Diet and risk of cardiovascular disease in the adult Norwegian achondroplasia population

Master thesis by Andrea Madsen

Supervisors: Hanne Bjørg Slettahjell and Christine Henriksen

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http://www.duo.uio.no

Trykk: Reprosentralen, Universitetet i Oslo

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Oslo, May 2018
Andrea Madsen

Abstract

Introduction: Achondroplasia is the most common form of skeletal dysplasia, and studies from other parts of the world show a high prevalence of obesity and risk of cardiovascular disease in the achondroplastic population. Diet is one of many factors that affect the risk of obesity and cardiovascular disease, and there are no studies describing the diet of those with achondroplasia. The main aim of this study was to describe the diet and risk of cardiovascular disease in the adult Norwegian achondroplasia population.

Methods: Adults with achondroplasia living in Norway and participating in "The Norwegian Adult Achondroplasia Study", was invited to participate in this master thesis with a cross-sectional design. Risk factors for cardiovascular disease were assessed by anthropometrics, in addition to blood pressure measurements and a blood test. Blood samples were analyzed for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides. SmartDiet and four-day dietary record was used for collection of dietary data and lifestyle habits. The 10-year risk of cardiovascular disease was estimated using NORRISK 2. Resting energy expenditure (REE) was measured and estimated for all participants using indirect calorimetry and two prediction equations.

Results: A total of 33 achondroplastic individuals with the mean age of 40 years participated. None of the participants had elevated total cholesterol. Mean BMI was 34 kg/m^2, and mean waist circumference was 94.1 cm and 82.2 cm for the men and women respectively. Their diet was classified as unhealthy (38 %) or in need of improvements (62 %). Median intake of macronutrients was in accordance with the recommendations, except for dietary fiber and saturated fatty acids. Micronutrient intake was low, especially vitamin D and folate. The mean REE was 1416 kcal/day and 1110 kcal/day for the men and women respectively. Mean energy intake was 1569 kcal/day for the men and 1287 kcal/day for the women. Calculations by use of the Mifflins equation overestimated REE by 24 % compared to measured REE.

Conclusion: This cross-sectional study indicated a low overall risk of cardiovascular disease in this young adult Norwegian achondroplasia population. The high frequency of central obesity and unhealthy diet may however lead to cardiovascular disease later in life, and we suggest that diet and life-style counseling should be offered to this patient group.

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Abbreviations

25(OH)D 25-hydroksy-vitamin D

ω-3 Omega-3

ω-6 Omega-6

ALA Alpha-linolenic acid

ARG Arginine

BP Blood pressure

CI Confidence interval

CONOR Cohort of Norway

CVD Cardiovascular disease

CVD-NOR Cardiovascular Disease in Norway

DASH Dietary Approaches to Stop Hypertension

DHA Docosahexaenoic acid

DNA Deoxyribonucleic acid

e.g. For example

EPA Eicosapentaenoic acid

FA Fatty acid

FGFR3 Fibroblast Growth Factor Receptor 3

GLY Glycine

HBEs (Harris Benedict equations)

HDL High-density lipoprotein

HR Hazard ratio

IC Indirect calorimetry

KCAL kilocalories

LDL Low-density lipoprotein

MJ Megajoule

MSJEs (Mifflin-St Jeor equations)

MUFA Monounsaturated fatty acid

NaCl Sodium chloride

NHANES National Health and Nutrition Examination Survey

NiK Norwegian Association of Short Stature

NORKOST 3 A Norwegian national nutrition examination survey from 2010/2011

PAL Physical activity level

PREDIMED Prevención con Dieta Mediterránea

PUFA Polyunsaturated fatty acid

RCT Randomized controlled trial

REE Resting energy expenditure

ROS reactive oxygen species

RR Risk ratio

SFA Saturated fatty acid

SSB Sugar-sweetened beverages

TE Tocopherol equivalents

TG Triacylglycerol

TMD Traditional Mediterranean diet

TRS National Resource Centre for rare Disorders

VLDL Very low-density lipoprotein

1 Introduction

1.1 Achondroplasia

Achondroplasia is a rare autosomal dominant genetic condition, and the most common form of skeletal dysplasia (1). There are approximately 150 persons with achondroplasia in Norway, and 3-4 newborns are diagnosed each year, with a prevalence between 1:15 000 – 1:25 000 (1, 2). Diagnostics are based on radiographic and clinical findings at birth, and a genetic test can confirm the diagnose (3, 4). Achondroplasia results in short stature due to a mutation, inherited or sporadic, on the short arm of the paternal segment of chromosome 4 in the gene coding for Fibroblast Growth Factor Receptor 3 (FGFR3) (1, 3). The most common mutation is substitution of glycine to arginine (Gly380Arg) in the transmembrane domain of FGFR3 due to a point-mutation at 1138 of the cDNA for the receptor, see Figure 1 (5, 6). The mutation leads to increased signaling of FGFR3 which results in decreased bone elongation due to increased inhibition of chondrocyte differentiation and proliferation (1, 5). In addition, the mutation in FGFR3 may lead to an abnormal energy metabolism that result in a predisposition for abdominal obesity (7).

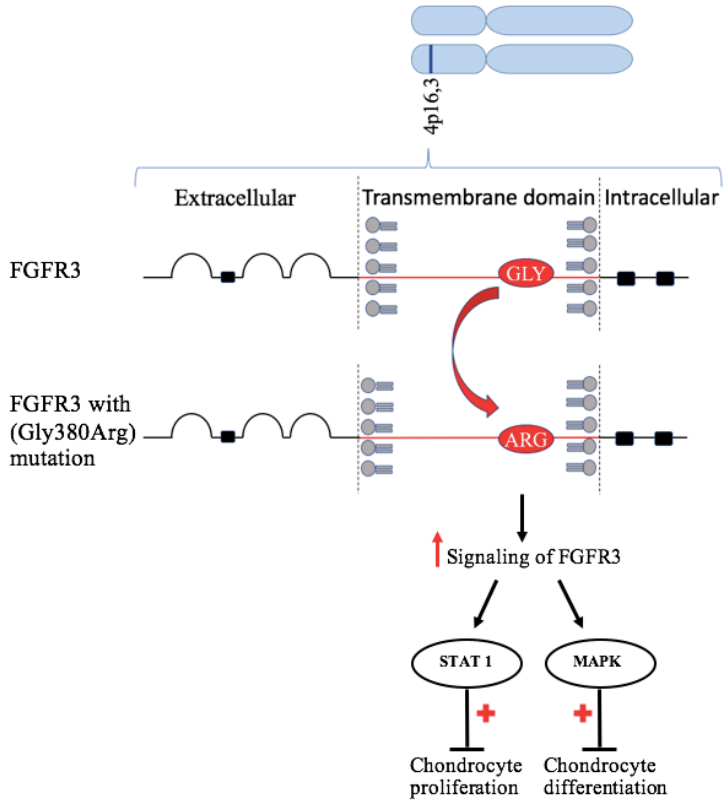

Figure 1: Mutation in FGFR3 that causes short stature

Normal length of the trunk and short extremities is the most characteristic of achondroplasia (5). Typical anomalies in addition to short limbs are genu varum, a large head with a prominent forehead and excessive lumbar lordosis, see Figure 2 (1, 3, 8). Achondroplasia is not more common among a specific gender or race, and do not affect the IQ (3, 8). The anticipated height and weight for adult females are 112-136 cm and 46 kg, and for adult males 118-145 cm and 55 kg (4, 8).

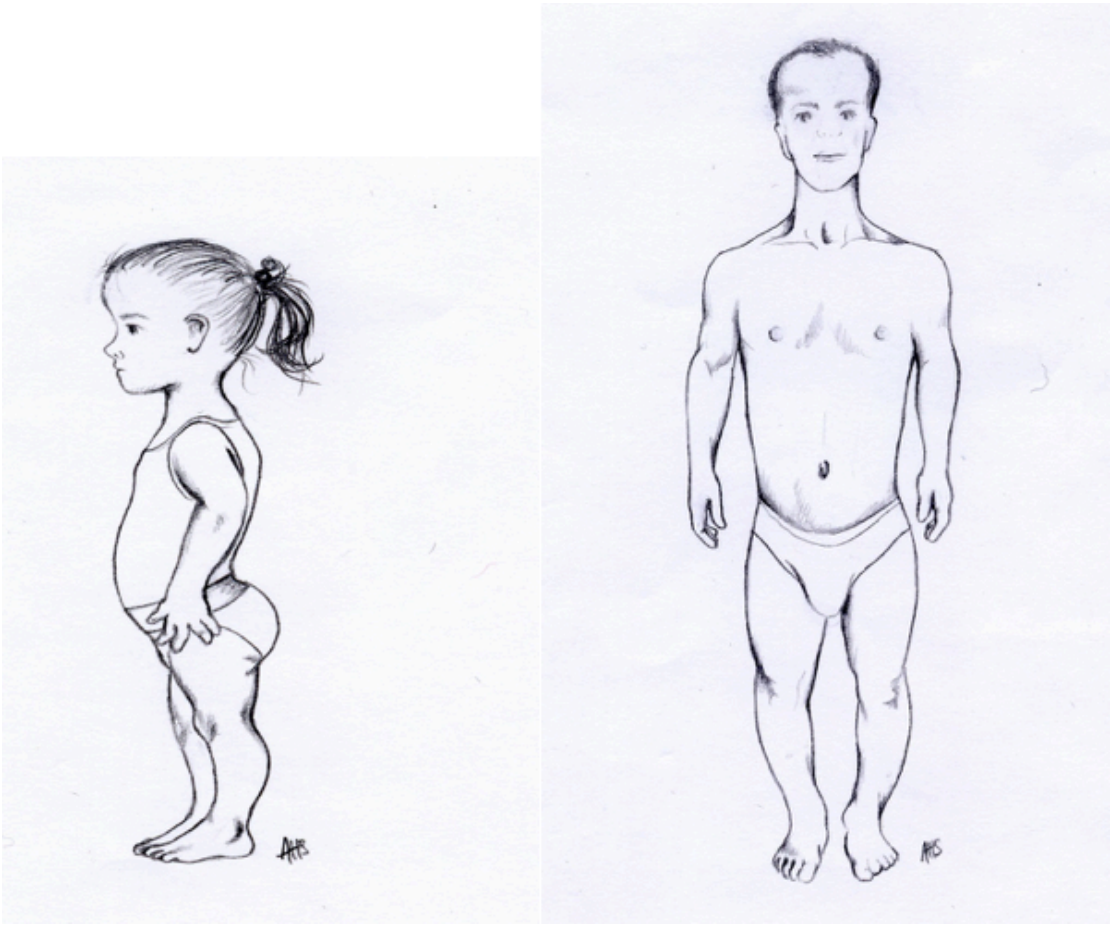

Figure 2: Characteristics of achondroplasia

Illustration: Annette Holth Skogan

Used with permission from National Resource Centre for rare Disorders (TRS)

Complications as sleep apnea, otitis media, hydrocephalus and spinal stenosis often follows with the disorder (8, 9). A cross-sectional study on pain and physical function in skeletal dysplasia patients reported a higher prevalence of pain among achondroplastic individuals compared to the general American population (10). Despite the high prevalence of pain, most of the subjects reported to have good mobility and no difficulty walking (10). However, a Finnish study on genetic skeletal dysplasias reported that achondroplastic individuals have

lower health-related quality of life compared to the general population, partially due to poorer mobility and difficulties with daily activities (employment, housework, free-time activities) (11). High prevalence of pain and low health-related quality of life have also been reported among achondroplastic Americans (12). Studies from other parts of the world show that the achondroplastic population has an increased risk of obesity, cardiovascular disease (CVD) and overall mortality (9, 13-15). Adults with achondroplasia have a heart disease-related mortality at all ages that is two times higher than the general American population (9). The heart disease-mortality among young adults with achondroplasia have been found to be even more critical, with a ten times higher heart disease-related mortality compared to the general American population (9). The reason(s) for the increased risk of obesity and CVD is currently unknown (9, 13, 14), but both genetic and lifestyle factors may be involved.

There are no studies describing the diet of those with achondroplasia and the prevalence of obesity in the Norwegian achondroplasia population is uncertain. Studies investigating the diet in the achondroplastic population is therefore needed to explore diet as a contributing factor to the increased risk of obesity and CVD.

1.2 Risk factors for cardiovascular disease

1.2.1 Cardiovascular disease

Cardiovascular disease is a collective term for several diseases of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral arterial disease among other (16). Atherosclerotic lesions are thickenings of the intima, the innermost layer of the artery, and the main cause of coronary heart disease (17). Several cardiovascular risk factors have been established, and the largest epidemiological study of CVD, The Framingham Heart Study, was the first to use the concept of risk factors in relation to CVD (18, 19).

1.2.2 Non-modifiable risk factors

Health in adulthood is being shaped already early in life. Socioeconomic status, health early in life and genetic factors affect the risk of developing CVD later on (20-24). Studies have shown that low birth-weight, which is often related to a poor socioeconomic status and a maternal inadequate diet during pregnancy, is associated with an increased risk of CVD (20, 23). Furthermore, maternal diet and obesity during pregnancy affects the offspring's risk of CVD (24). Several genetic loci have been found to be associated with CVD, where 25-30 %

are related to lipid metabolism and blood pressure (25). Familial hypercholesterolemia is a well-known genetic hereditary disease that gives predisposition to elevated cholesterol levels and premature coronary artery disease due to mutation in genes of the lipid metabolism (25). Sex and age also influences the risk of cardiovascular disease (18). The incidence of cardiovascular diseases are higher among men than women, and the risk increases with age (18). Being above the age of 45 years for men and 55 years for women is considered a risk factor for CVD (18).

1.2.3 Modifiable risk factors

There are several modifiable risk factors for CVD, such as low-density lipoprotein (LDL) cholesterol, serum triglycerides (TG) concentrations, hypertension, obesity, physical inactivity, use of tobacco and diet (26, 27).

Cholesterol and triglycerides

Elevated plasma LDL cholesterol increases the risk of CVD (28). LDL and oxidised LDL contributes to the development of atherosclerotic lesions (17, 29). In addition to LDL oxidation, the composition of cholesterol, TG and proteins in the LDL particle also plays a role for the atherogenic effect of the LDL particles, see Figure 3 and 4 (30).

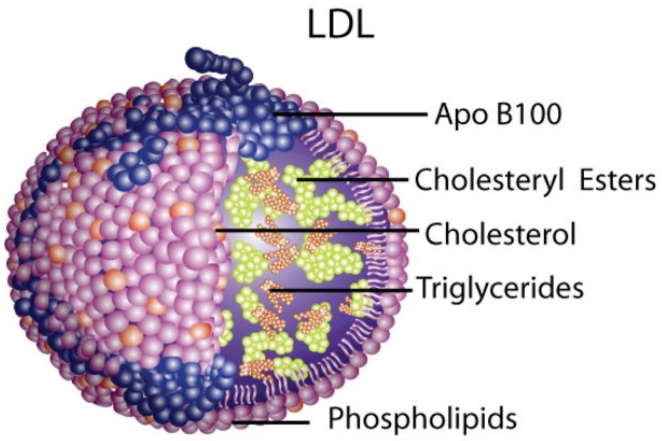

Figure 3: Components of the LDL particle

Retrieved from sigmaaldrich.com (https://www.sigmaaldrich.com/catalog/product/sigma/l7914?lang=en&region=NO)

Very low-density lipoproteins (VLDL) are precursors to LDL, and VLDL concentrations affects the serum TG levels, which is a strong risk factor for coronary heart disease (31). While high levels of LDL and VLDL cholesterol increases the risk of CVD, high levels of HDL cholesterol seem to have a cardioprotective role (32, 33). There are no studies reporting cholesterol levels in achondroplastic subjects.

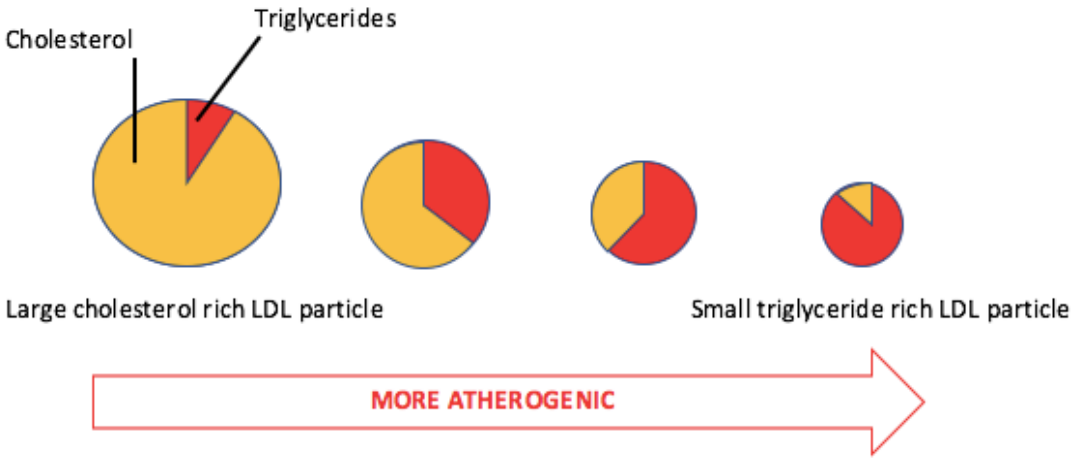

Figure 4: Composition of the LDL particle

Hypertension

Hypertension is an important risk factor for cardiovascular disease and the prevalence has dramatically increased worldwide (34-36). Hypertension is defined as high blood pressure, with systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg (37). Even a modest reduction in blood pressure can reduce the cardiovascular risk in the long term as much as 30-40 % (38). There are no studies investigating the prevalence of hypertension among achondroplastic individuals.

Obesity

Obesity is defined as body mass index (BMI), weight divided by height squared, ≥ 30 kg/m^2 (39), see Table 1. Obesity is strongly associated with several vascular risk factors, such as hypertension, systemic oxidative stress, endothelial dysfunction and low HDL cholesterol, and it is also positively associated with CVD (40-42). Increased waist circumference reflect central obesity, and a waist circumference >94 cm for men and >80 cm for women increases the risk of metabolic complications (43, 44). A waist circumference ≥102 cm for men and ≥88 cm for women is associated with an increased prevalence of CVD risk factors (45).

Waist circumference can therefore be used to predict CVD risk (43). Obesity-related cardiovascular risk factors can be improved with weight reduction in obese and overweight individuals (41, 46). The World Health Organization (WHO) recommend a combined use of BMI and abdominal measurements for the prediction of disease risk (43).

Table 1: International classification of adult underweight, overweight and obesity according to BMI (WHO)

Classification	*BMI (kg/m^2)
Underweight	< 18.5
Normal range	18.5-24.9
Overweight	≥ 25.0
Obese	≥ 30.0
Obese class I	30.0-34.9
Obese class II	35.0-39.9
Obese class III	≥ 40.0

*BMI (Body Mass Index)

The definition of obesity is dependent on height, hence it may be problematic to use BMI as a measure for body fat content in achondroplasia. One study found a 43 % prevalence of obesity in achondroplasia when BMI were used, and a 13 % prevalence when skinfold thickness were used (13). Another study found that abdominal obesity is particularly prominent in achondroplasia (40). Waist circumference and abdominal obesity is highly correlated (44), and waist circumference may therefore be a more accurate method for evaluating body fat content in achondroplasia than BMI. Obesity is an increasing problem in the general population, but it appears to give more adverse consequences for individuals with achondroplasia due to their short stature (47). Even a modest weight gain can exacerbate complications of the disorder such as sleep apnea and spinal stenosis, and perhaps also the risk of cardiovascular disease (47).

Physical activity

WHO defines physical activity as *any bodily movement produced by skeletal muscles that requires energy expenditure* (48). The interest of physical activity in association to CVD evoked already in the 1950s (19). Daily physical activity of moderate intensity has significant

health benefits, such as reduced risk of several non-communicable diseases as CVD and diabetes mellitus (48). The Norwegian Directorate of Health recommend at least 150 minutes activity of moderate intensity per week for adults (49). Energy balance, energy intake relatively equal to energy expenditure, is important to avoid obesity (50). A cross-sectional study of 430 participants showed that energy expenditure from sedentary and light activities were positively associated with BMI (50). The proportion of activity with moderate intensity were significantly lower among obese participants compared to participants within normal weight range (50). The same study also stated that activity of moderate-to-vigorous intensity is essential for weight management (50). Physical activity can be challenging for those with achondroplasia due to genu varum, spinal stenosis, pains or other complications that follows the disorder (10, 51).

Cigarette smoking and snuff

Cigarette smoking increases the risk of heart disease, this finding was the first milestone in the Framingham Heart Study (18, 52). Cigarette smoke contains reactive oxygen species (ROS) and in addition to supply the body with ROS, cigarette smoking leads to an increased production of ROS in the body, which leads to oxidative stress (53, 54). There is clear evidence for a positive association between oxidative stress and CVD (53). Cigarette smoking has toxic effects on the heart, such as fibrosis, necrosis and myocardial ischemia, in addition to indirect effects like increased blood pressure and cholesterol (54). Smoking increases the risk of CVD and smoking cessation is the most important single factor for reducing cardiovascular risk (27, 37, 55). Advice and guidance on smoking cessation give lifelong benefits on CVD risk (27). The association between snuff and risk of CVD is uncertain (56), however a systematic review and meta-analysis of twenty epidemiological studies showed an increased risk of fatal CVD among snuff users (57). Use of snuff can affect functions of the heart, and leads to increased blood pressure and heart rate (56). However, use of snuff in the long-term appears to not be associated with a permanent increase in blood pressure (56).

1.2.4 NORRISK 2

The Norwegian Institute of Public Health has developed a risk calculator, NORRISK 2, that calculates the 10-year risk of acute myocardial infarction or stroke, including cardiovascular death (58). NORRISK 2 is based on information about sex, smoking, use of antihypertensive

drugs, age, SBP, total cholesterol, HDL cholesterol and information about first-degree relatives with heart attack before the age of 60 years (58). In addition to these risk factors there are some additional factors that should be taken into consideration to get a complete risk assessment, such as abdominal obesity (>100 cm for men and >88 cm for women) (37). The risk calculator is based on data from the Cohort of Norway (CONOR) and Cardiovascular Disease in Norway (CVDNOR) (37). In the Norwegian national guidelines for prevention of CVD it is recommended to use NORRISK 2 to evaluate the 10-year risk of CVD and the need for preventive medications (37). If the estimated risk is ≥ 5 % for individuals in the age group 45-54 years, ≥ 10 % for the age group 55-64 years and ≥ 15 % in the age group 65-74 years, advice on lifestyle changes should be given, such as increased physical activity and healthy dietary habits. Medical treatment should be initiated if advice on lifestyle changes have not given sufficient effects after 3-12 months, or if total cholesterol is ≥ 7 mmol/L, LDL cholesterol ≥ 5 mmol/L (except in women above the age of 50 years without other CVD risk factors) or SBP ≥160 mmHg (37).

1.3 Diet and risk of cardiovascular disease

1.3.1 Dietary patterns

A healthy diet is important to maintain good health and to prevent non-communicable diseases, as CVD (59). It is well established that diet affects the risk of cardiovascular disease, directly or through risk factors such as blood pressure and cholesterol (60-62). How different dietary patterns as well as different components of the diet affects the risk of CVD has been widely investigated (60-63). There is strong evidence for a causal link between dietary patterns and cardiovascular risk (60). The traditional Mediterranean diet (TMD), the DASH (Dietary Approaches to Stop Hypertension) diet, the New Nordic Diet, a plant-based diet and the Western dietary pattern are some of the dietary patterns that have been widely investigated in association to risk of CVD and are presented in Table 2.

Table 2: Overview of dietary patterns

	Traditional Mediterranean diet	[a] DASH diet	New Nordic diet	Plant-based diet	Western dietary pattern
Effect on[b] CVD risk	**Reduced risk**	**Reduced risk**	**Reduced risk**	**Reduced risk**	**Increased risk**
High intake of:	Fruits, vegetables, nuts, beans, seeds, extra virgin olive oil	Fruits, vegetables, low-fat dairy products, whole grains, poultry, fish and nuts	Plant foods, fish, shellfish	Plant foods	Red and processed meat, high-fat dairy products, refined grains, egg
Moderate intake of:	Fish, poultry	Vegetable oils, mayonnaise	Rapeseed oil	Egg, fish, dairy products	
Low intake of:	Red meat, salt, refined grains, added sugar	Red meat, salt, cholesterol, total fat, [c] SFAs, added sugar	Meat, added sugar salt, refined grains	Cholesterol, sodium, animal products, sugar, fat	Fruits, vegetables, legumes, whole grains fish

[a] DASH (Dietary Approaches to Stop Hypertension)

[b] CVD (Cardiovascular Disease)

[c] SFA (Saturated Fatty Acid)

The traditional Mediterranean diet is characterised by high intake of fruits, vegetables, nuts, beans and seeds, a moderate intake of fish and poultry and a low intake of red meat (64). The diet is low in saturated fat (<7-8 E%), and the main source of fat is olive oil. The TMD is based on the dietary pattern seen in southern Italy and Greece in the early 1960s, where the risk of diet-related chronic diseases, as coronary heart disease, were among the lowest in the world (64). The many health benefits of this diet may be due to the high intake of minerals and vitamins, antioxidants, fiber, monounsaturated fatty acids and ω-3 fatty acids (65). The DASH diet is rich in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish and nuts (66). In addition, the diet promotes a low intake of red meat, sugar-containing beverages, sweets, total fat, cholesterol and saturated fat. The American Heart Association recommend DASH diet for non-pharmacological treatment of hypertension (66). Another dietary pattern that is important to include is the New Nordic Diet. The idea behind the diet was to develop a healthy diet based on Nordic and Northern European food culture (67). Health (e.g. prevention of obesity and CVD), gastronomic potential, Nordic identity and sustainability is important principles of the diet (67). The New Nordic diet is characterised by a low intake of meat and a high intake of plant foods, fish and shellfish (67). A plant-based diet has been shown to improve CVD risk factors and is therefore an important dietary pattern for preventing CVD (68). A plant-based diet is low in cholesterol, sodium, animal products, sugar and fat, have a moderate intake of eggs, fish and dairy products and a high intake of plant-based foods such as vegetables and legumes (68). The dietary patterns mentioned above have several similarities, and are often referred to as healthy or prudent dietary patterns.

The Western dietary pattern differs from the patterns aforementioned, and is often referred to as an unhealthy dietary pattern. It is characterised by a high intake of red and processed meat, butter, high-fat dairy products, refined grains and eggs, and a low intake of fruits, vegetables, legumes, whole grains and fish (69). The Mediterranean dietary pattern is significantly associated with a reduced risk of cardiovascular disease, while the Western dietary pattern is significantly associated with an increased cardiovascular risk (60).

The Norwegian Directorate of Health has developed twelve dietary advice to improve the public health and prevent chronic diseases in Norway (70). The dietary advice are based on a large amount of international and Norwegian research on diet and health (71). The recommendations are applicable for the general Norwegian population; children, adolescents, adults, pregnant and nursing women and the elderly. Moreover, the recommendations are also suitable for individuals with hypertension or overweight, in addition to individuals with increased risk of disease. Abbreviated, the Norwegian Directorate of Health recommends a healthy Nordic diet rich in fruits, vegetables, berries, whole grain, fish and low-fat dairy products, and a low intake of red and processed meat, added sugar and sodium (72). The Norwegian National Guidelines for prevention of CVD is consistent with the dietary recommendations from the Norwegian Directorate of Health (37, 72).

1.3.2 Effect of dietary patterns on cardiovascular risk

Dietary patterns and cholesterol

Dietary patterns have both beneficial and adverse effects on blood lipid profile (31, 66, 73-79). The traditional Mediterranean diet, the DASH diet and a healthy Nordic diet is associated with a beneficial blood lipid profile, opposed to the Western dietary pattern which is associated with an adverse blood lipid profile.

The PREDIMED study, a multicenter and randomized trial, investigated the benefits of the traditional Mediterranean dietary pattern for the primary prevention of cardiovascular disease (80). The participants had no cardiovascular disease at enrollment, but were at high cardiovascular risk (80). The PREDIMED study found that the traditional Mediterranean diet supplemented with extra-virgin olive oil or nuts reduce total cholesterol, LDL-cholesterol, VLDL-cholesterol and triglycerides, in addition to increase HDL-cholesterol (31).

Randomized controlled trials (RCTs) on subsamples of participants from the PREDIMED study found that the traditional Mediterranean diet supplemented with extra-virgin olive oil or nuts was associated with decreased oxidation of LDL particles, increased resistance against LDL-oxidation and less atherogenic LDL particles (low in triglycerides and proteins and rich in cholesterol) (30). In addition, the diet was found to improve the atheroprotective functions of HDL (32). A systematic review of RCTs that investigated the effect of the DASH diet on cardiovascular risk found that the DASH diet significantly reduced LDL concentrations and total cholesterol (66). Systematic reviews and randomized controlled trials, in addition to large cohorts have found an inverse association between the traditional Mediterranean dietary pattern and the DASH diet and oxidised LDL concentrations (30, 65, 66, 81, 82), which contributes to the development of atherosclerotic lesions (17). The protective effects are most likely due to the high content of antioxidants and the favorable fatty acid pattern in the two diets (30, 66).

A systematic review with meta-analysis of observational studies investigated the effect of vegan and vegetarian diets on different health outcomes (83). The meta-analysis included eighty-six cross-sectional studies and the results showed that vegans and vegetarians had significantly lower total cholesterol and LDL-cholesterol compared to omnivores (83). A RCT investigating the health effects of the New Nordic diet in adults with increased waist circumference showed that the diet significantly reduced total cholesterol, VLDL cholesterol and plasma TG compared to the average Danish diet (76). Studies have shown that a healthy Nordic diet that complies with the dietary advice given by The Norwegian Directorate of Health lowers total cholesterol and LDL-cholesterol (77). However, dietary patterns can also have adverse effects on blood lipid profile, like the Western dietary pattern, which is associated with a higher total cholesterol and LDL cholesterol and lower HDL cholesterol (73, 74, 78, 79).

Dietary patterns and blood pressure

The DASH diet was designed as a strategy to stop hypertension, and a review of seventeen RCTs showed that this dietary pattern has significant positive effects on blood pressure in adults (34). Another systematic review of RCTs stated that the improvements in blood pressure and cholesterol concentrations seen with the DASH diet would reduce the 10-year risk of CVD with approximately 13 % (using the Framingham risk equations) (66). The PREDIMED trial evaluated if complying with recommended sodium intake would have

beneficial effects for cardiovascular health and found that the risk of having a major cardiovascular event increased for participants that increased their sodium intake to >2300 mg/day after one and three years of follow-up (84). The results also showed that the beneficial effects of the traditional Mediterranean diet on cardiovascular risk could be enhanced with a reduction in sodium intake to <2300 mg/day (84). Furthermore, the PREDIMED trial showed that the traditional Mediterranean diet supplemented with either nuts or extra-virgin olive oil had lowering effect on SBP (31). A review of fifteen studies investigating health effects of a healthy Nordic diet found that this dietary pattern also has blood pressure lowering effects (77).

1.3.3 Food groups and risk of cardiovascular disease

Studies have found strong evidence for a causal link between consumption of fish, fruits, vegetables, legumes, whole grains, olive oil, nuts, red and processed meat and cardiovascular risk, see Table 3 (60, 61).

Table 3: Food groups and risk of cardiovascular disease

Foods with protective effects on CVD* risk	Foods that increses the risk of CVD*
Fish	Red meat
Fruits	Processed meat
Vegetables	Sugar-sweetened beverages
Legumes	
Nuts	
Whole grains	
Olive oil	

Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169(7):659-69.
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.
*CVD (Cardiovascular disease)

Dietary fat intake

Findings from the latest reviews show that it is fat composition rather than total fat intake and low-fat diets that has an impact on cardiovascular risk (85, 86). Several studies have investigated the effect of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) on cardiovascular risk (62, 80, 87-95). SFAs increases cardiovascular risk by increasing LDL cholesterol (89). A high

intake of MUFAs reduces the risk of coronary heart disease through different mechanisms, such as inactivation of a transcription factor in cholesterol synthesis (sterol regulatory element-binding protein) and increased oxidation of fatty acids and expression of hepatic LDL receptor (89). PUFAs, long chain ω-3 and ω-6 fatty acids, contribute to several anti-inflammatory effects through different mechanisms, such as synthesis of less biologically active leukotrienes and prostaglandins and reduction of inflammatory cytokines, in addition to antithrombotic effects (87, 92).

The PREDIMED trial evaluated the association between fat subtypes and total fat intake on cardiovascular risk in high-risk individuals (91). A lower cardiovascular risk was found in subjects with the highest intake of total fat, MUFAs and PUFAs, while a higher cardiovascular risk was found in subjects with the highest intake of SFAs and trans fatty acids (91). Furthermore, the study found that the effect of SFAs was dependent on the source of SFA. The analysis showed a trend of SFAs from fish and vegetal sources (oil, nuts, margarine and vegetables) to be associated with lower cardiovascular risk, while SFAs from processed foods and pastries tended to be associated with a higher cardiovascular risk (91). The PREDIMED trial also showed that it is preferable to have a diet rich in unsaturated fat from natural vegetable sources than a low-fat diet to reduce the risk of cardiovascular disease (91). Findings from systematic reviews show a reduced risk of CVD events with a reduced intake of saturated fat by exchanging SFAs with PUFAs (90, 96). The long-term trials in one of the reviews showed that a reduction in dietary SFAs gave a significantly 17 % reduced risk of CVD events (90). Randomized controlled trials show that replacing a diet rich in SFA with a diet rich in MUFAs, PUFAs or carbohydrates (whole grain) significantly reduce total cholesterol and LDL cholesterol (28, 89).

The PREDIMED trial also investigated the effect of α-linoleic acid and marine ω-3 fatty acids on CVD, and found that individuals with a combined fish-derived eicosapentaenoic- and docosahexaenoic acid (EPA and DHA) consumption above 500 mg/day had 39 % significant reduced risk of CVD (88). A systematic review and meta-analysis of prospective studies showed a significant protective effect of fish consumption on cardiovascular risk (62). In addition, a review of clinical trials investigating the effect of fish consumption on biomarkers for cardiovascular risk, also found a beneficial, but weak, effect of frequent consumption of fish on cardiovascular risk (97). Omega-3 supplementation does not seem to

have the same beneficial effects as fish-derived EPA and DHA (98). Olive oil and nuts are part of the TMD and a source of unsaturated fatty acids in addition to beneficial macro- and micronutrients, and findings from several studies show that a high intake of olive oil and nuts reduces the risk of cardiovascular disease (92-95, 99-102).

These findings substantiates that a high intake of SFAs increases the risk of CVD, while MUFAs and PUFAs are inversely associated with CVD, and that it is beneficial to reduce the intake of saturated fat from the diet by exchanging it with unsaturated fat. The daily intake of SFAs should not exceed 10 % of total energy intake (103). The daily intake of MUFAs and PUFAs should amount to respectively 10-20 % and 5-10 % of total energy intake (103).

Whole grain, fruit and vegetable consumption

Several studies have investigated the effect of a high consumption of fiber, fruits and vegetables on the risk of cardiovascular disease and the results show significant inverse associations (62, 104-113). Fruits and vegetables are rich in fiber and antioxidants and protect against cardiovascular disease (104, 114-117). Daily consumption of fiber has several beneficial effects on the risk of cardiovascular disease, such as better blood pressure control, reduction of chronic inflammation and improved blood lipid profiles (104-107, 114, 118-121). The body's own antioxidant defense system protect against increased levels of ROS and repairs oxidative damage, which could otherwise lead to increased risk of CVD (53). Several vegetables contain components that strengthens the antioxidant defense in the body (53). Phytochemicals, a group of bioactive components in plants, have been found to have beneficial effects on health and CVD (18). Phytochemicals can influence gene expression, protect against toxins from the environment and many have antioxidant properties (18, 116, 122). The many health benefits of fruit and vegetables may be due to the high content of phytochemicals, antioxidants and fiber (53, 108, 114, 123, 124).

Two RCTs investigating the effect of fruit and vegetable consumption on endothelial function, showed that a high intake of fruits and vegetables improved endothelial function in non-hypertensive and hypertensive subjects (123, 124). Endothelial function is essential for maintenance of normal blood pressure and influences accumulation of plaques in the blood vessels, and therefore central for cardiovascular risk (125). A meta-analysis of twenty-two cohort studies evaluated the effect of dietary fiber on cardiovascular risk and found a significant 9 % reduced risk of CVD for each 7g/day increase in fiber intake (108). In the

PREDIMED trial they investigated the effect of dietary fiber, fruit, vegetable and whole-grains alone for the risk of cardiovascular disease (109). The study showed that individuals that had a fruit and vegetable consumption of 9 servings per day or more had significant lower cardiovascular risk compared to individuals that consumed less than 5 servings per day (109). The PREDIMED trail showed a significant protective effect of fruit and fiber consumption on CVD mortality (110). It is recommended to have a daily fiber intake of at least 25-35 grams, where the major sources should be vegetables, whole fruit, nuts, legumes and whole grains (103).

Dietary sugar

A high consumption of sugar-sweetened beverages (SSB) is associated with exacerbated cardiovascular risk factors, such as increased blood pressure, dyslipidemia and weight gain (126-129). Systematic reviews investigating SSB and weight gain have found positive associations between SSB and obesity (130, 131). A systematic review on dietary sugar and body weight concluded that the weight gain from increased intake of dietary sugar was due to an increase in energy intake rather than effects of sugar alone (132). The same was stated in a review of RCTs (133). However, another systematic review found that associations between SSB and risk of obesity was inconsistent when the results were adjusted for total energy intake (134).

1.3.4 Micronutrients and risk of cardiovascular disease

Micronutrients have multifold and essential roles in the body and is a collective term for minerals and fat- and water soluble vitamins (18). Suboptimal levels of vitamins and minerals can give symptoms as blindness, goiter, constipation and increased hemorrhage and bone fracture and deficiency can lead to diseases such as rickets, osteomalacia and scurvy (18). Sub-optimal levels of micronutrients also affect the cardiovascular risk (135-138). To avoid suboptimal levels and deficiency, a healthy diet with adequate intake of vitamins and minerals is required (18).

Vitamin D

Vitamin D, a fat-soluble vitamin, is as an important regulator in phosphate and calcium metabolism, and have been shown to play a protective role in the cardiovascular system (139). Vitamin D affects the cardiovascular system by upregulate and downregulate proteins

and hormones, such as cytokines and natriuretic peptides (139). A systematic review on vitamin D and its effect on the cardiovascular system presented results from studies done in mice and humans (139). The results from the experimental studies done in mice showed that lack of vitamin D receptor led to hypertension and cardiac hypertrophy (139). The observational studies done in humans showed promising protective effects of a good vitamin D-status on CVD, while the RCTs only found a small blood pressure lowering effect of vitamin D (139). A systematic review conducted for the update of the Nordic Nutrition Recommendations, found that there is probable evidence supporting that a low vitamin D status increases the risk of CVD (135). Nevertheless, an adequate vitamin D status (25(OH)D levels between 50-100 nmol/L) may be of importance for cardiovascular risk (135, 139). In Norway, fatty fish and fortified butter and margarine are the most important sources to dietary vitamin D in addition to cod liver oil supplements (140). Adults (< 75 years) are recommended to have a Vitamin D intake of 10 μg/day or 1.4 μg/MJ (103, 141).

Vitamin E and Vitamin C

Vitamin E and Vitamin C from diet protect against oxidation of LDL and damage from ROS (53, 103, 136). In addition, vitamin C has been shown to improve endothelial function and autonomic nervous regulation of blood pressure (136). However, vitamin E and C supplements have not been found to have beneficial cardioprotective effects (142-144). The most important dietary sources to vitamin E in Norway are butter, margarine, oil, eggs, fish, fruit, berries and bread (140). Vegetables, fruit, berries and juice are the most important dietary sources to vitamin C in Norway (140). Men and women are recommended to have a daily intake of vitamin E of 10 and 8 alpha-tocopherol equivalents (TE) respectively, or 0.9 alpha-TE/MJ (103, 141). The daily recommended intake of vitamin C for adults is 75 mg or 8 mg/MJ (103, 141).

Folate

Folate, vitamin B9, plays an essential role in amino acid metabolism and is important for DNA synthesis and nervous system development (137, 145). In addition, folate has been shown to improve endothelial function by increasing the bioavailability of nitric oxide, and may thereby protect against CVD (137). A study consisting of three large population-based cohorts from Sweden found that participants with the highest folate concentrations had significantly lower risk of myocardial infarction (138). A systematic review and several

meta-analyses of RCTs have found protective effects of folate supplementation on stroke and overall CVD (146-148). The metabolism of the amino acid homocysteine requires folate, in addition to vitamin B6 and vitamin B12 (149). Folate deficiency can therefor lead to elevated levels of homocysteine, which have been shown to be associated with an increased risk of CVD and CVD mortality (149, 150). On the contrary, findings of the Norwegian Vitamin Trial showed that cardiovascular risk in patient that already had myocardial infarction did not decrease after lowering homocysteine levels (151). In addition, the trial also suggested that a combined treatment of folate, vitamin B6 and B12 could lead to increased cardiovascular risk (151). A meta-analysis of twelve clinical trials found no effect of a combined treatment of folate, vitamin B6 and B12 on cardiovascular risk (152). Nevertheless, findings indicate that an adequate dietary folate intake may be important to reduce the risk of CVD. The most important sources to dietary folate in Norway are bread, fruits and vegetables (140). Men are recommended to have a daily folate intake of 300 μg or 45 μg/MJ, and women of reproductive age are recommended to have a daily intake of 400 μg or 45 μg/MJ (103, 141).

Sodium

Sodium intake is an important dietary factor in reducing hypertension (153), an important risk factor for cardiovascular disease (154). In a Nordic climate with normal physical activity, a daily intake of approximately 1.5 grams of salt (NaCl) will cover the necessary daily amount of sodium (155). In Norway, bread, meat and meat products, fish and fish products, in addition to table salt are the main dietary sources of sodium (140). The general Norwegian population has a salt intake of 10 grams per person per day (155). The Norwegian Directorate of Health wants to gradually reduce the intake of salt in the population and aim to reduce the intake to 6 grams (2.4 grams sodium) per person per day in the long term (155).

1.4 Resting energy expenditure

WHO defines a person's energy requirement as the amount of food energy needed to balance energy expenditure in order to maintain body size, body composition and a level of necessary and desirable physical activity consistent with long-term good health (156). Total energy expenditure is the total amount of energy a person uses per day and is composed of resting energy expenditure (REE), thermogenesis (the thermic effect of food) and physical activity, see Figure 5 (18). REE is the amount of energy expended to sustain normal body functions,

as maintenance of body temperature, circulation, respiration and synthesis of organic compounds (18). Metabolically active tissues, as skeletal muscle, the brain and liver is the major contributors to REE (18). REE accounts for approximately 65-70 % of an individual's daily energy expenditure, see Figure 5 (18, 157).

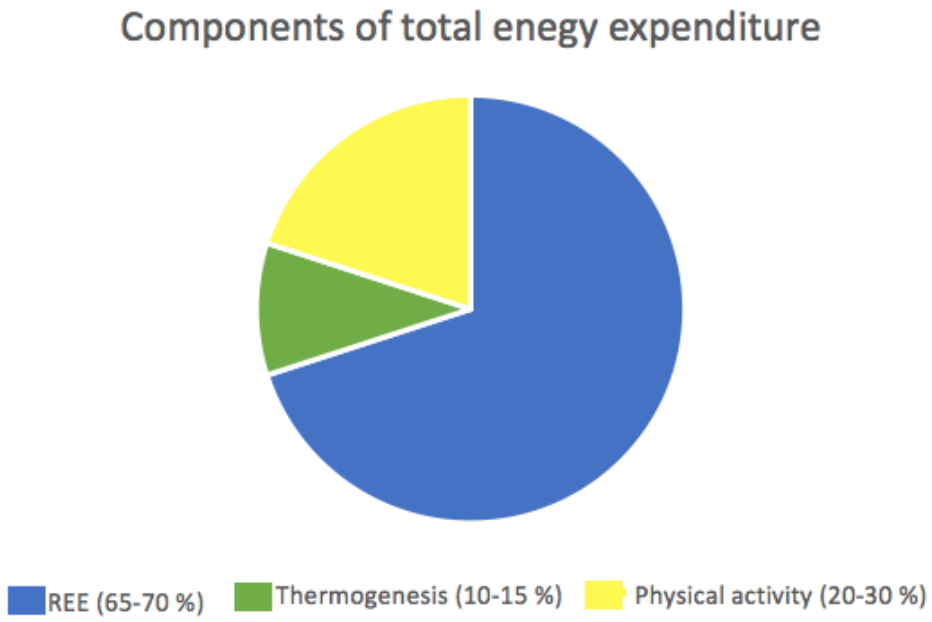

Figure 5: Components of total energy expenditure

Indirect calorimetry (IC) is one of the most accurate and sensitive methods for measuring energy expenditure (158), and it is a commonly used method for measuring REE (18). An individual's carbon dioxide production and oxygen consumption over a given time is measured and converted into REE. The Weir equation [(3.94(VO2) + 1.11(VCO2)) 1.44] is used for the conversion of oxygen consumption to REE (18). REE can also be estimated using predictive equations, such as the Harris-Benedict equations (HBEs) and Mifflin-St. Jeor equations (MSJEs), see Figure 6 (159, 160). Predictive equations provide an accessible and economical method to estimate REE (159). The Harris-Benedict equations have been widely used, but studies have shown that Mifflin-St. Jeor equations are more accurate in estimating REE in normal weight and obese individuals (160-163). However, a cross-validation study of thirty healthy adults found that on group level, HBE did not differ from the measured REE (159). A study validating twenty-seven prediction equations for REE found that the HBEs and MSJEs were equally accurate and precise (164). The MSJEs is recommended to use in overweight and obese individuals (165). To estimate daily energy requirement, the resting energy expenditure (measured or estimated) must be multiplied by a physical activity level

(PAL) value (18). The PAL values describe daily average activity level and range from 1.0 (sedentary behavior) to 2.5 (very active) (18).

Harris Benedict Equations	
Male	*REE = 66.47 + 13.75 x weight (kg) + 5.0 x height (cm) - 6.75 x age (years)
Female	*REE = 665.09 + 9.56 x weight (kg) + 1.84 x height (cm) - 4.67 x age (years)
Mifflin-St Jeor Equations	
Male	*REE = 10 x weight (kg) + 6.25 x height (cm) - 5 x age (years) + 5
Female	*REE = 10 x weight (kg) + 6.25 x height (cm) - 5 x age (years) - 161
*REE (Resting Energy Expenditure (kilocalories/day))	

Figure 6: Equations for prediction of resting energy expenditure

One study have investigated REE and body composition of American and Canadian achondroplastic individuals and found that individuals with achondroplasia had higher resting caloric requirements per unit body weight compared to lean and obese average-height adults (51). However, the REE in kcal/day was lower for the achondroplastic population than the men and women of normal height (51). REE is an important factor for establishing daily energy requirement and to evaluate adequate energy intake for an individual. Knowledge of energy requirements for the adult Norwegian achondroplasia population is lacking.

2 Objectives

This master thesis is a part of "The Norwegian Adult Achondroplasia Study", a study conducted as part of Svein O. Fredwalls' PhD with the main research questions:
- What is the prevalence and severity of cardiovascular disease (including known risk factors), sleep apnea, impaired hearing and spinal stenosis in adults with achondroplasia?
- Do adults with achondroplasia have a different body composition and fat distribution, measured by MRI, compared to the general population?

The main aim of this master thesis was to describe the diet and risk of cardiovascular disease in the adult Norwegian achondroplasia population. Specific aims of this master thesis were:

- to describe risk factors of cardiovascular disease, with focus on lipid profile, blood pressure and obesity
- to describe the body composition of men and women with achondroplasia using anthropometry
- to describe diet, energy and nutrient intake for men and women with achondroplasia
- to describe resting energy requirements for men and women with achondroplasia by indirect calorimetric method
- to explore associations between diet and risk factors of cardiovascular disease

The hypothesis was that individuals with achondroplasia have a diet high in saturated fat and low in dietary fiber compared to national recommendations, and a high total energy intake compared to their energy requirement. Dietary factors might contribute to hypertension and adverse lipid profiles, in addition to the increased risk of obesity and cardiovascular disease in this population.

3 Subjects and methods

3.1 Subjects

Participants were recruited from "The Norwegian Adult Achondroplasia Study", a clinical study conducted at Sunnaas Rehabilitation Hospital in collaboration with National Resource Centre for rare Disorders (TRS). A written invitation was sent to individuals 16 years of age or older registered with achondroplasia at TRS (n=45). The study was announced at TRS' website, and presented at the summer-gatherings of the Norwegian Association of Short Stature (NiK) in 2016 and 2017. An information video about the study was published on TRS' website and social media (YouTube and Facebook). Information about the study has also been given to relevant hospital departments and rehabilitation institutions that possibly meet adults with achondroplasia.

A total of thirty-five individuals were invited to participate in this master thesis and thirty-three of these wanted to participate. The participants were adults from the age of sixteen that lived in Norway and had the clinical and genetic diagnose achondroplasia, and spoke and understood Norwegian. Individuals with mental retardation, severe mental disorders or substance abuse were excluded.

3.2 Methods

3.2.1 Design

Thirty-three adult achondroplastic individuals participated in this master thesis with cross-sectional study design. Data collection was carried out from March to December 2017.

The following methods were used to collect data: Anthropometrics, a food and lifestyle questionnaire (SmartDiet), four-day dietary record and indirect calorimetry. Data from blood test results, blood pressure and waist circumference was collected from "The Norwegian Adult Achondroplasia Study" to avoid unnecessary strain for the participants.

3.2.2 Anthropometrics

On the morning of the second day at Sunnaas Rehabilitation Hospital the participants' weight and standing height were measured. Weight and standing height were measured using a combined weight and altimeter (Sliding weight column scale, M303300, ADE). All the participants wore indoor clothes during the weighing and 1 kg was therefore subtracted from the measured weight. Some of the participants was wearing shoes while their height was measured, and for those participants the height was subtracted with as many centimeters as the height of the shoes. The participants weight and standing height were measured by two different persons, as data collection started before the onset of this master thesis. The first sixteen participants were measured by the dietitian at Sunnaas Rehabilitation Hospital, and the next seventeen participants were measured by the master student. Waist circumference was measured one time for all participants in standing position using a measuring tape between the lateral lower rib and the upper part of the hip joint (crista iliaca) (166). Waist circumference measurements were conducted as part of "The Norwegian Adult Achondroplasia Study" by the PhD candidate.

3.2.3 Diet and nutrient intake

The SmartDiet questionnaire is a retrospective self-administered food and lifestyle questionnaire (167). SmartDiet was developed in Norway in 2001 through a collaboration between the Lipid Clinic at the University of Oslo and Nymoen Medical Center. The intentions behind the questionnaire was to develop a rapid tool for the assessment of patients habitual diet and to enable immediate feedback to the patients on how to improve their diet (167). It takes about ten minutes to complete the questionnaire and it contains twenty-one questions about food choices and frequencies in addition to the consumed amount of food groups. SmartDiet provide an overview of an individuals' consumption of saturated and unsaturated fatty acids, sugar, dietary fiber, fruits and vegetables and cholesterol (167). Fourteen of the twenty-one questions about food choices give points and the total score give an impression of how healthy and heart-friendly the diet is. A score of 27 or less means that you have an unhealthy diet, and you should do several improvements to your diet. A score of 28-35 means that you could improve your diet in some areas, and a score of 36 or more means that you have a healthy and heart-friendly diet. The participants were given instructions on how to fill out the questionnaire orally or over the phone.

The SmartDiet questionnaire was used in addition to a dietary record, to get information about the participants' general diet in addition to the exact dietary intake in the days of registration. Dietary record is a prospective method that provide information about the exact consume of foods and beverages over a specified period (168). The first participants recorded everything they ate and drank for seven consecutive days, but as they reported that it was too demanding to record for a whole week, the time period was changed to four consecutive days. To get information on the participants diet on both weekdays and weekends they were all asked to register their diet from Saturday through Tuesday. To assist the participants in defining portion sizes, a picture book was attached to the four-day dietary record (169). The picture book was developed in Norway through a collaboration between The Department of Nutrition at University of Oslo, The Norwegian Food Safety Authority and The Norwegian Directorate of Health for use in NORKOST 3, a Norwegian national nutrition examination survey from 2010/2011 (170). The picture book contained pictures of different serving sizes of various foods. In addition to the picture book the participants were given information on how to use household measurements to specify their intake. The participants were asked not to change their eating habits during the four days of registration to improve their diet or to simplify the registration. The participants were given instructions on how to fill out the dietary record orally or over the phone.

Two approaches were used to get as many participants as possible to fill out the four-day dietary record, see Figure 7 and 8. The first participants were given information about the study, SmartDiet and the dietary record on their second day at Sunnaas Rehabilitation Hospital, see Figure 7. During their second day, the participants filled out the SmartDiet questionnaire, and they were asked to fill out the dietary record for four consecutive days after they had returned home. Few participants completed the dietary record after they had returned home and much time was used to call up the participants to motivate them to complete the registration. For this reason, another approach was used for the next participants, see Figure 8. The four-day dietary record form together with the SmartDiet questionnaire, the consent form and information about the study was sent by mail before the participants' stay at Sunnaas Rehabilitation Hospital. They got a phone call were they were asked and motivated to fill out the forms before their hospital stay. The participants that had not completed the dietary record before their stay were asked to fill it out after they had returned home. Even fewer participants completed the four-day dietary record with this approach, and therefore, for the last participants the first approach were used, see Figure 7.

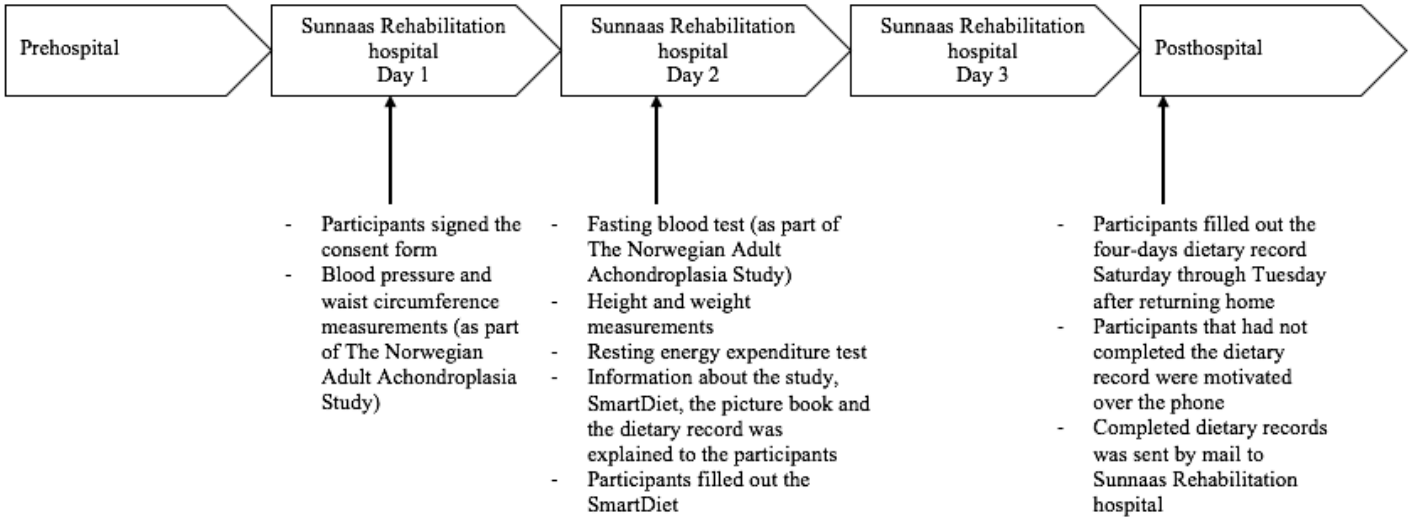

Figure 7: Approach 1 for data collection

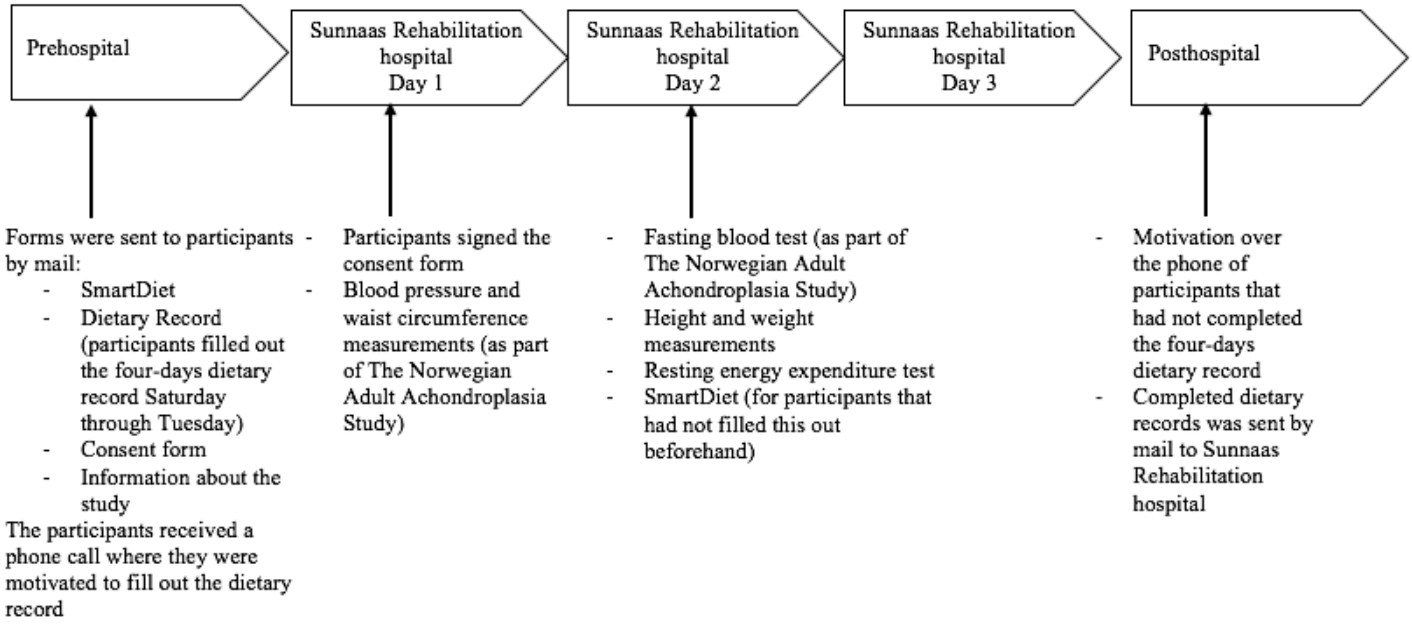

Figure 8: Approach 2 for data collection

Data on intake of macro- and micronutrients was obtained from the returned four-day dietary records, and the participants' intake of macro- and micronutrients were calculated using an online diet tool from the Norwegian Directorate of Health and the Norwegian Food Safety Authority, www.kostholdsplanleggeren.no (171). The intake of macro- and micronutrients and the composition of the diet was evaluated against the recommendations from the

Norwegian Directorate of Health (172). The participants received a phone call with feedback on their diet. Feedback were given to seventeen of the twenty participants that completed the dietary record. The three remaining participants were inaccessible at multiple occasions and did therefore not receive a feedback.

3.2.4 Resting energy expenditure

The participants' resting energy expenditure were measured on the morning of their second day at Sunnaas Rehabilitation Hospital. REE was measured using a computerized standard open-circuit technique breath-by-breath spirometer (V_{max} Encore 229D, CareFusion Corporation, San Diego, CA, USA). The equipment was calibrated before each test. For calibration of the gas analyzers, room air and medically certified calibration gases (16% O_2 and 4% CO_2 / 26% O_2 and 0% CO_2) were used. A 3-1 calibration syringe was used for the volume calibration. The participants were asked not to eat or drink for twelve hours prior to the test. The measurement of REE took fifteen minutes and the mean of the last five minutes was used in the statistical analyses.

3.2.5 Blood samples

Fasting blood samples were collected for all participants using venous blood and serum tubes with gel. The blood samples were analyzed for total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides content at the Clinical Chemistry laboratory at Oslo University Hospital.

3.2.6 Blood pressure

Blood pressure was measured on the participants right upper arm, by the PhD candidate in "The Norwegian Adult Achondroplasia Study", using a digital blood pressure monitor (A&D Medical Model UA-767 Plus 30). Participants were seated for thirty minutes before the measurement, and they were asked not to smoke or use snuff in the last hour before the measurement took place. Blood pressure was measured three times with one minute waiting time between each measurement, and a mean was calculated for the last two measurements.

3.2.7 Lifestyle habits

In addition to data on dietary habits, the SmartDiet questionnaire provides information about lifestyle, such as physical activity and smoking. The question on physical activity gave data

on how many times per week the participant were physical active for ≥ 30 minutes (rarely/never, 1-2 or ≥ 3), while the question on smoking habits gave dichotomous data (smoking/no smoking).

3.2.8 10-year risk of cardiovascular disease

NORRISK 2 was used to calculate the 10-year risk of cardiovascular disease in the study population. To calculate the 10-year risk, information about sex, smoking (yes/no), age, SBP, total cholesterol, use of antihypertensive drugs (yes/no) and low HDL cholesterol (yes/no) was entered the online calculator (173). In addition to the above-mentioned parameters, the number of first-degree relatives with heart attack before the age of 60 years can also be entered to the calculator. This information was not obtained in this master thesis, and the 10-year risk of cardiovascular disease calculated for the study population was therefore not accounted for early heart attack in first-degree relatives.

3.3 Statistical analyses

Data analyses was performed using IBM SPSS Statistics 25. Significance level was set at *p*-value <0,05.

The Shapiro-Wilk test of normality was performed for all continuous variables and histograms and Q-Q plots were used to interpret the test. The Shapiro-Wilk test was used as this is the most suitable test for small sample sizes (n ≤ 50) (174). Results from parametric data were presented as mean and standard deviation. For analyses of parametric data, Independent- or Paired-samples t-test were used and Pearson's product moment correlation coefficient (r) were calculated (175, 176). Results from non-parametric data were presented with median and 25th- and 75th percentiles. For the nonparametric data, Mann Whitney U-test were used and Spearman's rank correlation coefficient (*rho*) were calculated (175, 176). A small correlation was found for r/*rho*=0.10 to 0.29, a medium correlation was found for r/*rho*=0.30 to 0.49 and a large correlation was found for r/*rho*=0.50 to 1.0 (177).

To explore the relationship between to categorical variables in two independent groups, Chi Square test for independence were used (178). For 2x2 tables the Chi Square test assumes that at least 80 % of cells have expected frequency ≥ 10 (175). If this assumption was not met, the Fisher`s Exact Probability test was used (175).

3.4 Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics South East (Approval No 2016/2271). The project was carried out in accordance to The Declaration of Helsinki – ethical principles for medical research involving human subjects. All the participants signed a written consent on their first day at Sunnaas Rehabilitation Hospital, and were informed that they could at any time, without justification, withdraw from participation in the study. The participants were given identification numbers, and all sensitive data and personal information about the participants were deidentified. The identification numbers were used during collection, registration and processing of data. The SmartDiet and dietary registration forms were organized in folders and kept in a locked filing cabinet at Sunnaas Rehabilitation Hospital when not used.

3.5 My contribution

The master student handled most of the practical work of this cross-sectional study from August through December 2017. The student's contribution was:

- Anthropometrics (weight and height measurements)
- Assisted in the measurement of resting energy expenditure
- Instructed the participants on how to answer the SmartDiet questionnaire and made sure they filled it out
- Informed the participants on how to fill put the four-day dietary record and follow-up of participants that did not complete the registration
- Did the assessment of nutrient intake by use of the online diet tool: "Kostholdsplanleggeren"
- Gave feedback and dietary advices to all participants completing the dietary record

4 Results

4.1 Study population

A total of 33 out of 35 eligible individuals with achondroplasia participated in this cross-sectional study, 45.5 % (n=15) men and 54.5 % (n=18) women. One did not want to contribute dietary information, thus 32 participants completed the SmartDiet questionnaire and 20 completed the dietary record, see Figure 9 for inclusion of participants.

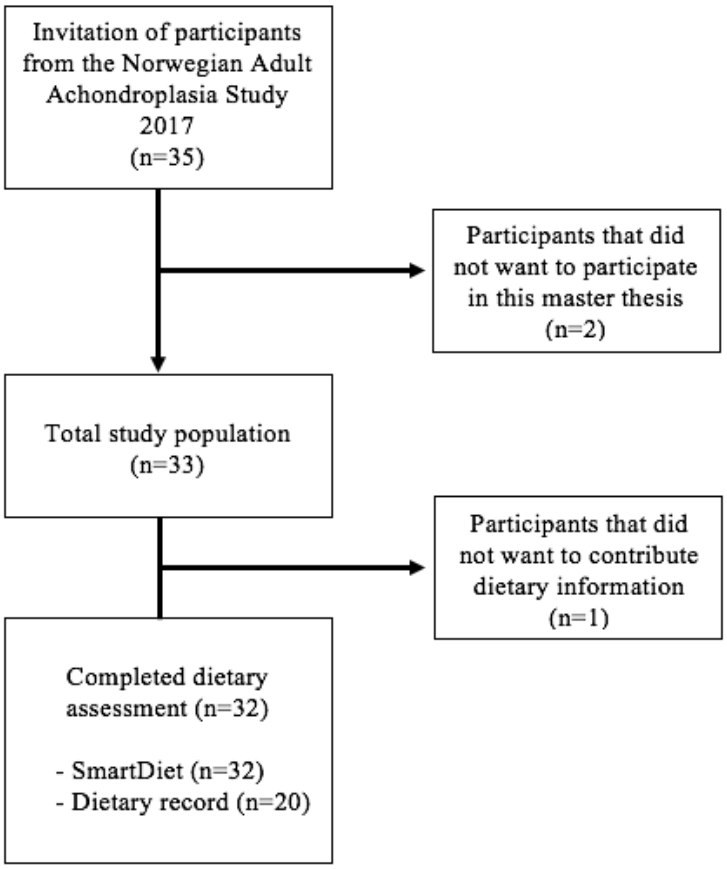

Figure 9: Study population

Characteristics of the study population are presented in Table 4. Mean height and weight for men was 135.6 cm and 66.3 kg and the mean height and weight for women was 130.7 cm and 55.6 kg. In this population, 36 % (n=12) worked or studied full time, and 30 % (n=10) received full disability benefit. Residence was divided according to the four health regions of Norway, and 76 % (n=25) of the participants were living in south-eastern Norway, see Table 4.

Table 4: Characteristics of the study population

	Mean (SD*)		
	All (n=33)	Male (n=15)	Female (n=18)
Age (years)	40 (15)	41 (17)	40 (14)
Height (cm)	132.9 (8.3)	135.6 (9.2)	130.7 (6.9)
Weight (kg)	60.5 (14.0)	66.3 (16.4)	55.6 (9.5)
	All (n=33)		
[a] Work	N (%)		
Full-time job/student	12 (36 %)		
Part-time job	4 (12 %)		
Retired	1 (3 %)		
Disability benefit (50-95 %)	4 (12 %)		
Disability benefit (100 %)	10 (30 %)		
[b] Higher education	20 (61 %)		
Residency			
Northern Norway	2 (6 %)		
Central Norway	1 (3 %)		
Western Norway	5 (15 %)		
South-eastern Norway	25 (76 %)		

*SD (Standard Deviation)

[a] Missing data (two participants were unemployed during data collection)

[b] Higher education (Education at university or college level)

4.2 Risk factors for cardiovascular disease

Plasma lipids, blood pressure, anthropometrics, information about physical activity level, smoking and snuff habits, together with the results from NORRISK 2 are presented in Table 5. Median total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels for all participants (n=33) were all within optimal range. Low HDL cholesterol levels (≤ 1.3 mmol/L for men and ≤ 1.0 mmol /L for women) was found in 20 % (n= 3) of the men and 39 % (n=7) of the women. Elevated triglyceride levels (≥1.7 mmol/L) was found in 27 % (n=4) of the men. SBP and DBP was measured for all participants (n=33), and mean blood pressure was 122/76 mmHg. 21.2 % (n=7) of the participants met the criteria for hypertension (37). Mean BMI in the population (n=33) was 34 kg/m^2. The mean waist circumference was 94.1 cm for men and 82.2 cm for women. An increased waist circumference (>94 cm for men and >80 cm for women) was found in 53 % (n=8) of the men and 50 % (n=9) of the women. An

even higher increase in waist circumference (≥102 cm for men and ≥88 cm for women) was found in 33 % (n=5) of the men 28 % (n=5) of the women.

Table 5: Cardiovascular risk factors

	All (n=33)		
	Median	(25th, 75th)	[a] Recommended level
Total cholesterol (mmol/L)	4.7	(3.9, 5.1)	< 7
[b] **LDL cholesterol** (mmol/L)	2.9	(2.0, 3.3)	< 5
[c] **HDL cholesterol** (mmol/L)			
Men	1.2	(1.1, 1.7)	> 1.0
Women	1.4	(1.2, 1.7)	> 1.3
Triglycerides (mmol/L)			
Men/women	1.0	(0.6, 1.3)	<1.7

	Mean ([d] SD)		
	All (n=33)	Male (n=15)	Female (n=18)
[e] **SBP** (mmHg)	122 (15)	124 (16)	120 (13)
[f] **DBP** (mmHg)	76 (9)	76 (9)	75 (9)
[g] **BMI (kg/m^2)**	34 (7)	36 (7)	33 (6)
Waist circumference (cm)	87.7 (13.9)	94.1 (15.6)	82.2 (9.8)

	n (%)
***Physical activity** (≥ 30 minutes)	
Rarely/never	12 (37.5)
1-2 times per week	12 (37.5)
3 or more times per week	8 (25)
***Smoking**	
Yes	3 (9.7)
No	28 (90.3)
***Snuff**	
Yes	5 (16.7)
No	25 (83.3)
[h] **NORRISK 2**	
Low 10-year risk of CVD	31 (94)
Elevated 10-year risk of CVD	1 (3)
High 10-year risk of CVD	1 (3)

[a] The Norwegian Directorate of Health, Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom. 2017

[b] LDL (Low-density lipoprotein)

[c] HDL (High-density lipoprotein)

[d] SD (Standard deviation)

[e] SBP (Systolic Blood Pressure)

[f] DBP (Diastolic Blood Pressure)

[g] BMI (Body Mass Index)

[h] NORRISK 2 (A 10-year risk calculator for acute myocardial infarction or stroke, including cardiovascular death)

* Missing data from SmartDiet

1 participant did not answer the question about physical activity

3 participants did not answer the question about snuff habits

2 participants did not answer the question about smoking habits

The distribution of BMI in the population is shown in Figure 10. None of the participants were classified as underweight, 91 % (n=30) were overweight and 76 % (n=25) were classified as obese according to BMI, see Table 1 for classification according to BMI.

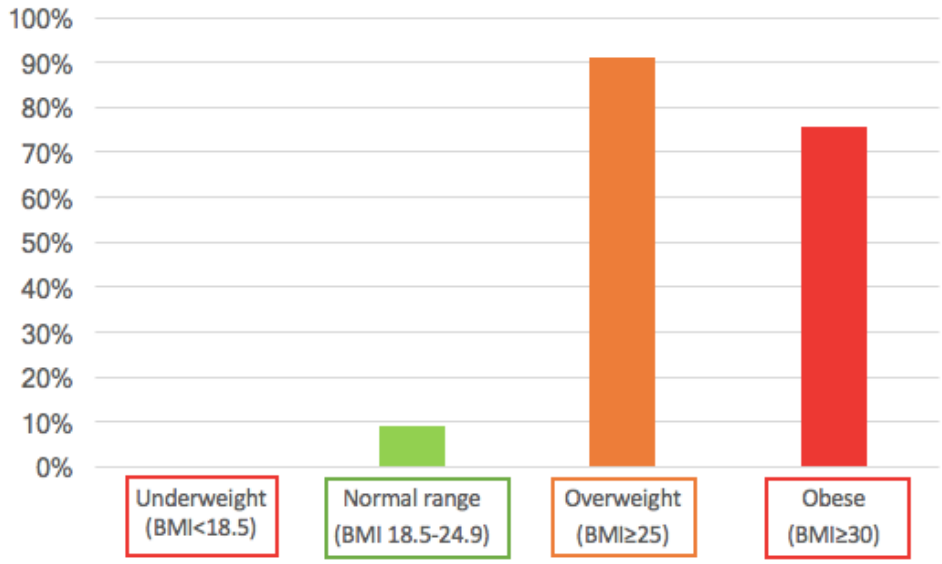

Figure 10: The distribution of BMI in the population

Data on physical activity was provided from 97 % (n=32) of the participants, see Table 5. Physical activity for at least 30 minutes at least once a week was reported by 63 % (n=20) of the participants, and 25 % (n=8) reported to be physical active for at least 30 minutes three or more times per week. There was not enough information about physical activity level from the SmartDiet questionnaire to form an opinion on PAL-values and to calculate daily energy requirements for this population. Data on smoking habits was provided from 94 % (n=31) of the participants, and 9.7 % (n=) reported to smoke tobacco, see Table 5. Data on snuff-habits was provided by 91 % (n=) of the participants, and 16.7 % (n=) reported to use snuff. Results from NORRISK 2 showed that only 6 % (n=2) of the participants had an increased 10-year risk for acute myocardial infarction or stroke, including cardiovascular death.

4.3 Dietary intake

4.3.1 SmartDiet

The SmartDiet questionnaire was filled out by 97 % (n=32) of the participants, and dietary information are presented in Table 6. An unhealthy diet (a score of ≤ 27) was found among 38 % (n=12) of the participants, and 62 % (n=20) had a score between 28 and 35, which means that their diet could be improved. None of the participants had a score of 36 or more, indicating a healthy and heart-friendly diet. The distribution of scores are presented in Figure 11. Mean SmartDiet score for both men and women were 28. Most of the participants ate 3-4 meals per day, see Table 6.

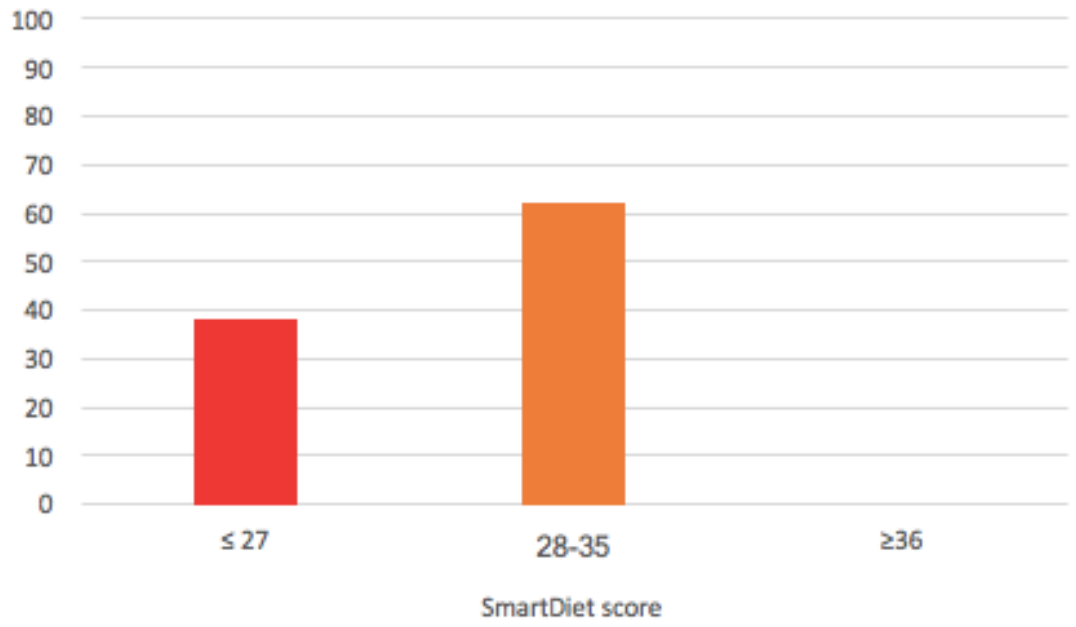

Figure 11: The distribution of SmartDiet scores in the population

Intake of dietary fat

Cheese, butter and fat used in cooking was the biggest sources to SFAs in the participants' diet, see Table 6. Use of cheese with high fat content was reported by 78 % (n=25) of the participants. Use of butter with high content of SFAs was reported by 40 % (n=13) of the participants, and 47 % (n=15) reported to use fat with high content of SFAs in cooking. Few used fish and mayonnaise on bread. Use of fish for dinner twice a week was reported by 53 % (n=17), but only 13 % (n=4) used fish for dinner 3 or more times per week. Most of the participants that used fish for dinner, ate fatty fish 1 time per week. Weekly intake of nuts and olives/avocado was reported by 34 % (n=11) and 28 % (n=9) of the participants

respectively. When it comes to consumption of milk and yogurt, 47 % (n=15) reported to use low-fat milk and 50 % (n=16) reported to use yoghurt weekly. For consumption of sour cream and cream, 40 % (n=13) reported to use foods with medium fat content. Use of coffee was reported by 84 % (n=27) of the participants, and it was mainly brewed coffee. Weekly consumption of eggs was reported by 81 % (n=26) of the participants, see Table 8.

Intake of dietary fiber, fruit and vegetables

Whole grains were the biggest source of dietary fiber in the participants' diet, see Table 6. Daily use of grain products rich in fiber was reported by 60 % (n=19) of the participants. Fruit, berry and vegetable consumption in this population was low. Consumption of less than 2 servings (<300g) per day of fruit, berries and/or vegetables was reported by 56 % (n=18) of the participants, and only 6 % (n=2) consumed 4 or more servings (≥600g) per day.

Intake of foods and beverages with high sugar content

Chocolate, ice cream, cake and other snacks as well as sweetened spreads or beverages were big sources to added sugar in the participants' diet, see Table 6. Consumption of this type of snacks twice a week was reported by 56 % (n=18) of the participants and 13 % (n=4) consumed snacks 3 or more times per week. Consumption of sweetened spreads or beverages 2 or more times per day was reported by 32 % (n=10) of the participants.

Table 6: Intake of food groups from SmartDiet

Food groups	% (n)	Food groups	% (n)
Milk		**Bread, crisp bread and cereals**	
Do not use/use rarely	25 (8)	Do not use bread/crisp bread/cereals	6 (2)
Skimmed milk	22 (7)	Products low in fiber	34 (11)
Low-fat milk	47 (15)	Products rich in fiber	60 (19)
Whole milk	6 (2)	**Fruits, berries and vegetables**	
Yogurt		<2 [b] servings/day	56 (18)
Do not use yogurt weekly	50 (16)	2-4 [b] servings/day	38 (12)
1-2 units of 1 dl/week	31 (10)	>4 [b] servings/day	6 (2)
3-4 units of 1 dl/week	6 (2)	**Beverages and spreads high in sugar**	
≥5 units of 1 dl/week	13 (4)	0-1 times/day	68 (22)
Cream/sour cream		2 times/day	16 (5)
Do not use/use rarely	22 (7)	≥3 times/day	16 (5)
With low fat content	19 (6)	**Snacks**	
With medium fat content	40 (13)	0-1 times/week	31 (10)
With high fat content	19 (6)	2 times/week	56 (18)
Cheese		≥3 times/week	13 (4)
Do not use/use rarely	6 (2)	**Weekly intake of legumes**	
With low fat content	0	No	72 (23)
With medium fat content	16 (5)	Yes	28 (9)
With high fat content	78 (25)	**Potato/rice/pasta**	
Meatproducts on bread		Do not use	9 (3)
Do not use/use rarely	16 (5)	0-1 [c] portion/day	66 (21)
With low fat content	56 (18)	2 [c] portions/day	6 (2)
With high fat content	28 (9)	≥3 [c] portions/day	19 (6)
Meat and meatproducts for dinner		**Weekly intake of nuts**	
Do not use/use rarely	9 (3)	No	66 (21)
With low fat content	47 (15)	Yes	34 (11)
With medium fat content	28 (9)	**Weekly intake of avocado/olives**	
With high fat content	16 (5)	No	72 (23)
Fishproducts on bread		Yes	28 (9)
On 1 slice of bread/week or never	50 (16)	**Coffe**	
On 2-4 slices of bread/week	34 (11)	No	16 (5)
On ≥5 slices of bread/week	16 (5)	Yes	84 (27)
Fish for dinner		**Alcohol consumption**	
1 time/week or never	34 (11)	No	25 (8)
2 times/week	53 (17)	<1unit/week	47 (15)
≥3 times/week	13 (4)	1-7 units/week	28 (9)
Fatty fish 1-2 times/week		8-14 units/week	0
No	38 (12)	≥15 units/week	0
Yes	62 (20)	**Eggs per week**	
Mayonnaise, remoulade and caviar		0	19 (6)
On ≤1 slice of bread/week	47 (15)	1-2	25 (8)
On 2-7slices of bread/week	44 (14)	3-4	34 (11)
On ≥8 slices of bread/week	9 (3)	≥5	22 (7)
Butter or margarine on bread		**Meals per day**	
Do not use butter/margarine	38 (12)	1-2	9 (3)
With low [a] SFA content	3 (1)	3-4	75 (24)
With medium [a] SFA content	19 (6)	≥5	16 (5)
With high [a] SFA content	40 (13)		
Fat used in cooking			
Do not use fat in cooking	9 (3)		
With low SFA content/oil	44 (14)		
With medium SFA content	0		
With high SFA content	47 (15)		

[a] SFA (Saturated fatty acids)

[b] servings: 1 serving = 150g

[c] portion: 1 portion = 2 potatoes/2 dl boiled rice/pasta

4.3.2 Dietary record and REE

The four-day dietary record was completed by 62 % (n=20) of the participants, 40 % were men and 60 % were women.

Macronutrients

Median intake of macronutrients and the percentage of subjects which had an intake of the various macronutrients in accordance to the recommendations are presented in Table 7. Median intake of all macronutrients was in accordance with recommendations, except SFAs and dietary fiber, see Table 7. Median intake SFAs was 12 E% and only two male and one female participant had an intake in accordance with recommendations (<10 E%). A larger proportion of the participants had an intake of unsaturated fatty acids that was in accordance with recommendations. Median intake MUFAs and PUFAs was 14 E% and 6 E% respectively, see Table 7. Median cholesterol intake was 168 mg/day, and 88 % (n=7) of the men and 92 % (n=11) of the women had an intake in accordance with recommendations (<300 mg/day). Median intake of dietary fiber was 16.5 grams, and only one male participant and none of the female participants had a fiber intake in accordance with recommendations (25-35 g/day), see Table 7.

Micronutrients

Intake of micronutrients were generally low, and median intake and the percentage of subjects which had an intake of the various micronutrients in accordance with recommendations are presented in Table 8. Median intake of vitamin D was 6 μg/day and 4 μg/day for the male and female participants respectively. Only 25 % (n=2) of the male participants and 17 % (n=2) of the female participants had an intake in accordance with recommendations (10 μg/day), see Table 8. Median intake of vitamin E was 11 alpha-TE for the male participants and 9.1 alpha-TE for the female participants. A large proportion of the participants had an intake in accordance with recommendations (10 alpha-TE for men and 8 alpha-TE for women), see Table 8. Median folate intake was 228 μg/day and 185 μg/day for the male and female participants respectively. Only 13 % (n=1) of the male participant and none of the female participants had a folate intake in accordance with recommendations (300/400 μg/day). Median intake of vitamin C was 89 mg/day and 75 mg/day for the male and female participants respectively, and 63 % (n=5) of the men and 50 % (n=6) of the women had an intake in accordance with recommendations (75 mg/day). Median intake of

salt was 5 g/day for the men and 4 g/day for the women, which gave a daily intake of sodium of approximately 2 g, see Table 8.

Median intake of micronutrients per megajoule (MJ) and the percentage of subjects which had an intake of the various micronutrients in accordance with recommendations are presented in Table 9. Median intake of vitamin D was 0.8 μg/MJ, and 25 % (n=5) of the participants had an intake in accordance with recommendations (1.4 μg/MJ). Median intake of vitamin E was 1.6 alpha-TE/MJ, and 90 % (n=18) of the participants had an intake in accordance with recommendations (0.9 alpha-TE/MJ). Median folate intake was 34 μg/MJ, and 25 % (n=5) of the participants had an intake in accordance with recommendations (45 μg/MJ). Median intake of vitamin C was 13 mg/MJ, and 70 % (n=14) had an intake in accordance with recommendations (8 mg/MJ).

Table 7: Intake of macronutrients

	All (n=20)		Intake in accordance with recommendations (%)			
Nutrient	Median	(25th , 75th)	All (n=20)	Male (n=8)	Female (n=12)	[a]Recommended intake
Carbohydrates (E%)*	47	(45, 51)	75	63	83	45-60
Carbohydrates (g)	177	(152, 199)				
Dietary fiber (g)	16.5	(11.1, 18.3)	5	13	0	25-35
Sugar (E%)*	6	(3, 9)	80	75	83	<10
Protein (E%)*	18	(17, 19)	80	88	75	10-20
Protein (g)	60	(50, 75)				
Fat (E%)*	36	(31, 39)	80	75	83	25-40
Fat (g)	53	(41, 64)				
[b] SFA (E%)*	12	(10, 15)	15	25	8	<10
[c] MUFA (E%)*	14	(10, 17)	85	88	83	10-20
[d] PUFA (E%)*	6	(4, 7)	75	75	75	5-10
Omega-3 (E%)*	2	(1, 2)	100	100	100	≥ 1
Cholesterol (mg)	168	(117, 240)	90	88	92	<300

*E% (% intake of total energy intake)

[a]Nordic Nutrition Recommendations 2012. 5th ed. Denmark; 2014

[b] SFA (Saturated fatty acids)

[c] MUFA (Monounsaturated fatty acids)

[d] PUFA (Polyunsaturated fattty acids)

Table 8: Intake of micronutrients

Nutrient	Male (n=8) Median	Male (n=8) (25th, 75th)	Female (n=12) Median	Female (n=12) (25th, 75th)	Intake in accordance with recommendations (%) Male (=8)	Intake in accordance with recommendations (%) Female (n=12)	[a]Recommended intake per day Male	[a]Recommended intake per day Female
Vitamin A [b](RAE)	501	(253, 811)	596	(306, 936)	13	42	900	700
Vitamin D (µg)	6	(3, 16)	4	(2, 7)	25	17	10	10
Vitamin E [c](alpha-TE)	11	(8, 19)	9.1	(6, 14)	63	67	10	8
Thiamin (mg)	1.6	(1.0, 1.8)	1.1	(1.0, 1.7)	63	58	1.4	1.1
Riboflavin (mg)	1.5	(1.2, 1.9)	1.4	(0.8, 1.7)	38	58	1.7	1.3
Niacin (mg)	15	(13, 19)	13	(8, 19)	25	33	18	15
Vitamin B6 (mg)	1.4	(1.0, 1.6)	1.2	(0.8, 1.6)	38	58	1.5	1.2
Folate (µg)	228	(167, 272)	185	(153, 280)	13	0	300	400
Vitamin B12 (µg)	5	(4,7)	4	(3, 5)	100	100	2	2
Vitamin C (mg)	89	(39, 114)	75	(30, 113)	63	50	75	75
Calsium (mg)	653	(575, 807)	619	(466, 845)	25	25	800	800
Iron(mg)	7	(6, 9)	7	(5, 9)	25	25	9	[d] 15
Salt (g)	5	(4, 7)	4	(3, 6)	50	92	6	6
Sodium (g)	2	(2, 3)	2	(1, 2)	50	92	2.4	2.4
Potassium (g)	2.8	(2.3, 3.1)	2.4	(2.1, 3.4)	0	25	3.5	3.1
Magnesium (mg)	234	(215, 278)	234	(188, 331)	13	42	350	280
zinc (mg)	9	(7, 10)	7	(5, 10)	50	50	9	7
Iodine (µg)	105	(52, 160)	74	(54, 112)	25	8	150	150
Selenium (µg)	42	(33, 53)	36	(23, 42)	13	8	60	50
Copper (mg)	0.8	(0.6, 1.2)	0.8	(0.5, 1.1)	38	50	0.9	0.9
Phosphorus (mg)	1218	(1128, 1488)	1047	(878, 1348)	100	92	600	600

[a]Nordic Nutrition Recommendations 2012. 5th ed. Denmark; 2014

[b] RAE (Retinol activity equivalents)

[c] alpha-TE (alpha-tocopherol equivalents)

[d] four women was >50 years, and had a recommended daily intake of 9 mg iron

Table 9: Intake of micronutrients per megajoule

	All (n=20)		Intake in accordance with recommendations (%)	
Nutrient	Median	(25th , 75th)	All (n=20)	[a] Recommended intake
Vitamin A [b] (RAE/MJ)	91	(58, 189)	55	80
Vitamin D (µg/MJ)	0.8	(0.4, 1.3)	25	1.4
Vitamin E [c] (alpha-TE/MJ)	1.6	(1.4, 2.8)	90	0.9
Thiamin (mg/MJ)	0.23	(0.17, 0.27)	100	0.12
Riboflavin (mg/MJ)	0.24	(0.19, 0.30)	100	0.14
Niacin (mg/MJ)	2.3	(2.1, 2.8)	100	1.6
Vitamin B6 (mg/MJ)	0.21	(0.18, 0.26)	100	0.13
Folate (µg/MJ)	34	(26, 43)	25	45
Vitamin B12 (µg/MJ)	0.8	(0.7, 1.0)	100	0.2
Vitamin C (mg/MJ)	13	(6, 17)	70	8
Calsium (mg/MJ)	115	(89, 147)	65	100
Iron(mg/MJ)	1.2	(1.0, 1.6)	25	1.6
Potassium (g/MJ)	0.43	(0.37, 0.52)	90	0.35
Magnesium (mg/MJ)	39	(35, 51)	95	32
zinc (mg/MJ)	1.3	(1.2, 1.8)	85	1.2
Iodine (µg/MJ)	15	(9, 23)	40	17
Selenium (µg/MJ)	6.8	(5.5, 7.5)	70	5.7
Copper (mg/MJ)	0.1	(0.1, 0.2)	100	0.1
Phosphorus (mg/MJ)	196	(182, 222)	100	80

[a] Recommended intake (The Norwegian Directorate of Health, Anbefalinger om kosthold, ernæring og fysisk aktivitet, 2014)

[b] RAE (Retinol activity equivalents)

[c] alpha-TE (alpha-tocopherol equivalents)

REE and total energy intake

REE was measured and calculated for all participants (n=33), see Table 9. Of the 33 participants, 32 had not been drinking or eating 12 hours prior to the REE measurement. Mean REE measured by indirect calorimetry for the population (n=33) was 1249 kcal/day, mean REE for the male (n=15) and female (n=18) participants were 1416 kcal/day and 1110 kcal/day respectively, see Table 9. The male participants had significantly higher measured REE compared to the females, with a mean difference of 306 kcal/day (p<0.001). Mean REE per unit body weight was 21 kcal/kg for the male participants, and 20 kcal/kg for the female participants. The mean REE from estimations by Harris-Benedict equations for the population (n=33), the male (n=15) and the female (n=18) participants were 1311 kcal/day, 1383 kcal/day and 1250 kcal/day respectively. The estimations by HBEs for all- and male participants was not significantly different from measured REE. But the estimations for the

female participants were significantly overestimated by a mean of 140 kcal/day (p=0.001). The mean REE from estimations by Mifflin St. Jeor equations for the population (n=33), the male (n=15) and the female (n=18) participants were 1552 kcal/day, 1719 kcal/day and 1413 kcal/day, respectively. The estimated REE by MSJEs significantly overestimated REE on group level (p<0.001), and for the male (p=0.001), and female (p<0.001) participants separately by 303 kcal/day, which gives an overestimation of 24 % on group level.

Table 10: Mean REE and total energy intake in the study population

	Mean (SD*)		
	All (n=33)	**Male (n=15)**	**Female (n=18)**
[a] REE measured by[b] IC	1249 (208)	1416 (161)	1110 (121)
[a] REE predicted by[c] HBEs	1311 (158)	1383 (182)	1250 (106)
[a] REE predicted by[d] MSJEs	1552 (258)	1719 (267)	1413 (147)
	All (n=20)	**Male (n=8)**	**Female (n=12)**
Total energy intake (kilocalories)	1400 (356)	1569 (239)	1287 (385)
Total energy intake (megajoule)	5.6 (1.6)	6.6 (1.0)	5.1 (1.3)

*SD (Standard Deviation)

[a] REE (Resting Energy Expenditure, (kilocalories/day))

[b] IC (Indirect Calorimetry)

[c] HBEs (Harris-Benedict Equations)

[d] MSJEs (Mifflin-St. Jeor Equations)

The men (n=8) and women (n=12) had a mean energy intake of 1569 kcal/day and 1287 kcal/day respectively, and the mean energy intake in the population (n=20) was 1400 kcal/day, see Table 9. REE compared to total energy intake (kcal) is presented in Figure 12. The mean energy intake for all participants was 10 % higher than the mean REE.

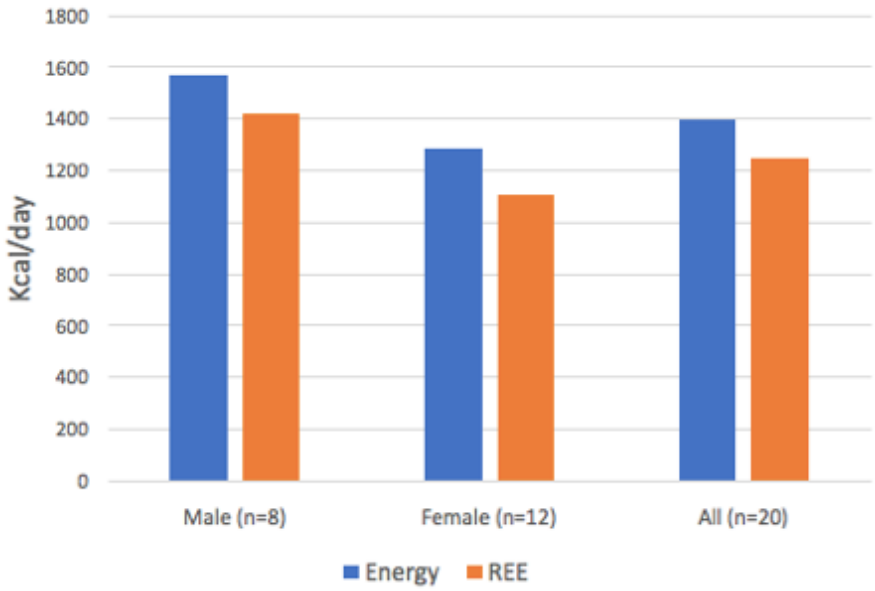

Figure 12: Mean energy intake and REE in the population and between genders

4.4 Correlation analyses

Correlations are shown in Table 10. A strong positive correlation was found between BMI and waist circumference (r=0.865). A strong positive correlation was also found between waist circumference and age (r=0.508) and weight (r=0.850). A medium positive correlation was found between BMI and age (r=0.459).

Table 11: Correlations

Pearson's product moment correlation coefficient (r)

	Age	Weight	[a] BMI	Waist circumference
Age	1.000			
Weight	0.513*	1.000		
[a] BMI	0.459*	0.829**	1.00	
Waist circumference	0.508*	0.850**	0.865**	1.00

[a] BMI (Body Mass Index)

* p<0.01

** p<0.001

4.5 Sub-analyses

Blood pressure

No significant relationship was found between hypertension and sodium intake. There was no significant difference in SBP or DBP for individuals with sodium intake <2 g/day and >2 g/day. The participants that were classified as overweight according to BMI had significantly higher SBP and DBP compared to participants of normal weight, with a median difference of 17 mmHg and 11 mmHg respectively.

BMI and waist circumference

There was no significant difference in BMI for the men and women. The mean waist circumference for the male participants was significantly higher than the females', with a mean difference of 11.9 cm. There was no significant difference in intake of total energy or any nutrient between men and women with a waist circumference ≥102 cm and ≥88 cm respectively and men and women with a waist circumference <102 cm and <88 cm respectively.

Physical activity

There appears to be no association between physical activity and gender, and there was no significant difference in age for the three categories of physical activity level.

Diet and REE

There were no significant differences in SmartDiet scores between the men and women, and there was no significant difference in energy intake between genders. One participant did not meet fasted for the REE measuring, however this did not affect the mean REE in the population.

5 Discussion

This cross-sectional study indicated a low overall risk of cardiovascular disease in the adult Norwegian achondroplasia population, despite high frequency of obesity assessed by BMI and waist circumference. According to the SmartDiet questionnaire, none of the participants had a healthy and heart-friendly diet. The diet was characterized by low intakes of fruit, vegetables, dietary fiber, vitamin D and folate and a high intake of saturated fatty acids. Total energy intake was approximately 10 % above resting energy expenditure, consistent with a low level of physical activity.

5.1 Method discussions

5.1.1 Study population

Of the thirty-five recruited individuals, thirty-three participated in this master thesis, which gave a participation rate of 94 %. The objectives of this master thesis is of high relevance to the Norwegian achondroplastic population, which may have been a contributing factor to the high participation rate despite the decline in participation seen in epidemiologic studies over the past decades (179). Most of the participants lived in south-eastern Norway and few lived in northern, central and western parts of Norway. All travel expenses were covered for the participants, so travel distance and expenses should not bias the selection of subjects that participated. The majority of the Norwegian population lives in the south-eastern parts of Norway (180), which reflects the residency of the subjects participating in this master thesis. Age and educational level in the study population was widespread, and there was also approximately equal participation from the two genders. "The Norwegian Adult Achondroplasia Study", which the participants of this master thesis were recruited, was presented at two summer-gatherings of the Norwegian Association of Short Stature (NiK), in addition to TRS' website, social media and relevant hospital departments and rehabilitation institutions that possibly met adults with achondroplasia. The study population can be regarded as representative for the general Norwegian achondroplasia population, with the proviso of possible selection bias.

One participant was under the age of 18 years, and was categorized as an adult for all the lipid values and all the recommended intake levels for macro- and micronutrients.

Considering the small sample size, if the participant was categorized as an adolescent, the risk of identification would greatly increase. In addition, this master thesis investigated the diet and risk of CVD in the adult Norwegian population, and a categorization including adolescents was therefore not needed.

In this study, a large proportion of the population had higher education at university or college level. However, 30 % received full disability benefit, which is three times higher compared to the Norwegian population in general (181). This may be due to the many complications that follows the disorder, as pain and sleep apnea, which can make it hard to keep a full-time job. Another reason can be that those with full-time jobs do not have time to participate in studies equally to those who receive disability benefit. Studies done in the American achondroplasia population have shown that affected individuals have lower level jobs and lower annual income compared to their unaffected first-degree relatives, but the results on educational level are inconsistent (182, 183). One study found no significant difference in the level of education between individuals with achondroplasia and their unaffected same-sex siblings (183), while another study found that achondroplastic individuals had lower educational level compared to their unaffected first-degree relatives (182). There are no studies describing the proportion of achondroplastic individuals receiving full disability benefit in other parts of the world. However, the lower annual income found in the American achondroplasia population (182), may indicate lower socioeconomic status among achondroplastic populations.

5.1.2 Methods

Weight and height data may contain measurement errors, due to instrument quality, data handling or inaccuracy. To minimize measurement errors from instrument quality, the same combined weight and altimeter were used for all participants. To minimize measurement errors due to inaccuracy, all the participants wore indoor clothes during the weighing and 1 kg was subtracted from all the participants' weight. Weight and standing height were not measure by the same person for all participants, as data collection started before the onset of the master thesis. This could lead to additional measurement errors, and to reduce the risk, the dietitian monitored the first measurement by the master student to ensure that they performed the measuring in a similar manner. BMI is a widely used method for evaluating body composition, but being dependent on height, this method may not apply for the

achondroplastic population (184). In addition, waist circumference have been proposed as a better predictor of cardiovascular risk than BMI (185). For these reasons, waist circumference was used in addition to BMI in the present study. This is consistent with the recommendations from World Health Organization of a joint use of BMI and abdominal measurements when predicting disease risk (43).

Two methods were chosen for the data collection of nutrient intake, the SmartDiet questionnaire and four-day dietary record. The SmartDiet questionnaire is a retrospective and self-administered food and lifestyle questionnaire, which gives an overview of the usual diet. It is not time-consuming and it is easy to count the scores and evaluate the diet, which made this method practicable for both the participants and the master student. SmartDiet is depended on the participant's memory, and there is a tendency of overestimation of healthy foods (fish, fruits and vegetables) (167). Although SmartDiet was used only at one occasion and depends on the memory of the participants, studies have shown that information about an individual´s food choices can say more about the cardiovascular risk than single food items (167).

The dietary record provides information about the exact intake of various food items and beverages over a specified time. The method has high precision and validity, but has some limitations (168). It only provides information about the current diet, which may not be the usual diet, and there is a tendency of idealizing the diet and not record what has truly been consumed (168). This method is precise as the foods and beverages are recorded as consumed with portion sizes and information about brand and type of product (e.g. whole milk/skimmed milk). The picture book that was attached to the dietary record assisted the participants in defining portion sizes, which made the portion sizes more standardizes. A dietary record of seven days or more will minimize the bias of day-to-day variations, but studies have shown that after four days the recording often decreases (168). The dietary record in this master thesis was initially meant to last for seven consecutive days, but the participants thought it was too demanding. After six participants, the procedure was reduced to four consecutive days to get as many to participate as possible. The change in method did probably not affect the results, except from increasing the participation. To minimize the bias of day-to-day variations, the participants was asked to record from Saturday through Tuesday. SmartDiet was completed by 97 % of the participants, but only 60 % completed the dietary record. SmartDiet is less time consuming and demanding than the dietary record, and most of the

participants filled out the questionnaire while staying at Sunnaas Rehabilitation Hospital and thus received a closer follow-up, which may be the reason for the higher completion. In an attempt to increase the number of completed dietary records, all participants who did not submit a dietary record were called up at least three different times. In addition, participants who did not answer the phone calls, received a motivating text. This increased the participation somewhat. The low completion rate for the dietary record may have caused non-response bias, where the subjects that are the most interested in health and diet are the ones who contributed.

Resting energy expenditure was measured on the morning of the participants second day at Sunnaas Rehabilitation Hospital. All participants, except one, met fasted for the measuring. Sub-analysis showed that the participant's REE did not affect the mean REE in the population, and was therefore included. The REE were measured using a mask and the measurements took place at the clinical physiological laboratory at Sunnaas Rehabilitation Hospital. Using a ventilated hood by the participant's bedside was initially considered, but was not possible to implement, due to extensive hygienic regulations at the hospital. Previous studies have shown that the results from IC with mask do not significantly differ from the results when a hood system are used (186, 187). In addition, the hood system that was initially considered only measured O_2, while the computerized standard open-circuit technique breath-by-breath spirometer uses both O_2 and CO_2, for the conversion to REE, which makes this method more accurate. To make sure that the participants waking distance from their bed to the clinical physiological laboratory did not affect the results of the REE measurement, only the mean of the last five minutes of the test was used in the analyses. All participants were asked if they were lying comfortably on the examination bench before the REE measurement started, to make sure that they were relaxed and not stressed. No activity was planned for the participants at the hospital the day before the REE measurement. Although everything was done to make sure that the REE measurements were as accurate as possible, factors aforementioned, such as the walking distance and stress, could have increased the REE-values.

5.2 Results

5.2.1 Risk factors for cardiovascular disease

Despite the high intake of saturated fatty acids in the study population and the high cardiovascular risk found in achondroplastic populations in other parts of the world, median levels of cholesterol and triglycerides was within optimal range. The same was found for triglyceride levels in American and Canadian achondroplastic subjects (51). However, low HDL cholesterol levels were found in 39 % of the women and 26 % of the men in the present study. Nevertheless, recent findings show that HDL composition and function are of greater importance for cardiovascular risk rather than HDL cholesterol level (188-190). Apart from triglyceride levels in the American and Canadian achondroplastic population, no studies have reported lipid levels in achondroplastic subjects. Hypertension was found in approximately 20 % of the participants in the present study, which is slightly below the prevalence assumed in the general Nordic population (191). There are no previous studies reporting blood pressure in achondroplastic individuals.

In the present study, we found obesity to be common in achondroplasia, and according to BMI 9 out of 10 adults categorized as overweight, and 3 out of 4 categorized as obese. These findings show a higher prevalence of obesity compared to the general Norwegian population where 1 out of 5 categorizes as obese (45), and findings from the American achondroplasia population (13). The American study investigating obesity in achondroplastic subjects was conducted in the late 1980s and found a 43 % prevalence of obesity according to BMI (13). Obesity is increasing in the general American population (192) and it is likely that the prevalence of obesity among in the American achondroplasia population also have increased. For this reason, the prevalence found in the study population of the present study may not deviate as much from the Americans after all. Sub-analyses showed that participants categorized as overweight by BMI had significantly higher blood pressure compared to participants of normal weight. This highlights the unfavorable effects of overweight and obesity on cardiovascular risk. Body mass index being dependent on height, may give an overestimated prevalence of obesity in this population due to short stature (184). However, the strong correlation was found between BMI and waist circumference in the study population supports a high frequency of obesity. Half of the study population had a moderately increased waist circumference, and about 30 % had a considerable increased waist circumference, which indicates a high prevalence of abdominal obesity and that

achondroplastic individuals have an increased risk of metabolic complications and CVD (43). BMI have been found to be correlated with waist circumference in previous studies, although with different levels of associations (43).

In addition to the suggested abnormal energy metabolism due to the mutation in FGFR3 (7), the abnormal anatomy of achondroplasia (1) may lead to an atypical fat distribution in the body, which may contribute to the high frequency of abdominal obesity in the achondroplastic population. Recent findings from mouse models show that therapy with soluble FGFR3 early in life may prevent abdominal obesity in achondroplasia (7). Although the transferability to humans is currently uncertain, this may be a potential treatment strategy in the future.

Self-reported physical activity was extracted from the SmartDiet questionnaire. Results showed that only one out of four were physically active for ≥30 minutes three or more times per week, and the majority of the study population did therefore not meet the recommended level of physical activity from the Norwegian Directorate of Health (49). This is not notably different from the general Norwegian population, where one out of three meets the recommendations (193). Complications that often follows achondroplasia, such as pain, spinal stenosis and genu varum, may be the reason for the low physical activity level in the study population. Despite high prevalence of pain among achondroplastic individuals, it has been reported generally good mobility and few difficulties with walking (10). Therefore, it is not likely that pain or difficulties linked to mobility or walking is the only reason for the low physical activity level. Both BMI and waist circumference increased with age in the present study, which may be due to a decrease in physical activity. However, analyses of physical activity showed that the level of activity did not significantly decrease with age. On the other hand, the physical activity level was self-reported and studies have shown that self-reported physical activity tends to be overestimated (194, 195).

Approximately 10 % of the study population reported to smoke tobacco. This is in agreement with smoking habits in the general Norwegian population according to Statistics Norway (196). Smoking have declined in the general Norwegian and Swedish population over the last decades (196, 197), and results from Sweden show that the decline in smoking is one of three main reasons for the decrease in coronary heart disease mortality (197). A study on smoking and sleep apnea found that individuals with sleep apnea that smoked had increased risk of

CVD compared to subjects that did not smoke (198). This highlights the relevance of smoking cessation and that smoking cessation should be of high concern in achondroplastic populations due to the allegedly increased risk of cardiovascular disease.

The results from the NORRISK 2 calculations of 10-year risk of CVD indicates that despite the high prevalence of obesity, the study population had a low cardiovascular risk based on lipid levels, blood pressure, age, gender and smoking habits. This is in contrast to a 42-year follow-up study in the American and Canadian achondroplastic population showing that achondroplastic individuals had an increased risk of CVD, and that young adults with achondroplasia had an even higher cardiovascular risk (9). The risk of CVD in the general population increases after the age of 45 years (37), and mean age of subjects in the present study being 40 years may be one reason for the low 10-year risk found by the NORRISK 2 calculator. There may be other factors than the traditional cardiovascular risk factors that give the increased risk among the achondroplastic population.

5.2.2 Dietary intake

According to the SmartDiet questionnaire, none of the participants had a healthy and heart-friendly diet. The results indicate a dietary pattern with high intake of unhealthy foods, such as processed meat and high-fat dairy products, and a low intake of healthy foods such as fruits, vegetables and legumes – a western dietary pattern. The distribution of energy intake from carbohydrates, protein and fat was in accordance with recommendations for most of the participants. Intake of unsaturated fatty acids was in accordance with recommendations for a large proportion of the participants. About half of the participants reported to eat fish for dinner twice a week. Of the participants reported eating fish for dinner, about 60 % reported eating fatty fish 1-2 timers per week, which is a good source to unsaturated fatty acids and vitamin D. However, intake of saturated fatty acids, dietary fiber, folate and vitamin D in this population matched poorly with recommendations. Only 15 % had an intake of saturated fatty acids within recommended level, and only 5 % of the participants reached the recommended dietary fiber intake. Intake of vitamin D and folate were generally low among the participants, and none of the women met recommended intake of folate. Although just over half of the participants reported eating fish twice a week and roughly 50 % reported to use low-fat milk, where one brand was fortified with vitamin D, the intake was not high enough to give an adequate intake of vitamin D. It must also be mentioned that without

supplements with vitamin D and folate, such as cod liver oil and multivitamins the intake in the population was even lower. In addition to vitamin D and folate, median intake of several other micronutrients was below recommended level. This was mainly due to a low total energy intake. Intake of micronutrients in the study population was also presented as nutrient density, intake per megajoule. The percentage of participants with recommended intake of micronutrients increased when viewing intake per megajoule compared to intake per day. However, the recommendations per megajoule may not be accurate to use due to the low energy intake in the study population (141). An adequate intake of micronutrients is difficult to achieve with a low daily energy intake, and dietary supplements may therefore be necessary in this population. Nevertheless, all recommendations from the Norwegian Directorate of Health and the Nordic Nutrition Recommendations 2012 have a margin of safety, where recommended intake is higher than the average requirement. Therefore, the Norwegian achondroplasia population may not have as suboptimal levels of micronutrients as it appears in this study. Studies investigating micronutrient status and the necessity for supplements in the achondroplastic population would be interesting.

Individuals and groups with low socioeconomic status are more likely to have an unhealthy diet (199). Nevertheless, a low intake of fruit, berries, vegetables and dietary fiber, and a high intake of saturated fatty acids was also found in the general Norwegian population in NORKOST 3 (140). The Norwegian directorate of health recommends at least five servings (500 grams) of fruit, berries and vegetables per day, but in the present study, only 6 % ate 4 or more servings (≥600 grams) per day. Studies have shown that there is a tendency of over-reporting healthy foods such as fish, fruits and vegetables, and under-reporting foods rich in sugar and fat (167, 200). Hence, the intake of fruits, berries, vegetables, folate and vitamin D may be even lower, and the intake of saturated fatty acids even higher than reported. The consume of fruit, berries and vegetables in Norway is generally low, NORKOST 3 found that only 25 % of the general Norwegian population consumed 5 or more servings of fruit, berries and vegetables per day and a dietary fiber intake of 25-35 grams/day (140). Furthermore, adequate consumption of fruit, berries and vegetables, dietary fiber and fatty acids may be even more important for the achondroplastic population due to the high frequency of obesity and the allegedly increased risk of CVD.

It appears to be a satisfying correspondence between the two chosen methods for collection of dietary data; SmartDiet and dietary record. Results from SmartDiet showed a low intake of

fruit, berries and vegetables in this population, which agrees with the low fiber and folate intake reported in the dietary record. A large proportion of the participants reported to eat meat and meat products, cheese and butter with a high content of saturated fatty acids in the SmartDiet, and the dietary record showed a high intake of SFAs. The reported intake of foods with high sugar content also seemed similar in the two methods. The satisfying correspondence between the two methods minimizes the possibility of non-response bias from the low completion of the dietary record. Although SmartDiet and the dietary record appeared to give the same results, interpretation of results from self-reported methods in nutritional research should be done with caution, thus self-reported intake does not always reflect actual intake (201).

Taken together, the study population had an unhealthy diet, though comparable to what have been found previously in the general Norwegian population. Although no increased cardiovascular risk was found at this time, the combination of overweight, low physical activity and poor diet in this population may lead to adverse consequences for disease risk in the long term. For this reason, the Norwegian adult achondroplasia population should be followed up with focus on lifestyle habits.

5.2.3 REE and energy intake

The reason for the high prevalence of obesity found in the achondroplastic population is uncertain, and it has previously been suggested that a predisposition for obesity follows with achondroplasia (51). REE of achondroplastic individuals may be different from individuals of normal height, and may be a contributing factor to the high prevalence of obesity.

Findings of this master thesis showed that Norwegian men and women with achondroplasia had significantly lower daily REE compared healthy men and women of normal height (157, 202-204). This is consistent with findings in the American and Canadian achondroplastic population by Owen et al (51). Metabolically active tissues, as skeletal muscle, the brain and liver, are a major contributors to REE (18). The reduced muscle mass and body surface area in achondroplasia may be one of the reasons for the low daily REE. When viewing REE per unit body weight, achondroplastic men and women in the present study had approximately equal REE/kg as men and women of normal height, reported by recent studies (203, 204). This is inconsistent with previous findings in the American and Canadian achondroplasia

population by Owen et al., where achondroplastic individuals had higher REE/kg compared to men and women of normal height (51). The REE/kg found in achondroplastic individuals in the present study was lower than REE/kg found in the American and Canadian achondroplasia population. This may be the reason for the inconsistence when comparing REE/kg of achondroplastic individuals to individuals of normal height. In addition, the reference group of men and women of normal height that Owen et al. compares the REE/kg in achondroplastic men and women with, had lower REE/kg compared to findings of recent studies (157, 202-204). When comparing REE/kg found in the present study with the same reference population as Owen et al., REE/kg for the achondroplastic men and women were higher compared to men and women of normal height, but the difference did not deviate as much as for the American and Canadian population. These findings indicate a difference in REE/kg for the Norwegian and American/Canadian achondroplasia populations.

The estimated REE using Harris-Benedict equations was not significantly different from measured REE on group level or for the male participants. However, the HBE overestimated REE for the female subjects by 13 %. Estimation of REE by Mifflin-St. Jeor equations was significantly different from measured REE by indirect calorimetry, and overestimated REE by 24 % on group level and by 21 % and 27 % for male and female subjects respectively. These findings indicate that HBEs are more accurate in estimating REE than MSJEs. This is not consistent with the majority of previous research on prediction equations which show that Mifflin-St. Jeor equations are the most accurate in estimating REE, especially for overweight and obese individuals (160-163, 205, 206). Prediction equations may be used to predict daily resting energy expenditure of those with achondroplasia, but it should be noted that the result may be overestimated by 100-300 kcal.

The achondroplastic population in the present study had lower resting energy expenditure compared to men and women of normal height, suggesting that achondroplastic individuals have lower energy requirements and that a high total energy intake may be a contributing factor to the high frequency of obesity. However, reported mean total energy intake and measured REE in the study population was 1400 kcal/day and 1249 kcal/day respectively, which resulted in an energy intake of 10 % above REE. In addition, no significant difference in energy intake was found between participants with increased and normal waist circumference. This indicates that a high total energy intake may not be the only reason for the high prevalence of abdominal obesity in the achondroplastic population, and that the

reason may be related to activity level or the mutation in FGFR3 or other factors, rather than the diet. However, it is common that study subjects underreport their energy intake (195, 201).

There was not enough information about physical activity level to calculate PAL and further to calculate daily energy requirements for the study population. In addition, there are no specific PAL values for the achondroplastic population, and it may not be accurate to use the normal PAL values to calculate daily energy requirements in this population. Further studies are needed to assess the role of physical activity on energy balance.

5.3 Strengths and limitations

The present study is the first in the world, to our knowledge, to investigate the diet of individuals with achondroplasia. The study provides important insight to the diet of a population that has been shown to be at increased risk of a disease where diet is a modifiable risk factor. To get as accurate dietary data as possible, two methods were used for collection of dietary information. Test results and measurements from "The Norwegian Adult Achondroplasia Study" gave a broader insight to the cardiovascular risk factors in the study population, and made it possible to investigate the diet in relation to other risk factors.

Some limitations of this study should be addressed. First, there may have been non-response bias in the dietary data. However, the satisfying correspondence between the two dietary methods minimized the possibility. Secondly, the participants' walking distance to the resting energy expenditure measurements could have affected the results. Thirdly, there are several cardiovascular risk factors that were not investigated in this study, such as HbA1c, C-reactive protein, depression and air pollution. Last, there are some limitations in the cross-sectional design (207). Anthropometrics were only measured once and diet were only recorded at one occasion. The cross-sectional design can therefore only provide associations, and not causality (207). Despite the limitations in the cross-sectional design, this was the most suitable design within the time frame of this master thesis.

6 Conclusions

The investigation of diet and risk of cardiovascular disease in the adult Norwegian achondroplasia population led to the following conclusions:

Elevated total cholesterol levels were not found in the adult Norwegian achondroplasia population. However, low levels of HDL cholesterol and elevated triglyceride levels were observed. The prevalence of hypertension in this population did not differ from the general Norwegian population. The 10-year risk of cardiovascular disease (measured by NORRISK 2) in this population was low.

The mean height and weight was 132.9 cm and 60.5 kg, resulting in a mean BMI of 34 kg/m^2. Increased waist circumference was found in approximately 1/3 of the population. The high BMI and increased waist circumference show a high frequency of obesity, and specifically abdominal obesity, among men and women with achondroplasia.

The adult Norwegian achondroplasia population had an unhealthy diet with similarities to the Western dietary pattern. The hypothesis that individuals with achondroplasia have a diet high in saturated fat and low in dietary fiber compared to national recommendations was confirmed. Median intake of dietary fiber, vitamin D, folate and saturated fatty acids matched poorly with recommendations. Energy intake was only 10 % higher than measured resting energy expenditure.

The achondroplastic population in the present study had lower daily resting energy expenditure compared to men and women of normal height. The hypothesis that this population have a high total energy intake compared to daily energy requirements could not be confirmed or canceled at this point. The results of this study must be interpreted with caution due to the cross-sectional design and the small sample size.

Despite the low overall risk of cardiovascular disease in the adult Norwegian achondroplasia population, the combination of unhealthy diet and central obesity may however lead to cardiovascular disease later in life, and we suggest that diet and life-style counseling should be offered to this patient group.

7 Future perspectives

- The reason(s) for the high prevalence of obesity in the adult achondroplasia population is uncertain, and should be further investigated.
- To be able to calculate daily energy requirements for achondroplastic individuals, information on physical activity in achondroplastic subjects beyond what was collected in this study should be of focus. In addition, further research should also investigate REE and total energy expenditure using the whole room indirect calorimetry method.
- Studies of longitudinal design with focus on additional risk factors should be conducted in the adult Norwegian achondroplasia population to investigate causality between diet, cardiovascular risk and the high frequency of obesity.
- The adult Norwegian achondroplasia population has an unhealthy diet with similarities to the Wester dietary pattern. Further research in this population should focus on how to increase the knowledge about a healthy diet and how to exchange foods to increase consumption of unsaturated fatty acids and decrease consumption of saturated fatty acids, in addition to an increased consumption of fruits and vegetables.
- The adult Norwegian achondroplasia population have a low total energy intake, and studies investigating the micronutrient status and the necessity of dietary supplements in this population should be conducted.

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Appendices

Appendix 1 SmartDiet questionnaire

Appendix 2 Dietary record

Appendix 3 The Norwegian Regional Committees for Medical and Health Research Ethics (REC), region South East, reply to application

Appendix 4 Written consent form and information about the study

Appendix 1

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

Sett ett kryss til hvert spørsmål ved å krysse av i sirkelen ved det alternativet som passer best med det du vanligvis spiser.
Vær oppmerksom på at spørsmålene veksler mellom å spørre etter daglig og ukentlig forbruk.

1. Melk (sur/søt) og yoghurt

Hvor mange glass melk drikker/bruker du daglig som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te o.l.? Antall:.....

Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke? Antall:.....

Hvilken type melk bruker du oftest?

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett .....
Lettmelk • Cultura • Biola naturell (syrnet lettmelk) • Ekstra Lett melk • Melk med smak .....
Skummet melk • Skummet kultur melk • Biola bærdrikk 0,1 % fett .....
Drikker/bruker mindre enn 1 liter melk i uken eller bruker aldri .....

2. Fløte, rømme o.l.

Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te o.l.

Kremfløte • Créme Fraiche • Seterrømme • Pisket krem.....
Matfløte • Lettrømme • Créme Fraiche lett.....
Kaffefløte • Ekstra lett rømme • Vikingmelk • Kesam • Matyoghurt • Créme Fraiche 10 % fett .....
Bruker ikke dette ukentlig eller bruker aldri .....

3. Ost på brødmaten, i matlaging, på pizza o.l.

Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost), spiser du daglig? Antall:.....

Til hvor mange middager per uke bruker du ost? (eks pizza, lasagne, i saus, i salat o.l.) Antall:.....

Hvilken type ost bruker du oftest?

Hvitost • Nøkkelost • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan .....
Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak .....
Ost med raps- og solsikkeolje (Vita Gul o.l.) • Cottage cheese • Gammalost • Pultost • Mager mysost • Prim • Mager prim • "Så lett" ost 10 % fett .....
Bruker ost kun en gang i uken eller bruker aldri .....

4. Kjøttpålegg

Hvilken type kjøttpålegg bruker du oftest?

Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse • Reinsdyrpølse • Falukorv • Fleskepølse • Sylte • Lammerull • Paté • Fenalår • Leverpostei (vanlig) .....
Kokt/røkt skinke • Hamburgerrygg • Krydderskinke • Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand • Oljebaserte posteier (Vita, Mills, Delikat, Gilde) • Mager leverpostei.....
Bruker kjøttpålegg kun en gang i uken eller bruker aldri .....

5. Kjøtt til middag

Hvilken type kjøtt bruker du oftest?

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake • Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt .....
Kjøttdeig (okse, lam) • Kyllingpølse • Lettpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt • Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand • Hamburgerrygg med fettrand .....
Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett • Kylling, kalkun og høne uten skinn • "Go og mager" pølser • Vita pølser.....
Spiser kjøtt kun en gang i uken eller spiser aldri .....

6. Fiskepålegg

Hvor ofte har du fisk som pålegg eller i salater til lunsj?

Eksempel: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker o.l.
På inntil 1 brødskive i uken eller aldri.....
På 2-4 brødskiver i uken .....
På 5 eller flere brødskiver per uke .....

7. Fisk til middag

Hvor mange ganger i uken spiser du fisk, fiskemat og/eller fiskeretter?

Inntil en gang i uken eller aldri .....
2 ganger i uken .....
3 eller flere ganger i uken .....

Til hvor mange av disse middagene spiser du fet fisk ukentlig? Antall:.....
Eksempel: Ørret • Laks • Makrell • Kveite • Sild

8. Majones, remulade og kaviar

Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?

Eksempel: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix o.l.
På inntil 1 brødskive i uken eller aldri.....
På 2-7 brødskiver i uken .....
På 8 eller flere brødskiver per uke .....

9. Smør eller margarin på brødmaten

Hvilken type bruker du oftest?

Meierismør og alle andre typer smør • Smøregod • Bremyk • Brelett • Brelett Oliven • Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta .....
Soft Flora (beger) • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin • Soft Ekstra • Brelett omega-3 margarin.....
Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin.....
Bruker vanligvis ikke smør eller margarin på brødmaten .....

10. Plantesteroler

Bruker du et produkt som inneholder plantesteroler?
Eksempel: Vita Pro-aktiv • Becel Pro-aktiv ◯ Ja ◯ Nei

11. Fett i matlagingen

Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing o.l.

Meierismør og alle andre typer smør • Bremyk • Smøregod • Melange margarin (kube) • Per margarin • Soft Flora stekemargarin (kube) • Soya stekemargarin • Palmeolje .....
Soft Flora (beger) • Soya margarin • Solsikke margarin • Oliven margarin • Olivero • Soft Ekstra.....
Olje • Flytende margarin • Vita .....
Bruker vanligvis ikke fett i matlagingen .....

12. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig? Antall:.....

Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokostblandinger spiser du ukentlig? Antall:.....

Hvilken type brød og kornprodukter spiser du oftest?

Kneippbrød • Firkornbrød • Landbrød • Jegerbrød • Loff • Fine rundstykker • Baguetter • Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter • Frokostkorn (med sjokolade, honning, sukker) o.l. .....
Rugbrød • Pumpernikkel • Bakers havre-, spelt- og byggbrød • Vita brød • Goman havrebrød • Mesterbakeren grovbrød • Birkebeinerbrød • Mørke knekkebrød • Rugsprø • Fiberrik • Havregryn • Weetabix • Havrefras • Shredded wheat o.l.....
Spiser ikke brød, knekkebrød eller andre kornprodukter.....

13. Grønnsaker, frukt og bær

Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?

1 porsjon = 150 g som tilsvarer ca 2 gulrøtter eller ca et stort eple
Mindre enn 2 porsjoner (< 300 g) .....
2-4 porsjoner (300-600 g).....
Mer enn 4 porsjoner (> 600 g).....

Hvor mange av disse porsjonene er grønnsaker? Antall:.....

Hvor mange ganger i uken spiser du salat til lunsj? Antall:.....

14. Søtt pålegg og søt drikke

Hvor ofte bruker du søtt pålegg eller søt drikke med sukker eller fruktsukker?

Eksempel: Syltetøy • Marmelade • Prim • Geitost • Sjokoladepålegg • Honning • Brus • Saft • Fruktjuice/juice • Nektar o.l.
0-1 ganger daglig .....
2 ganger daglig .....
3 eller flere ganger daglig.....

15. Sjokolade, snacks, kaker, kjeks o.l.

Hvor ofte spiser du snacks?

Eksempel: Sjokolade • Fløteis • Potetgull • Ostepop • Baconcrisp • Tortilla chips • Kaker • Kjeks • Smågodt o.l.
0-1 ganger ukentlig .....
2 ganger ukentlig.....
3 eller flere ganger ukentlig.....

Totalt antall poeng: ____

16. Belgvekster

Spiser du belgvekster ukentlig? ◯ Ja ◯ Nei
Eksempel: Hvite tomatbønner • Brune bønner • Kikerter • Linser • Erter • Sukkererter o.l.

17. Potet, ris og pasta

Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?
En porsjon tilsvarer 2 poteter eller 2 dl kokt ris eller 2 dl kokt pasta/spaghetti
◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

Hva spiser du oftest? ◯ Potet ◯ Ris ◯ Pasta

18. Nøtter, mandler o.l.

Spiser du nøtter/mandler ukentlig? ◯ Ja ◯ Nei
Spiser du avokado eller oliven ukentlig? ◯ Ja ◯ Nei

19. Kaffe

Drikker du kaffe? ◯ Ja ◯ Nei

Hvis ja, hvilken type? .....
Eksempel: Cappuccino • Café latte • Presskannekaffe • Kokekaffe • Traktekaffe • Pulverkaffe o.l.

20. Alkohol

Drikker du alkohol? ◯ Ja ◯ Nei

Hvis ja, hvor mange enheter drikker du til sammen per uke?
◯ Mindre enn 1 ◯ 1-7
◯ 8-14 ◯ 15 enheter eller flere

1 enhet =
1 glass vin (125 ml)
1 glass øl (0.33 l)
4 cl brennevin

21. Egg

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

1. Måltidsmønster

Hvor mange måltider, inkludert mellommåltider, spiser du daglig?
◯ 1-2 måltider ◯ 3 måltider
◯ 4 måltider ◯ 5 eller flere måltider

2. Høyde, vekt og midjemål

Høyde: ..... cm Vekt: ..... kg

Ønsker du å gå ned i vekt? ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

Midjemål: ..... cm (Fylles ut av helsearbeider)

3. Røyk/snus

Røyker du? ◯ Nei ◯ Ja ◯ selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du i gjennomsnitt per dag? Antall .....

Snuser du? ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du i gjennomsnitt per dag? Antall .....

4. Mosjon

Hvor ofte mosjonerer du i minst 30 minutter slik at du blir lett andpusten eller svett?
Eksempel: Rask gange • Løping • Skigåing • Svømming • Sykling o.l.
◯ Sjeldnere enn 1 gang per uke eller aldri
◯ 1 til 2 ganger per uke
◯ 3 eller flere ganger per uke

Hvilken type mosjon bedriver du? .....

5. Kosttilskudd

Bruker du kosttilskudd?
◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler
◯ Multivitaminpreparat ◯ Annet .....

UiO : Universitetet i Oslo

SUNNAAS SYKEHUS

Kostregistreringsskjema

ID-nummer:

_____

Alt du spiser og drikker i 4 dager registreres på skjemaet

Beskriv all mat og drikke, mengder og tidspunkt du inntar dette så nøyaktig som mulig. **Bruk vedlagt bildehefte fra NORKOST til hjelp for å beskrive porsjonsstørrelsene.** Beskriv;

- Type brød (f.eks loff). Angi mengde, fasong, tykkelse og grovhet (se side 5 til 9 i vedlagt hefte).
- Type smør/margarin (f.eks Meierismør), og mengde (f.eks bilde 10 B).
- Type pålegg, f eks: kaviar (Mills blå, bilde 10 D), 1 skive kokt skinke (Gilde).
- Middagsmat (f.eks 2 eggstore, kokte poteter uten skall, 3 kjøttkaker Gilde). På baksiden av arkene angis oppskriften på hjemmelagde retter. Salat kan angis som på bilde 34 eller gryterett bilde 25.
- Dersom det ble brukt salt i eller over mat oppgis type (f.eks jozo rød pakke).
- Tilberedning angis; kokt, stekt, grillet, panert (f.eks kokt fullkornpasta, grillet biff).
- Tilbehør angis som mengde og type (f.eks ½ dl Toro sjysaus eller bilde 33 B).
- F.eks 1 plomme, 4 Ritz kjeks, 4 seigmenn, 1 pose potetskruer med salt (100 g).
- Type og mengde kosttilskudd (f.eks 5 ml tran, 500 mg kalsiumtbl).
- Drikke (f.eks 2 glass vann eller bilde 3 B, til øverste streken), 1/2 krus kakao (bilde 4 J) - (hjemmelaget – se egen oppskrift), ½ L solo.
- Beskriv gjerne mengdene på de vanlige glassene/koppene du bruker, mål opp ved hjelp av dl mål hjemme:
    - 1 glass = _____dl
    - 1 kopp = _____ dl
    - 1 krus = _____dl
- Dersom du bruker sondeernæring noteres produktnavn, mengde pr måltid/døgn og tidspunkt for inntak (fra-til/infusjonshastighet).
- Dersom du bruker parenteral ernæring, oppgis produktnavn (f.eks egen blanding), mengde pr døgn og tidspunkt for tilførsel (fra-til/infusjonshastighet).

Husk:

- Spis som du pleier selv om du skal registrere!
- Noter det du spiser og drikker mellom måltidene.

Start på nytt ark for hver ny dag, og begynn på ny linje for hver matvare. Eksempel:

TIDSPUNKT (klokkeslett)	MENGDE	MAT OG DRIKKE	BESKRIVELSE, FOR EKSEMPEL TILBEREDNING, PRODUKTNAVN
8:00	2 skiver (*Bilde 8 B*)	Kneippbrød	*Bilde 6 B* (halvgrovt)
	1 ss (*Bilde 10 D*)	Lettmargarin på brødskivene	Soft margarin
	1	Stekt egg	Stekt i soft margarin (*Bilde 10 B*)
	Tynt lag (*Bilde 12 A*)	Leverpostei	Go og mager
	4 skiver	Sylteagurk	Nora
	4	Druer	
	1 glass (*Bilde 3 B til øverste*	Lettmelk	Rosa, økologisk
	½ kopp (*Bilde 4 L*)	Kaffe	Traktet
	1 ss	Tran	Møllers med sitronsmak
10:30	2 dl	Vann	
12:15	1 porsjon (*Bilde 20 D*)	Lasagne	Toro, laget med karbonadedeig og Lett Synnøve Finden ost

DATO:……

TIDSPUNKT (klokkeslett)	**MENGDE**	**MAT OG DRIKKE**	**BESKRIVELSE, FOR EKSEMPEL TILBEREDNING, PRODUKTNAVN**

Egne oppskrifter:

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tove Irene Klokk	22845522	10.03.2017	2016/2271/REK sør-øst A
			Deres dato:	**Deres referanse:**
			07.03.2017	

Vår referanse må oppgis ved alle henvendelser

Grethe Månum
Forskningsavdelingen

2016/2271 Akondroplasistudien - kartlegging av helseutfordringer, medisinske komplikasjoner og helsetjenestetilbud til voksne med akondroplasi

Forskningsansvarlig: Sunnaas sykehus HF
Prosjektleder: Grethe Månum

Vi viser til søknad om prosjektendring datert 07.03.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
Følgende endringer er vurdert:

- To nye prosjektmedarbeidere: Hanne Bjørg Slettahjell og Andrea Madsen.
- Tillegg av blodprøveanalyser: ASAT og CRP.
- Inkludere fotografering av trommehinnene.
- Noen mindre endringer i spørreskjemaet.
- Tilbud om frivillig deltakelse i ernæringsstudie: protokoll og infoskriv er sendt inn.

Komiteens leder har vurdert søknaden og har ingen innvendinger til de endringer som er beskrevet.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Tove Irene Klokk
Rådgiver

Kopi til: *johan.stanghelle@sunnaas.no, Sunnaas sykehus HF ved øverste administrative ledelse: firmapost@sunnaas.no*

Sunnaas sykehus HF

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

KARTLEGGING AV ERNÆRING - DEN NORSKE AKONDROPLASI-STUDIEN

Ønsker du å vite litt mer om eget kosthold og ernæringsbehov? Dette er en invitasjon til å gjøre en ernæringskartlegging som et tillegg til den norske akondroplasi-studien.

BAKGRUNN

Kortvoksthet er assosiert med økt risiko for hjerte- og karsykdom, men årsakene er lite kartlagt. Det er godt dokumentert at kostholdet påvirker risiko for hjerte- og karsykdom, men hvordan dette er hos personer med akondroplasi er mindre klart. I den forbindelse ønsker vi å samle inn kunnskap om kosthold og energibehov hos personer med akondroplasi.

HVA INNEBÆRER PROSJEKTET?

Hvis du sier ja til å delta, registrerer du alt du spiser og drikker i 4 dager i vedlagte kostregistreringsskjema og tar med til Sunnaas sykehus. Bildeboken er et hjelpemiddel for å estimere porsjonstørrelser og mengde på det du spiser. I tillegg vil du i løpet av ditt opphold på Sunnaas bli spurt om å krysse av i et enkelt spørreskjema kalt Smart Diet og vi vil utføre en måling av hvilestoffskiftet ditt. For å måle hvilestoffskiftet ditt brukes en maske som legges over nese og munn (se bilde under). Denne måler oksygenopptaket og karbondioksidutslippet og beregner hvor mye energi du forbruker i hvile.

Målingen gjøres på morgenen rett etter en natts søvn, i fastende og hvilende tilstand. For å få gode målinger vil vi sørge for at du ligger eller sitter komfortabelt i avslappet stilling under undersøkelsen og puster fritt. Hele prosedyren tar om lag 15-20 minutter og det vil være helsepersonell tilstede under hele målingen.

Dataene blir analysert etter oppholdet ditt og du mottar en samlet tilbakemelding på resultatene fra kostregistreringen og hvilestoffskiftet.

Sunnaas sykehus HF

Figur 1: Illustrasjonsbilde for måling av hvilestoffskiftet med indirekte kalorimetri

Kriterier for deltakelse

For å delta må du være 16 år eller eldre, ha akondroplasi og være inkludert i hovedstudien.

Tidsskjema

Gjennomføringen skjer i løpet av oppholdet ditt på Sunnaas sykehus og noe på hjemmebane:

Dag 1: Måling av vekt, høyde og midjemål.

Dag 2: Muntlig informasjon om studien og utfylling av skjemaet Smart Diet. Måling av hvilestoffskiftet (indirekte kalorimetri) på morgenen ca. kl. 8.00 (på Kliniskfysiologisk lab)

Dag 3: Hjemreise

Dag 4 – 7 (hjemme): Kostregistrering 4 dager

MULIGE FORDELER OG ULEMPER

Fordelen med å delta er at du vil få en tilbakemelding på kostholdet ditt og en beregning av ernæringsbehovet. Du vil også bidra med viktig informasjon til studien som helhet. Mulige ulemper er at det kan være krevende å registrere matinntaket i 4 dager. Muligheten er også til stede for at man kan oppleve ubehag/klaustrofobi i forbindelse med indirekte kalorimetri. Undersøkelsen gjøres i fastende tilstand, men det legges opp til at dette gjøres så tidlig som mulig på morgenen for å unngå ubehag knyttet til sult.

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FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Andrea Madsen, masterstudent i klinisk ernæring, telefon: 473 71 224 eller klinisk ernæringsfysiolog på Sunnaas Hanne Bjørg Slettahjell: mobil 481 07 330 eller e-post: habjsl@sunnaas.no

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Analysene som blir tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Resultatene fra analysene som blir gjort av deg blir lagret avidentifisert på en forskningsserver tilhørende Sunnaas sykehus HF. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Informasjon om deg vil bli slettet senest fem år etter prosjektslutt (senest 31.12.2022).

Vi tar sikte på å publisere resultatene i et anerkjent fagtidsskrift der din identitet ikke vil bli avdekket.

ØKONOMI

Studien blir finansiert av interne midler fra Sunnaas sykehus og avdeling for ernæringsvitenskap, UiO.

GODKJENNING

Prosjektet er søkt godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, saksnummer 2016/2271.

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SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver