) between test and retest. Particularly for

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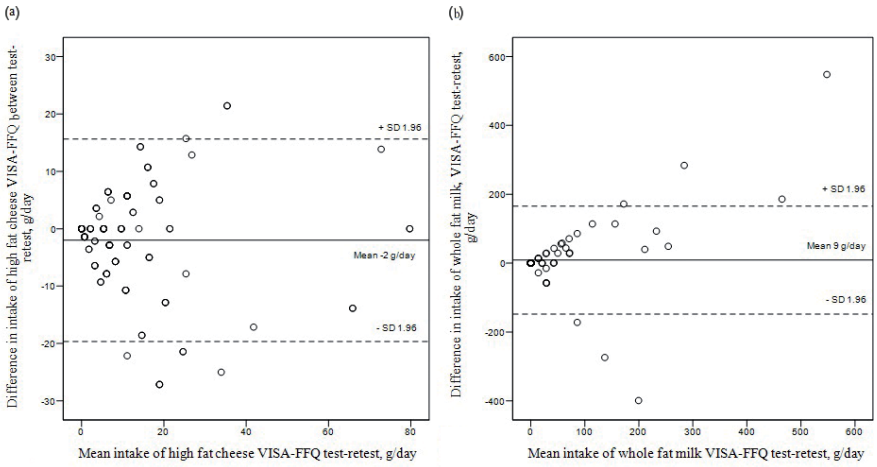

Fig. 2. Bland–Altman plot of intake of high-fat cheese (a) and whole-fat milk (b) as estimated from test and retest completion of the VISA-FFQ (N = 122).

Table 4. Measures of reproducibility for 44 food and lifestyle factors[a] in the test-retest sample (N = 122).

	Test (time 1)[b]	Retest (time 2)[c]	P-value of difference[d]	Correlation coefficient[e]
	Total (N = 122)	Total (N = 122)	Total (N = 122)	Total (N = 122)
	Median (P_{25}, P_{75})	Median (P_{25}, P_{75})	p	r
Fruits (g/day)				
Large fruit	57.0 (43.0, 93.0)	57.0 (39.5, 93.0)	0.46	0.69*
Medium-size fruit	14.5 (6.1, 43.0)	14.5 (0, 43.0)	0.45	0.46*
Nuts (g/day)				
Unsalted	5.4 (1.3, 12.6)	3.6 (0, 11.6)	0.13	0.58*
Salted	0.9 (0, 3.6)	1.8 (0, 3.6)	0.73	0.53*
Vegetables (g/day)				
Garlic	0.1 (0, 0.7)	0.1 (0, 0.6)	0.49	0.81*
Onion	5.8 (2.5, 12.9)	5.8 (1.4, 8.7)	0.08	0.65*
Tomato	30.2 (18.2, 60.5)	28.0 (14.0, 55.9)	0.03	0.53*
Mixed salad	28.5(13.2, 49.1)	28.5 (7.3, 46.5)	0.14	0.47*
Other vegetables	68.4 (34.7, 111.6)	55.8 (34.8, 104.9)	0.92	0.50*
Cereals (g/d)				
Sweetened cereals	0 (0, 0)/3.51±10.2[f]	0 (0, 0)/1.34±5.8[f]	0.01	0.65*
Unsweetened	7.3 (0, 35.5)	17.8 (0, 46.5)	0.003	0.62*
Beverages (g/d)				
Tap water	274 (186, 548)	274 (186, 548)	0.01	0.61*
Sodas with no added sugar	28.0 (0, 114.0)	28.0 (0, 86.0)	0.01	0.71*
Juice	28.0 (0,86.0)	28.0 (0, 93.0)	0.40	0.75*
Other beverages with no added sugar	0 (0, 28)	0 (0, 28)	0.83	0.53*
Beer with alcohol	0 (0, 70.0)	0 (0, 140.0)	0.44	0.77*
Liquor, g/d	0 (0, 0)	0 (0, 0)	0.36	0.69*
Wine with alcohol	15.4 (0, 63.8)	15.4 (0, 63.8)	0.67	0.73*
Filtered coffee	342.5(0, 685.0)	342.5 (13.1, 465.0)	0.72	0.71*
Other coffee (espresso, etc.)	0 (0, 142.5)	0 (0, 107.5)	0.37	0.77*

Table 4. Continued

	Test (time 1)[b]	Retest (time 2)[c]	*P*-value of difference[d]	Correlation coefficient[e]
	Total (*N* = 122)	Total (*N* = 122)	Total (*N* = 122)	Total (*N* = 122)
	Median (P_{25}, P_{75})	Median (P_{25}, P_{75})	*p*	*r*
Bread (g/d)				
Bread (60 % cereals) with 0-25 % wholemeal flour	0 (0, 0)	0 (0, 0)	0.77	0.09
Bread (60 % cereals) with 25-50% wholemeal flour	0.0 (0, 72.0)	0.0 (0, 72.0)	0.66	0.49*
Bread (60 % cereals) with 50-75 wholemeal flour	60.0 (0 , 180.0)	60.0 (0, 120.0)	0.38	0.54*
Bread (60 % cereals) with 75-100 wholemeal flour	0 (0, 60.0)	0 (0, 60.0)	0.85	0.44*
White crispbread (0-25% wholegrain)	0 (0, 0)	0 (0, 0)	0.56	0.10
Wholemeal crispbread (100% wholegrain)	14.0 (0, 28.0)	14.0 (0, 28.0)	0.83	0.62*
Spreads on bread				
Sweetened spreads(g/week)	20.0 (0, 90.0)	20.0 (0, 60.0)	0.56	0.59*
Fruits and vegetables as spreads (g/day)	37.5 (0, 75.0)	37.5 (0, 67.5)	0.42	0.48*
Fish spreads (g/ week)	90 (0, 162)	90 (0, 162)	0.82	0.66*
Fat spreads and oils % (n/N)				
Oils, margarine, butter or not using any	97.5 (119/122)[g]		0.16	0.41*
Types of fat spreads or not using any	93.4 (114/122) [g]		0.80	0.77*
Fish for dinner (g/day)				
Fatty fish	42.1 (20.3, 62.4)	20.3 (20.3, 42.05)	<0.001	0.68*
Processed fish	6.3 (0, 25.2)	25.2 (0, 25.2)	0.94	0.55*
Lean fish	20.3 (0, 42.1)	20.3 (7.6, 42.1)	0.79	0.55*
Rice and pasta (g/day)				
White rice	0 (0,14.0)	0 (0, 22.4)	0.88	0.41*
Wholegrain rice	0 (0,0)	0 (0,0)	0.75	0.61*
White pasta	0 (0, 17.5)	0 (0, 17.5)	0.63	0.53*
Wholegrain pasta	0 (0,17.5)	0 (0, 17.5)	0.17	0.73*
Cake, dessert and sweets (g/d)				
Cakes	16.8 (0, 25.8)	17.4 (8.4, 34.8)	0.01	0.52*
Dessert	12.6 (0, 26.1)	12.6 (0, 25.2)	0.03	0.58*
Chocolate/candy	3.5 (0, 15.3)	7.3 (0, 14.5)	0.61	0.59*
Chips	0 (0, 6.5)	0 (0, 8.4)	0.04	0.67*
Physical activity (min/day)				
Moderate intensity	18.1 (10.8, 35.3)	18.1 (11.0, 37.6)	0.69	0.57*
High intensity	0.8 (0, 11.0)	0.5 (0, 11.0)	0.30	0.64*

VISA-FFQ, Vascular lifestyle-Intervention and Screening in pharmacies- food frequency questionnaire. g/day, grams per day min/day, minutes per day.
*Spearman's rank order correlation (rho) coefficient is significant at the 0.05 level (2-tailed).
[a]These 44 items in the VISA-FFQ were unaltered from the original questionnaire, NORDDIET-FFQ (8).
[b]VISA-FFQ completed at pharmacy.
[c]VISA-FFQ completed at home.
[d]Tested by Wilcoxon Signed-Rank test or McNemars test for fat spreads and oils.
[e]r= Spearman's rho coefficient or Weighted Kappa coefficient fat spreads and oils.
[f]Mean± standard deviation.
[g]Percent and frequency of participants reporting the same category (not using/ using soft margarines/ using butter / using oils) both at test and retest.

sweetened cereals, tap water, sodas with no added sugar, dessert and chips, median and 25th and 75th percentiles were similar between time test and retest, but *p*-value for difference was significant due to small number of users or differences in the extremes of intake.

Furthermore, significant correlations defined as satisfactory or good were observed for the items large fruit (but not medium fruit, $r = 0.46$), all vegetables except for mixed salad ($r = 0.47$), all spreads on bread (except for fruit and vegetables spreads, $r = 0.48$) and all rice and pasta items except for white rice ($r = 0.41$). Correlations for the category bread were more various ranging from $r = 0.49$ for bread with 75–100% wholemeal flour to $r \leq 0.1$ for white bread and crispbreads (0–25% wholemeal flour).

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In total 97% responded to the same category for use of oils (or other cooking fats) between test and retest, but correlation was fair with $r = 0.41$ (Table 4).

Discussion

The VISA-FFQ's ability to give a relatively valid estimate of milk fat was acceptable, displayed as postive correlations between consumed 15:0 milk fat estimated from the VISA-FFQ (grams/day) and biomarker 15:0 (% of FAME). The VISA-FFQ also showed good and consistent reproducibility for intake (in grams/day) or frequency of use of most of the items in the VISA-FFQ.

Relative validity

Since not all milk products supply the same amount of fat (26), relative validity of milk fat intake was assessed by comparing the approximate, total intake of 15:0 and 17:0 estimated from consumed milk fat in grams/day, with biomarker fatty acids 15:0 and 17:0 % of FAME (27, 28). These fatty acids are assumed to originate mainly from milk fat because they are produced in relatively high levels in ruminants by rumen microbial fermentation and microbial de novo lipogenesis which may again transfer to the host animal (29). Although milk fat is believed to be the primary source of odd-chain fatty acids, a recent study found that humans can also synthesise them as products of gut fermentation, particularly using propionate as a source (30). Moreover, these fatty acids can also be found in lamb, beef, venison and fatty fish (31), but no significant correlations of these foods with these two fatty acids have been observed (28).

Adjusting for total intake of foods (as the questionnaire was judged not to be sufficient to estimate energy intake) increased the correlation between 15:0 in consumed milk fat and biomarker 15:0 from $r = 0.26$ to $r = 0.32$. The agreement between consumed milk fat and biomarker milk fat was comparable to other studies using whole-blood biomarker 15:0 as reference (32, 33). Supported by others (26, 27), we observed that biomarker 15:0 was a better reference for milk fat intake than 17:0, reflecting the nutritional distribution of fatty acids in milk fat (26).

This validation standard is however imperfect because nutrition composition databases for calculations of milk fat are approximate (26, 34). Additionally, perfect agreement cannot be expected when the periods over which intake was assessed were different (35). VISA-FFQ measures diet for the previous 1–2 months, but the fatty acids in whole blood reflect dietary intake from the last hours to several days (36). There might even be lower proportion of fatty acids in whole blood compared to other blood constituents (32). However, similar correlations for the total sample at time 1 ($r = 0.32$) and 2 ($r = 0.30$) strengthen the validity of the results. Fatty acid concentrations in blood are also affected by metabolism, absorption and genetics that differ among individuals (29). These anticipated variations in biomarker fatty acids can also elucidate variation patterns in correlations with fatty acids in consumed milk fat among genders and age groups. Our observed results on gender difference were similar to a comparable study of Swedish adults (28) and could also be due to women being more likely than men to under-report according to social desirability and approval (37).

Reproducibility

Reproducibility was measured by assessing how consistently reported food intake and lifestyle factors could be repeated in the same participants within 4 weeks (5, 38). Correlations indicate ability to rank individuals according to the items evaluated and whether this ranking was maintained relative to other participants in the test–retest period (7). Previous studies have shown that short FFQs show good ability to rank individuals according to food intake (7, 38). Our results add to this, with significant correlations defined as satisfactory or good ($r \geq 0.50$) for 76% ($n = 47$) of the VISA-FFQ's items (24), whereas the correlation coefficients were less satisfactory ($r = 0.40$–0.47) for intake of LF and MF cheese and meat (dinner or hot lunch), in accordance with other studies (39). When LF and MF items aggregated into one item, the correlations increased to $r = 0.50$. We acknowledge that the fat content in LF and MF meat and cheese is too alike to justify the need for three categories of cheese and meat according to fat intake, as suggested elsewhere (40). Nonetheless, 81% ($n = 50$) of the items had non-significantly difference in intakes between test and retest administration of the VISA-FFQ. The majority of the remaining items had small differences, not considered to be of clinical relevance as supported by others (8). Accordingly, only intake of unsweetened cereals, fatty fish, cakes, oils, white rice, white bread and crispbread showed divergent measures of reproducibility. This could be due to either systematic errors in the VISA-FFQ, true changes in food intake, few responders or extreme outliers (13). Our results are consistent with a Norwegian study evaluating reproducibility of large and comprehensive FFQs (41), the NORDIET-FFQ that were validated against 7-days weighed record (8) and a screener assessing ability to rank intake of HF foods among individuals with elevated cholesterol level (42). Since the test–retest sample consisted of only 26 men, we did not have power to stratify the results by gender. However, we performed a sensitivity analysis on gender and the results appeared similar for men and women.

Strengths and limitations

The 62-item VISA-FFQ was self-administered, and it appeared to be convenient in many ways; it had 98% completion rate in a clinical setting and 70% at home, and it was quick to self-administer and less time-consuming to analyse compared to other questionnaires (6).

However, the skewed distribution of gender may affect the representativeness of the results.

The evaluation was strengthen by the use of objective biomarkers for milk fat intake, twice, which reduces limitations associated with self-report of dietary intake (36). Although the relative validity correlation coefficient was only 0.32, we considered that to show that the diet items and the objective marker were measuring the same construct. We note that biomarkers have their own limitations, and full energy computation of VISA-FFQ was not possible. Since variation in dietary intake can be due to both errors in measurements and true changes in food intake (43) that cannot be separated (5), we attempted to improve the evaluation of reproducibility by using data solitary from participants who did not receive any intervention. However, it is well known that the awareness of being studied in itself can affect behaviour and consciousness of own habits (44). For instance, in line with current national recommendations for CVD prevention (4), intake of HF meat showed a tendency to decrease after 4 weeks, while MF meat increased. In a group of individuals with elevated risk of CVD, there is therefore a high possibility that these changes truly occurred, supporting the evaluation of the VISA-FFQ. Short FFQs can be used to assess changes in diet and lifestyle frequently (6). Such monitoring is likely to be beneficial for people at risk of disease, such as the VISA study sample (11). As the relationships between today's food intake and risk of CVD and T2D still have uncertainties (45), we aim to use VISA-FFQ as a tool to further assess the relationship between food intake and risk of disease. To broaden the use of the VISA-FFQ, the next step would be to evaluate if the VISA-FFQ is suitable for dietary counselling. However, the counsellor should keep in mind that the assessment will be less comprehensive than with longer and more complete FFQs.

Conclusion

Milk fatty acid 15:0 estimated from the VISA-FFQ showed positive correlations with biomarker 15:0 % of FAME (r = 0.32 and r = 0.30, P <0.05). In this sense, the VISA-FFQ has acceptable validity in its estimation of milk fat intake. Reproducibility of the VISA-FFQ was considered satisfactory, though varied, for intake of foods and lifestyle factors among a group of individuals with moderately high risk of CVD. We therefore suggest that the VISA-FFQ can be a convenient tool for assessment of (but not limited to) diet and lifestyle factors associated with CVD risk, in various settings.

Availability of data and material

The datasets used and/or analysed during the current study and the questionnaire (VISA-FFQ) in Norwegian are available from the corresponding author on reasonable request.

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Authors' contributions

KS had the main responsibility for writing the manuscript. KS, KR, VHTH and DRJ were responsible for the design of the VISA study. All authors contributed to analysis and/or interpretation of data, and writing and approval of the final manuscript.

Conflict of interest and funding

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References

1. Global Burden of Disease 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1459–544.
2. Micha R, Penalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA 2017; 317: 912–24.
3. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. Circulation 2011; 123: 2870–91.
4. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017; 136(3): e1–e23.
5. Willet W, Lenart E. Reproducibility and validity of food-frequency questionnaires. Nutritional epidemiology. New York: Oxford University Press; 1998, pp. 101–47.
6. Andersen LF, Johansson L, Solvoll K. Usefulness of a short food frequency questionnaire for screening of low intake of fruit and vegetable and for intake of fat. Eur J Public Health 2002; 12: 208–13.
7. England CY, Andrews RC, Jago R, Thompson JL. A systematic review of brief dietary questionnaires suitable for clinical use in the prevention and management of obesity, cardiovascular disease and type 2 diabetes. Eur J Clin Nutr 2015; 69: 977–1003.
8. Henriksen HB, Carlsen MH, Paur I, Berntsen S, Bøhn SK, Skjetne AJ, et al. Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients. Food Nutr Res 2018; 62: 1306.
9. Henriksen HB, Raeder H, Bohn SK, Paur I, Kvaerner AS, Billington SA, et al. The Norwegian dietary guidelines and colorectal

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cancer survival (CRC-NORDIET) study: a food-based multicentre randomized controlled trial. BMC Cancer 2017; 17: 83.
10. Nasjonalt råd for ernæring. Kostråd for å fremme folkehelsen og forebygge kroniske sykdommer: metodologi og vitenskapelig kunnskapsgrunnlag. Oslo: Helsedirektoratet; 2011.
11. Svendsen K, Jacobs DR Jr., Røyseth IT, Byfuglien MG, Mørch-Reiersen LT, Garstad KW, et al. Pharmacies offer a potential high-yield and convenient arena for total cholesterol and CVD risk screening Unpublished results. Submitted EJPH. 2018.
12. Svilaas A, Strom EC, Svilaas T, Borgejordet A, Thoresen M, Ose L. Reproducibility and validity of a short food questionnaire for the assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60–70.
13. Edelbroek PM, van der Heijden J, Stolk LM. Dried blood spot methods in therapeutic drug monitoring: methods, assays, and pitfalls. Ther Drug Monit 2009; 31: 327–36.
14. Holen T, Norheim F, Gundersen TE, Mitry P, Linseisen J, Iversen PO, et al. Biomarkers for nutrient intake with focus on alternative sampling techniques. Genes Nutr 2016; 11: 12.
15. Rise P, Eligini S, Ghezzi S, Colli S, Galli C. Fatty acid composition of plasma, blood cells and whole blood: relevance for the assessment of the fatty acid status in humans. Prostaglandins Leukot Essent Fatty Acids. 2007; 76: 363–9.
16. Aued-Pimentel S, Lago JH, Chaves MH, Kumagai EE. Evaluation of a methylation procedure to determine cyclopropenoids fatty acids from Sterculia striata St. Hil. Et Nauds seed oil. J Chromatogr A 2004; 1054: 235–9.
17. Matportalen. Food database (Matvaretabellen). [cited 2018 Apr 9th]; Available from: http://www.matvaretabellen.no/?language=en
18. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Printed with corrections, January 2014.
19. Spence JD, Jenkins DJ, Davignon J. Egg yolk consumption and carotid plaque. Atherosclerosis 2012; 224: 469–73.
20. Pedersen JI, Kirkhus B, Muller H. Serum cholesterol predictive equations in product development. Eur J Med Res 2003; 8: 325–31.
21. Henriksen HB, Berntsen S, Paur I, Zucknick M, Skjetne AJ, Bøhn SK, et al. Validation of two short questionnaires assessing physical activity in colorectal cancer patients. Accepted BMC Sports Sci Med Rehabil, 2018.
22. Hulley SB. Designing clinical research: an epidemiologic approach. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
23. UCSF: Clinical & Translational Science Institute. Correlation sample size. [cited 2018 Apr 9th]; Available from: http://www.sample-size.net/correlation-sample-size/
24. Hankin JH, Wilkens LR, Kolonel LN, Yoshizawa CN. Validation of a quantitative diet history method in Hawaii. Am J Epidemiol 1991; 133: 616–28.
25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Int J Nurs Stud 2010; 47: 931–6.
26. Jenkins B, West JA, Koulman A. A review of odd-chain fatty acid metabolism and the role of pentadecanoic acid (c15:0) and heptadecanoic acid (c17:0) in health and disease. Molecules 2015; 20: 2425–44.
27. Albani V, Celis-Morales C, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, et al. Exploring the association of dairy product intake with the fatty acids C15:0 and C17:0 measured from dried blood spots in a multipopulation cohort: findings from the Food4Me study. Mol Nutr Food Res 2016; 60: 834–45.
28. Warensjö Lemming E, Nälsén C, Becker W, Ridefelt P, Mattisson I, Lindroos AK. Relative validation of the dietary intake of fatty acids among adults in the Swedish National Dietary Survey using plasma phospholipid fatty acid composition. J Nutr Sci 2015; 4: e25.
29. Vlaeminck B, Fievez V, Cabrita ARJ, Fonseca AJM, Dewhurst RJ. Factors affecting odd- and branched-chain fatty acids in milk: a review. Anim Feed Sci Technol 2006; 131: 389–417.
30. Weitkunat K, Schumann S, Nickel D, Hornemann S, Petzke KJ, Schulze MB, et al. Odd-chain fatty acids as a biomarker for dietary fiber intake: a novel pathway for endogenous production from propionate. Am J Clin Nutr 2017; 105: 1544–51.
31. Risérus U, Marklund M. Milk fat biomarkers and cardiometabolic disease. Curr Opin Lipidol 2017; 28: 46–51.
32. Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, et al. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol 2005; 162: 373–81.
33. Albani V, Celis-Morales C, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, et al. Exploring the association of dairy product intake with the fatty acids C15:0 and C17:0 measured from dried blood spots in a multipopulation cohort: Findings from the Food4Me study. Molecular nutrition & food research. 2016; 60(4): 834–45.
34. Stefanov I, Baeten V, Abbas O, Vlaeminck B, De Baets B, Fievez V. Evaluation of FT-NIR and ATR-FTIR spectroscopy techniques for determination of minor odd- and branched-chain saturated and trans unsaturated milk fatty acids. J Agric Food Chem 2013; 61: 3403–13.
35. Kaaks RJ. Biochemical markers as additional measurements in studies of the accuracy of dietary questionnaire measurements: conceptual issues. Am J Clin Nutr 1997; 65: 1232s–9s.
36. Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM. Dietary biomarkers: advances, limitations and future directions. Nutr J 2012; 11: 109.
37. Kuhnle GG. Nutritional biomarkers for objective dietary assessment. J Sci Food Agric 2012; 92: 1145–9.
38. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutr Res Rev 2004; 17: 5–22.
39. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires the eating at America's table study. Am J Epidemiol. 2001; 154: 1089–99.
40. Taylor AJ, Wong H, Wish K, Carrow J, Bell D, Bindeman J, et al. Validation of the MEDFICTS dietary questionnaire: a clinical tool to assess adherence to American Heart Association dietary fat intake guidelines. Nutr J 2003; 2: 4.
41. Parr CL, Veierod MB, Laake P, Lund E, Hjartaker A. Test-retest reproducibility of a food frequency questionnaire (FFQ) and estimated effects on disease risk in the Norwegian Women and Cancer Study (NOWAC). Nutr J 2006; 5: 4.
42. Retzlaff BM, Dowdy AA, Walden CE, Bovbjerg VE, Knopp RH. The Northwest Lipid Research Clinic Fat Intake Scale: validation and utility. Am J Public Health 1997; 87: 181–5.
43. Willet W. Nutritional epidemiology. 3rd ed. Oxford: Oxford University Press; 2013.

44. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol 2014; 67: 267–77.
45. Schwab U, Lauritzen L, Tholstrup T, Haldorssoni T, Riserus U, Uusitupa M, et al. Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. Food Nutr Res 2014; 58: 25145.

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Supplementary file 1. Changes of items in the VISA-FFQ relative to the NORDIET-FFQ.

Categories	NORDIET-FFQ items	VISA-FFQ items*
Beverages	Low fat milk (corresponding to skimmed + low fat milk in the VISA-FFQ)	Skimmed milk (<0.1 % fat)
	Whole-fat milk	Low fat milk (~1% fat)
		Whole-fat milk (~4% fats)
Milk products	Low fat (corresponding to low + medium fat in the VISA-FFQ)	Low fat (e.g. yoghurt, coffee cream, low fat sour cream ~10% fats)
	High fat	Medium fat (e.g. low-fat crème fraiche, sour cream ~18% fats)
		High fat (e.g. whole fat crème, crème fraiche, sour cream ~35% fats)
Spreads (meat)	Red processed	Low fat (e.g. ham, chicken)
	White processed	High fat (e.g. liver paste, salami)
Spreads (cheese)	Low fat (corresponding to low + medium fat in the VISA-FFQ)	Low fat (cottage cheese, cheese with ~10% fats)
	High fat	Medium fat (low fat cheese ~16% fats)
		High fat (high fat cheese ~27% fats)
Meat (dinner or hot lunch	Red unprocessed	Low fat (e.g. chicken and pork filets, game, processed meat ~5% fats)
	Red processed	Medium fat (e.g. processed meat ~14% fats)
	White unprocessed	High fat (e.g. hamburger, hot dogs processed meat ~17% fats)
	White processed	

*Portion sizes were unaltered from those estimated in the NORDIET-FFQ.
Additional alterations included adding; eggs, cigarettes per day, smoking and use of cholesterol lowering margarine to the VISA-FFQ. Further, deleting; use of dietary supplements, intake of "small fruits", "berries and dried fruit" from the category "Fruit", tomato sauce from the category "Vegetables", "tea" from the category beverages and age, height, weight and gender.

Supplementary file 2: Nutritional content (fat and fatty acids) calculated from the food composition and nutrient calculation system (KBS) (version AE-14, University of Oslo, Oslo, Norway) of milk products included in the VISA-FFQ.

	Total fat/ 100 grams*	**Pentadecanoic acid (15:0) /100 grams***	**Heptadecanoic acid (17:0)/100 grams***
Food groups			
Whole fat milk	3.70	0.034	0.018
Low fat milk	1.08	0.009	0.005
High fat milk products	36.0	0.32	0.16
Medium fat milk products	19.7	0.18	0.09
High fat cheese	27.2	0.25	0.12
Medium fat cheese	16.1	0.14	0.068

*Amounts are averages of all products mentioned in the VISA-FFQ within each food group.
VISA-FFQ= Vascular lifestyle-Intervention and Screening in phArmacies (VISA)-FFQ.

Appendix 1

SPØRRESKJEMA KOSTHOLD OG FYSISK AKTIVITET

Vi ønsker opplysninger om ditt vanlige kosthold for en gjennomsnittlig uke.
Ha de siste 2 månedene i tankene når du fyller ut.

Skjemaet skal leses av en maskin og det er derfor viktig at du setter tydelige kryss i rutene. Bruk blå eller sort kulepenn. Alle svar vil behandles fortrolig.

Riktig markering i rutene er slik: ☒
Ved feil markering, fyll hele ruten slik: ■

Av hensyn til den maskinelle lesningen - pass på at arkene ikke brettes.
Har du spørsmål angående utfyllingen av skjemaet kan du ringe:
Karianne Svendsen på prosjekttelefon: 22 85 12 10

ID ☐☐☐☐☐

Besøk 1

1. FRUKT

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang				
	0	1	2	3	4	5	6-7	8+		1/2	1	2	3+
Stor frukt (f.eks. et helt eple, nektarin, banan, appelsin, en skive melon o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐
Mellomstor frukt (f.eks. klementiner, kiwi, plommer o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐

2. NØTTER

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang				
	0	1	2	3	4	5	6-7	8+		1/2	1	2	3+
Usaltede nøtter (f.eks. mandler, peanøtter, valnøtter, cashew, ferdig blandinger o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(neve= 25g)	☐	☐	☐	☐
Saltede nøtter (f.eks. peanøtter, valnøtter, ferdige blandinger, chilinøtter, pekannøtter, mandler o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(neve= 25g)	☐	☐	☐	☐

3. GRØNNSAKER (ikke potet)

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang					
	0	1	2	3	4	5	6-7	8+		1/4	1/2	1	2	3+
Hvitløk (friske, hermetiske)	☐	☐	☐	☐	☐	☐	☐	☐	(fedd=båt)	☐	☐	☐	☐	☐
Løk, vårløk og purre	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Tomat (friske, 6 cherry= 1 vanlig tomat)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Blandet salat (f.eks. bladsalat, paprika, agurk, mais o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(liten bolle=100g)	1/4 ☐	1/2 ☐	1 ☐	2 ☐	3+ ☐
Andre grønnsaker (f.eks. gulrot, brokkoli, blomkål,kålrot, hodekål, frosne blandinger o.l)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐

4. KORN

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang				
	0	1	2	3	4	5	6-7	8+		1/2	1	2	3+
Søtet frokostblanding (f.eks.Corn Flakes, Chocofrokost o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Usøtet frokostblanding eller grøt (f.eks. havregrøt, 4-Korn o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐

35872

5. DRIKKE

	Hvor mange ganger pr. uke drakk du								Hvor mye drakk du pr.gang						
	0	1	2	3	4	5	6-7	8+		1/2	1	2	3-4	5-6	7+
Vann (springvann, flaskevann)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Annen drikke uten tilsatt sukker (f.eks. farris, lettsaft, lettbrus o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Juice (f.eks. eplejuice, appelsinjuice, Manajuice o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Annen drikke tilsatt sukker (f.eks. brus, saft, nektar o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Helmelk, kulturmelk, kefir o.l.	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Lettmelk, ekstra lettmelk, cultura, biola naturell o.l.	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Skummet melk, skummet kulturmelk, biola bærdrikk 0,1 % fett o.l.	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Øl med alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Vin med alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Brennevin	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	☐	☐	☐	☐	☐	☐
Kaffe (filtermalt)	☐	☐	☐	☐	☐	☐	☐	☐	(kopp)	☐	☐	☐	☐	☐	☐
Annen type kaffe (espresso,presskanne,kapsel, kokmalt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(kopp)	☐	☐	☐	☐	☐	☐

6. MEIERIPRODUKTER

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang						
	0	1	2	3	4	5	6-7	8+		1/4	1/2	1	1 1/2	2	3+
Fete produkter (f.eks. kremfløte, creme fraiche, seterrømme o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	☐
Halvfete produkter (f.eks. matfløte, lettrømme, yoghurt med sukker, lett creme fraiche o.l)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	☐
Magre produkter (f.eks. kaffefløte, ekstra lett rømme, kesam, matyoghurt yoghurt naturell/Dobbel 0% o.l)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	☐

7. BRØD (f.eks. 1/2 rundstykke = 1 skive, 1 baguett = 4 skiver, 1 ciabatta = 2 skiver)

	Hvor mange skiver spiste du pr. DAG													
	0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød, 0-25% sammalt mel (f.eks. loff, baguetter, fine rundstykker, ciabatta)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Halvgrovt brød, 25-50% sammalt mel (f.eks. helkornbrød, kneipp, grove rundstykker)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød, 50-75% sammalt mel (f.eks. havrebrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ekstra grovt brød, 75-100% sammalt mel (f.eks. mørkt rugbrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fint knekkebrød (f.eks. kavring, frokost knekkebrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt knekkebrød (f.eks. Husmann, Sport, Solruta o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr.dag=_____ Antall skiver pr.uke:_____x 7=_____. Tallet brukes i spørsmål 8.
(sum skiver pr.dag)

35872

8. REGISTRER PÅLEGGET DU VANLIGVIS SPISER PÅ DISSE SKIVENE I LØPET AV EN UKE:

	Antall skiver pr. UKE									
	0	1	2-3	4-5	6-7	8-12	13-18	19-24	25-30	31+
Fete oster som pålegg (f.eks. hvitost, nøkkelost, Gudbrandsdalsost, brie o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Halvfete oster som pålegg (f.eks. lettere hvitost,lettere Gudbrandsdalsost, lettere smørbare oster, prim o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Andre oster som pålegg (f.eks. Vita gulost, cottage cheese, lettere prim, "lett gulost" med 10 % fett o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fete kjøttpålegg (f.eks. salami, servelat, falukorv, vanlig leverpostei o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Magre kjøttpålegg (f.eks. kokt/røkt skinke, kylling/kalkunpålegg, lett servelat, mager eller oljebaserte leverposteier o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pålegg med sukker (f.eks. honning, syltetøy, nøttepålegg o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grønnsaker og frukt som pålegg (f.eks. paprika, agurk, avokado, banan, eple o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fiskepålegg (f.eks. makrell i tomat, røket/gravet laks, sild o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9. EGG

	Antall pr. uke
Hvor mange egg, inkludert i matlaging, spiser du pr. uke?	☐☐

10. Hvilken type smør / margarin / olje brukte du oftest til:

NB! Sett **ETT** kryss på hver linje	Bruker ikke	Mykt margarin (Soft Flora, Vita, Soft oliven)	Hardt smør (meierismør, Bremykt, Melange)	Oljer (olivenolje, soyaolje, rapsolje, Vita hjertego)
Matlaging, steking, baking	☐	☐	☐	☐
På brød, baguette, rundstykke	☐	☐	☐	☐

11. KOLESTEROLSENKENDE MARGARIN

	Nei	Ja, daglig	Ja, av og til	Vet ikke
Bruker du Vita Pro-Aktiv eller Becel Pro-Activ?	☐	☐	☐	☐

12. FISK TIL MIDDAG / VARM LUNSJ

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang						
	0	1	2	3	4	5	6-7	8+		½	1	2	3	4	5+
Fet fisk (f.eks. laks, ørret, sild, kveite o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 145g)	☐	☐	☐	☐	☐	☐
Mager fisk (f.eks. torsk, sei, hyse, rødspette, breiflabb o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 145g)	☐	☐	☐	☐	☐	☐
Bearbeidet fisk (f.eks.fiskegrateng, fiskepudding, fiskeboller, fiskegryte o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 180g)	☐	☐	☐	☐	☐	☐

35872

13. KJØTT TIL MIDDAG/VARM LUNSJ

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang						
	0	1	2	3	4	5	6-7	8+		½	1	2	3	4	5+
Fete kjøttprodukter (f.eks. familiedeig, vanlig grillpølser/wienerpølser, stek med fettrand, bacon, flesk o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐
Halvfete kjøttprodukter (f.eks. kjøttdeig (okse,lam), kyllingpølse, lettpølse, hamburger, kylling med skinn o.l)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐
Magre kjøttprodukter (f.eks. karbonadedeig, kjøttdeig (svin,kylling), biff, filet (kylling, svin, okse, lam), viltkjøtt, "Go' og mager pølser" o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐

14. RIS OG PASTA

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang					
	0	1	2	3	4	5	6-7	8+		1	2	3	4+	
Polert, hvit ris	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	
Upolert, naturris	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	
Vanlig pasta	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	
Fullkornspasta	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	

15. KAKER, DESSERT, GODTERI

	Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang						
	0	1	2	3	4	5	6-7	8+		1	2	3	4	5+	
Kaker, hvetebakst, vafler, søt kjeks	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	☐	☐	☐	☐	☐	
Dessert (f.eks. is, hermetisk frukt, pudding)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	
Sjokolade, godteri	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =100g)	1/4 ☐	1/2 ☐	1 ☐	1 1/2 ☐	2+ ☐	
Potetgull, chips	☐	☐	☐	☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-5 ☐	6-8 ☐	9-11 ☐	12+ ☐	

16. RØYKING

	Nei	Ja, av og til	Ja, daglig
Røyker du?	☐	☐	☐
Hvis ja, hvor mange sigaretter/piper røyker du i gjenomsnitt *pr. dag*? Antall:	☐☐		

17. DAGLIG FYSISK AKTIVITET (Registrer hele treningsøkter og vanlig fysisk aktivitet i dagliglivet)

	Hvor mange ganger pr. uke var du fysisk aktiv								Hvor lenge var du fysisk aktiv pr. gang (minutter)							
	0	1	2	3	4	5	6-7	8+	1-4	5-9	10-15	16-20	21-30	31-45	46-60	60+
Moderat intensitet (f.eks. hurtig gange, fysisk aktivitet i arbeid, hardt husarbeid, annen aktivitet der du blir lett andpusten)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Høy intensitet (f.eks. jogging, skigåing, hard fysisk aktivitet i arbeid, driver trening/idrett, annen aktivitet der du blir veldig andpusten)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

35872

Appendix 2

For internt bruk:

Respondentid

HVORDAN SKAL DU BESVARE SPØRSMÅLENE?

Nesten alle spørsmål skal besvares på samme måte - ved å sette kryss i det svaralternativ som passer best, slik det er vist nedenfor:

Slik: ☒ Ikke slik: ☒

Spørreskjema til 1-års oppfølging av deltagere i studien «Effekt av vaskulær screening i apotek»

Skjemaet tar ca. 5-7 minutter å fylle ut.

Spørsmålene som følger, gjelder tiden fra du målte deg første gangen og ble med i studien i fjor høst, og frem til i dag:

1 Hva var hovedgrunnen til at du benyttet deg av tilbudet om målingene første gangen du var i apotek?

Flere kryss mulig

- ☐ Det var en tilfeldighet
- ☐ Jeg ønsket å sjekke kolesterolnivået mitt
- ☐ Jeg ønsket å sjekke blodtrykket mitt
- ☐ Jeg ønsket å sjekke blodsukkeret mitt
- ☐ Det var et gratis tilbud
- ☐ Vet ikke/husker ikke

2 Da du var på apotek i fjor høst og målte deg, husker du om:

Merk: Sett ett kryss på hver linje	Høyere enn forventet	Lavere enn forventet	Som forventet	Husker ikke/ Vet ikke
Kolesterolnivået ditt var:	☐	☐	☐	☐
Blodtrykket ditt var:	☐	☐	☐	☐
Langtids-blodsukkeret (Hba1c) ditt var:	☐	☐	☐	☐

3 Har du målt en eller flere av følgende etter at du var i apotek for andre gang og målte deg i fjor?

Flere kryss mulig

- ☐ Kolesterol
- ☐ Blodtrykk
- ☐ Langtids-blodsukker (Hba1c)
- ☐ Nei, ingen → Gå til 5

4 Dersom du har målt noe på nytt etter du var i apotek i fjor, husker du om:

Merk: Sett ett kryss på hver linje	Høyere enn i apotek	Lavere enn i apotek	Omtrent likt	Husker ikke/ Vet ikke	Fikk ikke vite svaret
Kolesterolnivået ditt var:	☐	☐	☐	☐	☐
Blodtrykket ditt var:	☐	☐	☐	☐	☐
Langtids-blodsukkeret ditt var (Hba1c):	☐	☐	☐	☐	☐

5 **Ble du anbefalt av helsepersonell i apotek å oppsøke lege på grunn av verdiene du målte i apotek i fjor?**

Merk: Sett ett kryss

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke/husker ikke

6 **Har du vært hos lege på grunn av verdiene du målte i apotek i fjor?**

Merk: Sett ett kryss

- ☐ Ja → Gå til **8**
- ☐ Nei

7 **Hvis du ikke har vært hos legen, hva er hovedgrunnen til det?**

Merk: Sett ett kryss

- ☐ Ikke nødvendig
- ☐ Har ikke råd
- ☐ Har ikke lyst
- ☐ Har ikke hatt tid
- ☐ Legen min har ikke hatt tid
- ☐ Vet ikke
- ☐ Har glemt det

8 **Har du startet med en eller flere av disse medisinene etter at du var i apotek i fjor?**

Kryss av for ja:	Ja, i 2014	Ja, i 2015
Kolesterolsenkende	☐	☐
Blodtrykksenkende	☐	☐
Mot sukkersyke (diabetes)	☐	☐
Albyl-E eller Acetylsalisylsyre	☐	☐
Andre blodfortynnende medisiner	☐	☐
Nei, ingen	☐	

9 **Dersom legen din har diskutert medisiner for høyt kolesterol, blodtrykk og/eller blodsukker med deg, uten at du har startet med det, hva er grunnen til det?**

Merk: kryss av for det mest passende alternativet

- ☐ Jeg ønsker ikke å ta medisin
- ☐ Legen anbefalte det, men jeg ønsket ikke
- ☐ Legen anbefalte det ikke, men jeg ønsket
- ☐ Legen anbefalte meg ikke
- ☐ Jeg har glemt/ikke hatt tid til å hente ut resepten
- ☐ Vet ikke/husker ikke

10 **Har du vært hos lege eller på sykehus for en eller flere av følgende sykdommer etter at du var i apotek i fjor?**

Flere kryss mulig

- ☐ Kreftsykdom
- ☐ Hjerte-kar hendelse
- ☐ Stoffskifte
- ☐ Annet
- ☐ Nei, ingen

11 Her kommer noen påstander om din deltagelse i studien. Hvor enig eller uenig er du i følgende:

Merk: Sett ett kryss på hver linje	Helt enig	Enig	Verken enig eller uenig	Uenig	Helt uenig
Jeg ble motivert til å få et sunnere kosthold etter jeg var i apotek og målte meg i fjor:	☐	☐	☐	☐	☐
Jeg ble motivert til å bli mer fysisk aktiv etter at jeg var i apotek og målte meg i fjor:	☐	☐	☐	☐	☐
Jeg ble motivert til å redusere forhøyede verdier etter at jeg var i apotek og målte meg i fjor:	☐	☐	☐	☐	☐
Jeg synes materiellet jeg fikk om hvordan jeg kan beskytte meg mot hjerte- og karsykdom, motiverte meg til å få et sunnere kosthold og bli mer fysisk aktiv:	☐	☐	☐	☐	☐
Jeg synes det å få vite mine verdier av kolesterol, blodtrykk og kolesterol motiverte meg til å få et sunnere kosthold og bli mer fysisk aktiv:	☐	☐	☐	☐	☐

12 Her kommer noen generelle påstander. Hvor enig eller uenig er du i følgende:

Merk: Sett ett kryss på hver linje	Helt enig	Enig	Verken enig eller uenig	Uenig	Helt uenig
Jeg opplever at fastlegen er positiv til å måle kolesterolet mitt:	☐	☐	☐	☐	☐
Jeg opplever at fastlegen er positiv til å måle blodtrykket mitt:	☐	☐	☐	☐	☐
Jeg opplever at fastlegen er positiv til å måle blodsukkeret mitt:	☐	☐	☐	☐	☐
Jeg er fornøyd med tilbudet om å måle kolesterol, blodtrykk og blodsukker i apotek:	☐	☐	☐	☐	☐
Jeg synes det er enklere å måle kolesterolet mitt på apotek enn hos legen:	☐	☐	☐	☐	☐
Jeg synes det er enkelt å finne informasjon om hvordan jeg kan redusere min hjerte-kar risiko:	☐	☐	☐	☐	☐
Jeg synes det er enkelt å vurdere om informasjon om plager/ sykdommer i media er pålitelige:	☐	☐	☐	☐	☐
Jeg synes det er enkelt å endre kostholdet mitt:	☐	☐	☐	☐	☐
Familien min gjør det enkelt for meg å spise slik jeg ønsker:	☐	☐	☐	☐	☐
Jeg mener kostholdet jeg har er sunt:	☐	☐	☐	☐	☐
Jeg mener å spise «lavkarbo» er riktig for å redusere risikoen for sykdom:	☐	☐	☐	☐	☐

13 I hvilken grad påvirker, etter din mening, følgende matvarer kolesterolnivået i blodet?

Merk: Sett ett kryss på hver linje	Øker mye	Øker litt	Nøytralt:	Reduserer litt	Reduserer mye
Karbohydrater	☐	☐	☐	☐	☐
Mettet fett	☐	☐	☐	☐	☐
Umettet fett	☐	☐	☐	☐	☐
Majones (ekte og lett)	☐	☐	☐	☐	☐
Meierismør	☐	☐	☐	☐	☐
Plantemargarin	☐	☐	☐	☐	☐
Kokosolje	☐	☐	☐	☐	☐
Karbonadedeig	☐	☐	☐	☐	☐
Kjøttdeig	☐	☐	☐	☐	☐

14 **Hvor viktig eller uviktig er følgende for å unngå hjerte-karsykdom?**

Merk: Sett ett kryss på hver linje	Svært viktig	Viktig	Verken viktig eller uviktig	Ikke viktig	Svært uviktig
Spise mindre karbohydrater	☐	☐	☐	☐	☐
Spise mindre fett	☐	☐	☐	☐	☐
Spise mindre mettet fett	☐	☐	☐	☐	☐
Spise mindre salt	☐	☐	☐	☐	☐
Mosjonere i 30 minutter eller mer hver dag	☐	☐	☐	☐	☐
Være normalvektig	☐	☐	☐	☐	☐
Følge helsemyndighetenes kostråd	☐	☐	☐	☐	☐

Takk for hjelpen!

Appendix 3

DITT KOLESTEROLNIVÅ

Du har nå fått målt ditt kolesterolnivå.
Totalkolesterol kan gi en pekepinn på om du bør ha økt bevissthet på hjertesunne levevaner, men sier ikke noe om forholdet mellom det gode HDL-kolesterolet og det ugunstige LDL-kolesterolet.

I Norge er gjennnomsnittlig totalkolesterol omkring 5,8 mmol/l. Hos friske voksne er anbefalt totalkolesterolnivå under 5 mmol/l. Høyere verdier skal ikke automatisk betraktes som farlig, og gir i seg selv ikke grunn til å starte med medisiner. Hvis totalkolesterolet ditt er over 7,8 mmol/l bør du ta kontakt med din fastlege og få målt LDL-kolesterol og HDL-kolesterol. Legen kan også vurdere om du har andre risikofaktorer.
Alle med forhøyet totalkolesterol tjener på livsstilsendringer. Både økt fysisk aktivitet, røykeslutt og et kosthold med lite mettet fett påvirker kolesterolet i gunstig retning.

	Tilfredsstillende	Lett forhøyet	Moderat forhøyet	Klart forhøyet
Totalkolesterol	< 5 mmol/l	5-6,4 mmol/l	6,4-7,8 mmol/l	>7,8 mmol/l

Totalkolesterol (mmol/l)		Boots apotek	Signatur
Dato			

sjekkedagen.no

VÆR FYSISK AKTIV
Voksne bør være fysisk aktive minst 30 minutter om dagen. Bruk bena og sykkelen fremfor bilen. Ta trap-pen i stedet for heisen.

Med jevnlig fysisk aktivitet vil det gode kolesterolet (HDL) øke, blodtrykket synke, vekten stabiliseres og du får mer overskudd.

SJEKK FAMILIEHISTORIEN
Risikoen for hjerte- og karsykdommer kan være dobbelt så høy når foreldre eller søsken er rammet i tidlig alder. Har du noen i nær familie som er rammet, er det desto viktigere å følge de hjertesunne rådene.

VI BRYR OSS OM HJERTET

Nasjonalforeningen for folkehelsen er en frivillig, humanitær organisasjon med helselag og de-mensforeninger over hele landet. Vårt mål er å bekjempe hjerte- og karsykdommer og demens. Dette gjør vi med forskning, informasjon, forebyggende tiltak og helsepolitisk arbeid. Har du spørsmål om hjerte- og karsykdommer og sunn livsstil, ring vår Hjertelinje, 23 12 00 50.

www.nasjonalforeningen.no

I **Boots apotek** bryr vi oss om helsen din. For oss er det viktig å bidra med gode råd, slik at du kan ta et aktivt valg for en sunnere hjertehelse. I alle våre 150 Boots apotek kan du måle ditt kolesterolnivå og få informasjon om hjertesunne levevaner.

www.boots.no **facbook/bootsapotek** **@bootsapotek**

Mills DA er en norsk matvarebedrift som ønsker å gjøre det enkelt å samles rundt sunn og god mat. Gjennom våre merkevarer og særlig Vita hjertego'-produktene kommer vårt fokus på helse- og ernæring forbrukeren til gode, med høyt innhold av det gunstige, umettede fettet. I Mills er vi opptatt av å utvikle produkter i tråd med Helsemyndighetene sine anbe-falinger.

www.vitahjertego.no **www.suntfett.no** **#suntfett** **@suntfett_no**

Grete Roede as Grete Roede as er landets ledende leverandør av sunn vektreduksjon og hold-er kurs på over 350 steder i landet samt på nett. Roede-metoden er en helthetlig metode med fokus på hele mennesket, kosthold og trening, motivasjon og mental trening. Vi er opptatt av å hjelpe den enkelte med å gå ned i vekt og legge om til sunne vaner.

www.greteroede.no

SJEKK DITT KOLESTEROLNIVÅ I BOOTS APOTEK 8.-13. SEPTEMBER 2014
sjekkedagen.no

DEN STORE SJEKKEDAGEN 2014

Den store sjekkedagen er en folkeopplysningskampanje om kolesterol og hjertehelse. Det er viktig at du tar vare på hjertet ditt – og det er ikke vanskelig. Hjerte- og karsykdommer er den største dødsårsaken i Norge, og høyt kolesterol er en av de viktigste risikofaktorene. Kjenner du ditt kolesterolnivå og har kunnskap om hjertesunne levevaner, har du et godt utgangspunkt for å gjøre de riktige grepene for god hjertehelse.

Hjertet er din viktigste muskel. I hvile slår hjertet vanligvis mellom 60-80 slag i minuttet og i løpet av en hel dag har det slått minst 86 000 slag. Hjertet hviler aldri, det jobber hvert sekund og tar seg aldri en pust i bakken. Hjertets oppgave er å holde deg i live - din oppgave er å ta vare på hjertet ditt.

Husk at små grep i hverdagen kan ha store effekter på helsen din.

KJENN DINE VERDIER
- Kolesterolnivå
- Blodtrykk
- Blodsukker
- BMI

HJERTE- OG KARSYKDOMMER

Hjerte- og karsykdommer er en samlebetegnelse for sykdommer som oppstår i hjertet og blodårene. De to vanligste er hjerteinfarkt og hjerneslag. Sykdommene skyldes at kolesterol avleires i blodåreveggen og medfører åreforkalkning. Dersom en blodåre blir helt tilstoppet rundt hjertet eller i hjernen oppstår et hjerteinfarkt eller et hjerneslag. Hjerte- og karsykdommer kan i stor grad forebygges med sunne levevaner.

STUMP RØYKEN
Røyker du er røykestopp det beste du kan gjøre for helsen din.
Røyking øker LDL-kolesterolet og reduserer HDL-kolesterolet.

KOLESTEROL

Høyt kolesterol kan ikke merkes på kroppen.
Maten vi spiser påvirker kolesterolnivåene i blodet. Anbefalt verdi for totaltkolesterol er 5 mmol/l. Høyt inntak av mettet fett øker kolesterolet.

I blodet finner vi kolesterol som LDL-kolesterol (det dårlige kolesterolet) og HDL-kolesterol (det gode kolesterolet). LDL-kolesterol kan bidra til at fett og kolesterol avleires i åreveggene og føre til at blodårene tettes. HDL-kolesterolet frakter kolesterol til leveren hvor det kan skilles ut.

FORSKNING PÅ HJERTEHELSEN

Antall hjerte- og karsykdommer har gått betraktelig ned de siste 30 årene. Likevel er det fortsatt de mest utbredte livsstilssykdommene i Norge. Viktige risikofaktorer for hjerte- og karsykdommer er blodsukker, blodtrykk og kolesterol. Du kan ikke kjenne på kroppen om du har høyt kolesterol, og ofte ikke om blodtrykket eller blodsukkeret er høyt. Du må derfor måle deg for å kjenne ditt nivå. Små endringer i livsstil og kosthold vil kunne senke nivået ditt betydelig, og dermed redusere risikoen din for sykdom.

Under **"Den store sjekkedagen"** gjennomføres det en studie som del av et doktorgradsprosjekt ved Universitet i Oslo. Hensikten med studien er å kartlegge nordmenns nivåer av sentrale risikofaktorer for hjerte- og karsykdommer. Studiet vil vurdere om apotek er en egnet arena for enkle helsetjenester.

UiO : Universitetet i Oslo

SPIS HJERTESUNT

Å spise hjertesunt er gunstig for alle. Et sunt kosthold handler om variasjon, og ikke nødvendigvis om å kutte ut matvarer. Følger du myndighetenes kostråd kan du være trygg på at dette er råd som er godt dokumentert. Det er overbevisende dokumentasjon på at å erstatte mettet fett i kosten med umettet fett bidrar til å opprettholde normale kolesterolverdier og derfor reduserer risikoen for hjerte- og karsykdommer.

Det er ikke mye som skal til å gjøre kostholdet mer hjertesunt. Det handler om å spise mye grønnsaker, frukt og bær, grove kornvarer, mindre sukker, mindre salt og velge matvarer som inneholder umettet fett fremfor mettet fett. Vita hjertego'-produktene har et høyt innhold av det gunstige umettede fettet og bør derfor inngå i et hjertevennlig kosthold.

Sjekk bytt-ut-listen på
www.suntfett.no

SUNTFETT.no

Vita hjertego