Prediction of

cardiovascular risk markers

during long-term follow-up of young men

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ABBREVIATIONS

AAT	Abdominal adipose tissue
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CT	Computed tomography
DM2	Diabetes mellitus type 2
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GDR	Glucose disposal rate
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance
HR	Heart rate
HT	Hypertension
HUNT	Nord-Trøndelag Health Study
ICC	Intraclass correlation coefficient
MSNA	Muscle sympathetic nerve activity
MST	Mental stress test
PAMELA	Pressioni Arteriose Monitorate e Loro Associazioni (Italian BP study)
SAT	Subcutaneous adipose tissue
TGs	Triglycerides
VAT	Visceral adipose tissue
WHR	Waist-hip-ratio
WHtR	Waist-height-ratio

LIST OF PAPERS

This thesis is based on the following publications referred to in the text by their roman numerals.

Paper I: Skårn SN, Flaa A, Kjeldsen SE, Rostrup M, Brunborg C, Reims HM, Fossum E, Høieggen A, Aksnes TA. High screening blood pressure at young age predicts future masked hypertension: A 17 year follow-up study. *Blood Press 2015; 24: 131-8*.

Paper II: Skårn SN, Flaa A, Kjeldsen SE, Rostrup M, Brunborg C, Reims HM, Fossum E, Høieggen A, Aksnes TA. Family history of hypertension and serum triglycerides predict future insulin sensitivity: a 17-year follow-up study. *J Hypertens 2015; in press*.

Paper III: Skårn SN, Eggesbø HB, Flaa A, Kjeldsen SE, Rostrup M, Brunborg C, Reims HM, Aksnes TA. Predictors of abdominal adipose tissue compartments: 18-year follow-up of young men with and without family history of diabetes. *Submitted*.

INTRODUCTION

During the last decades the incidence and prevalence of cardiovascular disease among people in both developed and developing countries have escalated, mainly due to population growth and aging [1]. In addition, the prevalence rates of diabetes and obesity are rising steeply, leading to a large increase in morbidity and additional deaths if this development continues [2]. The negative impact on both the affected individual and on society is considerable. Nevertheless, most cardiovascular diseases can be prevented, but early detection is then of utmost importance [3]. Expanded knowledge of prediction and detection of cardiovascular risk markers is one way to potentially reduce the future disease burden.

Historical context

During the past 20-30 years, our research group has studied cardiovascular risk markers in young men with high and normal screening blood pressure (BP). This selection was made with the intent to examine the interaction between the sympathoadrenal system and cardiovascular and metabolic risk markers in persons with a wide range of BP levels. The first studies were of cross-sectional design. Rostrup *et al.* showed that high screening BP was associated with increased cardiovascular reactivity to mental stress, which again was related to the level of plasma adrenaline. Further, they showed that adrenaline was negatively related to lipids in the group with the highest screening BP [4]. Moan *et al.*, on the other hand, found that the relationship between insulin sensitivity and BP, heart rate (HR) and the levels of the catecholamines adrenaline and noradrenaline were independent of the participants' screening BP. Insulin sensitivity also had a stronger negative association with BP and HR during mental stress than at rest. Moreover, catecholamine levels during a mental stress test (MST) correlated with stress diastolic BP and HR. Only stress diastolic BP and body mass index (BMI) remained explanatory variables of insulin sensitivity in a multiple regression analysis [5]. Reims *et al.* found that the catecholamine levels were similar between men with normal versus high screening BP, and that the catecholamine levels were related to BP response, especially among

men with high screening BP [6]. They also observed a negative association between adrenaline release and obesity [7].

After some years, several follow-up studies were conducted. In a 20-year follow-up study, Strand *et al.* found that noradrenaline was a positive predictor of future left ventricular mass, independent of baseline BP and BMI, in middle-aged men who developed hypertension (HT) [8]. Gudmundsdottir *et al.* using the same material, suggested that screening BP, even within the normotensive range, could identify individuals that developed HT [9]. In the men who developed HT, baseline adrenaline was found to be an independent predictor of future BP. Flaa *et al.* found that adrenaline and noradrenaline levels during MST were significant predictors of future systolic BP [10], but did not influence future homeostatic model assessment for insulin resistance (HOMA-IR) [11]. Noradrenaline response to a cold pressor test was however found to predict future HOMA-IR [11]. They also discovered that adrenaline response during mental stress was a negative predictor of future BMI, waist circumference and triceps skinfold [12]. In a paper by Hassellund *et al.*, cardiovascular and sympathoadrenal responses to mental stress were found to be relatively stable individual features [13]. In this study they also found a tendency of higher mental stress response among the men with the highest screening BP.

In this thesis we had a great opportunity to further explore in which way cardiovascular and metabolic risk markers at a young age predict future cardiometabolic risk profile. In *Paper I*, we investigated what could predict masked HT. In *Papers II* and *III*, we examined which cardiovascular risk markers predicted insulin sensitivity and amount of abdominal adipose tissue, respectively.

Masked HT

The term "masked hypertension" was introduced by Pickering *et al.* in 2002, though the phenomenon had previously been described [14]. The different combinations of office and out-of-office BP values can yield four BP categories, as shown in **Figure 1**. Masked HT is defined as normal office BP and hypertensive out-of-office BP values [15]. In several studies patients who

use BP lowering medication has been included in the group labelled as masked hypertensives. However, as argued in the 2013 ESH guidelines, HT is then diagnosed, and not masked [15]. As in *Paper I*, the term will here only be used in regard to untreated individuals.

White Coat hypertension		**Sustained hypertension**
Normotension		**Masked hypertension**

Office BP 140/90 (vertical axis) — 135/85 Ambulatory BP (horizontal axis)
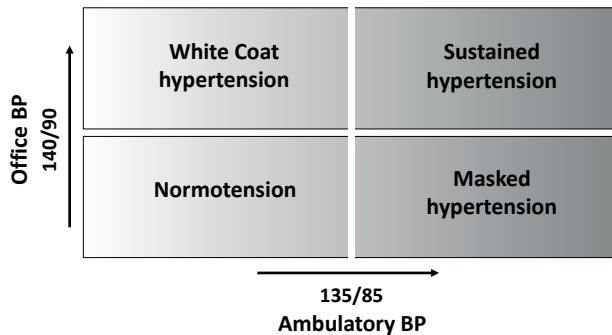
Figure 1. Classification of blood pressure status according to office and ambulatory blood pressure values.

Prevalence of masked HT is by definition somewhat uncertain, with estimates from 10-20% in the general population, and even higher in predisposed individuals [16-20]. Masked HT is regarded as a cardiovascular risk marker similar to sustained HT [20-23], with comparable degree of target organ damage [23-25]. The proportion of affected individuals who develop sustained HT is uncertain. In a 5-year follow-up study the authors found 34% persistence of masked HT and 31% progression to sustained HT among male white-collar workers [26]. The study is limited by the inclusion of the first measurement of BP in their calculations, probably leading to a higher office BP than if measured according to guidelines [19]. Further, conducting ambulatory BP measurements only during working hours complicates generalisation, especially since job strain is associated with masked HT [27]. Moreover, progression according to age-groups was not accounted for. In a mean 6.6-year follow-up study of pre-hypertensive persons, 42% of those with masked HT developed sustained HT [28]. And in a 10-year epidemiological follow-up study of BP in a randomly selected Italian population (the PAMELA-study), the odds ratio of developing sustained HT among men with masked HT was 1.7 with 95% confidence interval (CI) 1.3-2.2 [29].

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In studies of cross-sectional design, male gender, obesity, diabetes, mental stress, job strain, smoking and left ventricular hypertrophy have been associated with masked HT [20, 30-32]. This is in addition to pre-hypertensive BP values and a hypertensive response to exercise [31-33]. Intriguingly, despite the high prevalence and extensive consequences of masked HT, long-term predictors of masked HT have to our knowledge not been investigated.

Insulin sensitivity

Insulin sensitivity describes how sensitive the body is to the effect of insulin. A person being insulin sensitive will require smaller amounts of endogenous or exogenous insulin to lower the blood glucose level than a person with low insulin sensitivity. Low insulin sensitivity is not only essential in the development of diabetes mellitus type 2 (DM2), but it is also, in itself, a cardiovascular risk marker [34-36]. Still, far more attention has been paid to predictors of DM2, than of insulin resistance (low insulin sensitivity). For instance, how insulin sensitivity predicts future insulin sensitivity, i.e. its long-term stability, is not well described. A few studies found that markers of glucose metabolism had relatively low long-term stability in children and young adults, while insulin sensitivity appeared more stable in middle-aged men [37-40]. Given the wide-ranging consequences of reduced insulin sensitivity, other potential predictors are rather scarcely described. We know that family history of diabetes yields an increased risk of reduced insulin sensitivity [41]. Also family history of HT is associated with lower insulin sensitivity [42, 43]. In addition, intrauterine influence is thought to play a role, and there is an inverse relationship between birth weight and insulin resistance [44, 45]. Elevated sympathetic reactivity, measured as noradrenaline response to a cold pressor test, is further found to be a positive predictor of future insulin resistance in a similar cohort investigated in our laboratory [11]. In addition, plasma noradrenaline levels at rest were found to predict higher plasma insulin levels in a study with slightly older participants [46]. In an even older population, both metabolic and lifestyle factors were found to predict insulin sensitivity after 20 years of follow-up [40]. In these 50-year-old men, BMI was the strongest predictor of future insulin sensitivity. Family history of diabetes or HT was, however, not accounted for.

Prediction of abdominal adipose tissue and family history of diabetes

Obesity and abdominal adipose tissue (AAT) have for a long time been recognized as central elements in the pathogenesis of cardiovascular and metabolic diseases such as reduced insulin sensitivity, dyslipidaemia and HT [47-49]. Countless numbers of articles have been written about AAT and its impact on cardiovascular and metabolic risk markers and diseases. Yet, few have examined possible predictors of AAT in long-term follow-up studies. It has been shown that 40-70% of variability of BMI can be attributed to genetic factors [50]. BMI has a high degree of long-term stability, which makes it a predictor of obesity in later life [51]. However, adipose tissue distribution and dysfunction may increase the cardiovascular risk more than obesity *per se* [52]. An interesting study compared persons with either family history of obesity or family history of diabetes, and found that adipose tissue dysfunction was only associated with the latter [53]. Ensuing studies have also found that family history of diabetes is associated with adipose tissue dysfunction, and increased amount of AAT [45, 54]. Family history of HT has also been linked to overweight [55-57]. In follow-up studies of non-diabetic Japanese Americans, insulin level, C-peptide and circulating leptin level all predicted increased abdominal visceral adipose tissue (VAT) after 5 and 10 years [58]. Further, our research group has previously established a negative association between adrenaline response to mental stress test and future body fat [12]. While noradrenaline, on the other hand, was found to be a positive predictor of future weight gain [59].

Traditionally, the AAT has been divided into subcutaneous adipose tissue (SAT) and VAT. The recognition of two distinct different layers of SAT, namely the superficial and the deep SAT, were essentially first appreciated in the late 1990s and early 2000s [60-62]. Still, surprisingly few studies have investigated these metabolically different layers separately. As follows, there have been diverging results regarding the association between SAT and cardiovascular and metabolic risk markers [63]. Deep SAT has been associated with insulin resistance and higher cardiovascular risk independent of other adiposity measures [61, 62, 64]. No study has investigated the impact of family history of diabetes on the two SAT sub-compartments. Moreover, predictors of AAT in men with family history of diabetes are also unknown.

AIMS OF THE THESIS

In this thesis, a mean 17.3 years follow-up study of a homogenous group of healthy young men was performed. The aims were:

- To test if high blood pressure at the military screening or at baseline examinations could predict future blood pressure, measured as both office and ambulatory blood pressure. We also wanted to investigate whether level of catecholamines during rest or a mental stress test was related to future blood pressure (*Paper I*)

- To test if common cardiovascular risk markers, including baseline insulin sensitivity, body mass index and family history of diabetes or hypertension predicted future insulin sensitivity, when measured by the "gold standard" method (hyperinsulinaemic isoglycaemic glucose clamp) both at baseline and at follow-up (*Paper II*)

- To test if baseline insulin sensitivity, body mass index, adrenaline response to a mental stress test, and family history of diabetes or hypertension predicted future amount of the abdominal adipose tissue layers assessed by computed tomography (*Paper III*)

MATERIAL AND METHODS

Participants

A flow diagram of the examinations is presented in **Figure 2**. All participants were young men initially recruited from the yearly military draft procedures in Oslo and Akershus, Norway, in the period 1988-1996. The participants were selected from different BP percentiles to ensure a good BP-range in the ensuing studies of the relation between BP and other cardiovascular risk markers. Two to six years after the military draft, five independent studies were conducted by four medical doctors during the years 1991-2002. These five studies were gathered, and constitute the baseline examination in the present study. Of the 103 men re-examined at follow-up (2012-2013), 73 had high screening-BP (≥ 140/90 mm Hg) at the military draft.
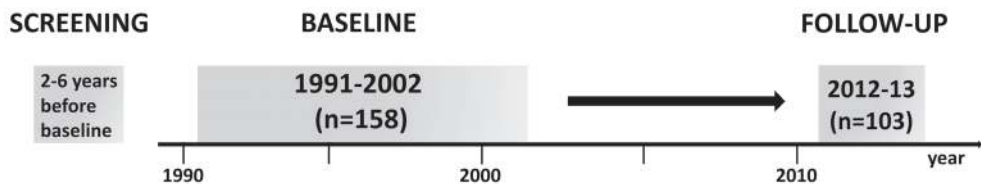
Figure 2. Flow diagram. Baseline examinations (1991-2002) were conducted 2-6 years after military draft screening. Follow-up examinations were performed in 2012 and 2013.

All participants were Caucasian men, mean age of 22.0 (± 0.9) years at baseline, and none used any medication. In our follow-up study, we wanted to investigate the influence from early cardiovascular risk markers, including clamp-derived insulin sensitivity, on the future cardiovascular risk profile. An absolute inclusion criterion was therefore having conducted a satisfactory hyperinsulinaemic isoglycaemic glucose clamp at baseline, which was achieved in 158 men. From January 2012 to November 2013, 17.3 (12.3-21.3) years after baseline examinations, we re-examined 103 of these 158 men. We were unable to get in contact with 29

men and 19 did not respond or responded negatively to the invitation. Of the 110 men initially wanting to participate, seven were unable to attend due to mental health problems (n=2), practical challenges (n=3), a change of mind (n=1), and one died in a traffic accident. In *Paper I* three participants did not want to undergo ambulatory BP measurements, leaving 100 men included in the study. In *Paper II* the clamp was technically unsuccessful in three participants, leaving 100 men in that study as well. In *Paper III*, we were not able to attain computed tomography (CT) in eight men and one was excluded due to a 36 % weight loss since baseline, leaving 94 participants.

Of the 103 men examined at follow-up, 13 used one or more of the following drugs: thyroid hormone replacement drug (n=1), antidepressants (n=3), oral anti-diabetic drug (n=1), antipsychotics (n=1), BP lowering medication (n=7) and cholesterol lowering medication (n=3).

Methods

Baseline examinations

Differences and similarities between baseline examinations are outlined in **Table 1**. A hyperinsulinaemic isoglycaemic glucose clamp was conducted on all participants at baseline. As outlined in **Table 1**, 39 participants were clamped for only 90 minutes, the rest for 120 minutes. During four of the examinations, sitting office BP was measured. In a fifth, only supine measurements were done after vein puncture and with a heating sleeve attached [65]. Due to potential stress induced by having a venflon and a heating sleeve, and different BP due to posture [66], office BP from this study was not used. In the studies by Dr Høieggen and Dr Fossum, ambulatory daytime BP was undertaken in most of the participants, resulting in 28 valid measurements. In one study, adrenaline was infused after 90 minutes of clamp [67], and catecholamine values from subsequent MST were therefore not included in the analyses. Otherwise, MST was conducted in all studies, with the catecholamines noradrenaline and adrenaline measured during rest (mean of four samples during clamp) and MST (mean of four samples). This yielded catecholamine-values in 86 participants, all measured by a radioenzymatic technique. Due to multicollinearity between adrenaline at rest and during MST,

we only used the latter, being the most clinically relevant in previous studies [12, 68]. In one of the studies a heating sleeve for "arterialization" of venous blood was not used during clamp [69]. Due to the use of incomparable methods of insulin analyses in the baseline studies, insulin measurements are not included. As follows, we could not calculate the HOMA-IR.

Table 1. Differences and similarities in baseline studies

	Moan	Høieggen (a)	Høieggen (b)	Fossum	Reims
Military draft, year	1988	1991 and 1993	1993	1993	1996
Birth, year	1969-1971	1971-72	1972-75	1974-75	1977-78
Baseline, year	1991-1993	1994 and 1996	1995-96	1995-96	2000-02
Clamped at baseline, n*	50	18	20	28	51
Study participants, n	39	11	13	14	26
Clamp duration, min	120	120	90	120	90
Heating sleeve, yes/no	Yes	Yes	Yes	Yes	No
Screening BP	98th, 50th and 2nd percentile	≥ 140/90 mmHg	≥ 140/90 mmHg	≥ 140/90 mmHg	≥ 140/90 and ≤ 115/75 mmHg

a = study without adrenaline infusion, b= study with adrenaline infusion
*Some participants were included in more than one study

Follow-up examinations

Hyperinsulinaemic isoglycaemic glucose clamp

Insulin sensitivity was assessed with a 120 minutes hyperinsulinaemic isoglycaemic glucose clamp, using a modification of the method first described by DeFronzo *et al.* [70] and later validated [71, 72] (**Figure 3**). We did not use a heating sleeve, and in contrast to our previous examinations, we used the human insulin analogue Humalog (Insulin Lispro, Eli Lilly, Houten, The Netherlands) instead of Actrapid (Novo Nordisk, Bagsvaerd, Denmark), which was used at baseline. After intravenous catheterization (BD Venflo Pro 18GA, Helsingborg, Sweden) into the left antecubital vein, baseline blood samples were drawn. The venflon was kept patent using physiological saline. The average of 3 blood glucose values (Accu-Chek Performa meter system, Roche, Mannheim, Germany) was used as clamping value. Right antecubital vein, to be used for insulin and glucose infusions, was subsequently catheterised (BD Venflon Pro 18GA,

Helsingborg, Sweden). To prevent insulin from adhering to the thin extension line (CODAN SET green line E07-P, Lensahn, Germany), 4 of the 100 mL NaCl (9 mg/mL, B. Braun, Melsungen, Germany) were replaced with 4 mL of the person's blood, and then gently mixed with 30 IE of the human insulin analogue. This was infused (Pilot Delta, Fresenius Vial, Brézins, France) at a constant rate of 1 mU/min/kg body weight. Using an Optima MS Fresenius pump (Vial, Brézins, France), glucose (200 mg/mL, B. Braun, Melsungen, Germany) infusion was started 5 minutes after the infusion of insulin was started, initially at 20 mL/h for 5 minutes, then 30 mL/h for 5 minutes, and subsequently adjusted according to glucose values measured in the opposite arm every 5 minutes. Glucose disposal rate (GDR) was calculated as the average glucose infusion rate from the last 20 minutes divided by body weight (mg/min/kg), hence the higher GDR, the better insulin sensitivity. This technique has shown acceptable short-time reproducibility [71-73].
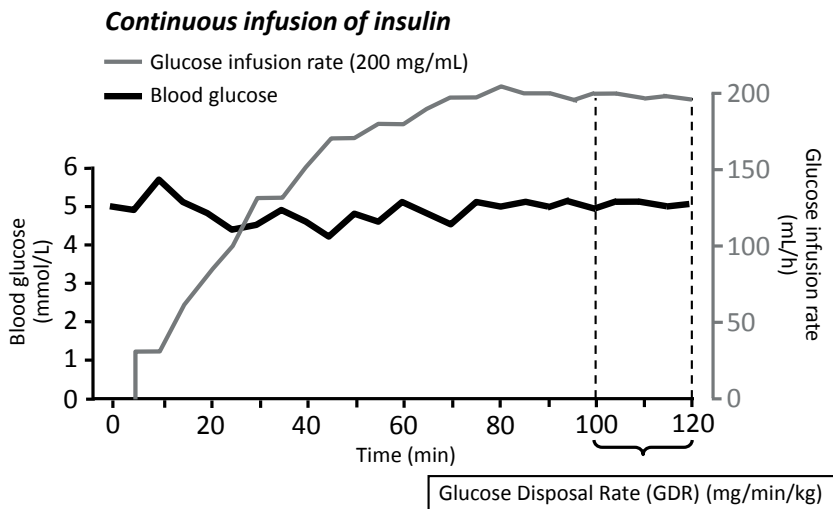
Figure 3. Hyperinsulinaemic isoglycaemic glucose clamp. A constant insulin infusion is initiated. After 5 minutes, the glucose infusion starts (grey line), and we attempt to keep the participants' blood glucose (black line) at their fasting level by adjusting the glucose infusion rate depending on blood glucose values measured every 5 minutes. Based on the glucose infusion rate the last 20 minutes, divided by body weight, glucose disposal rate is calculated. Adapted from Moan A *et al. Metabolism* 1994; 43: 423-27. Created by Reims, HM.

Office blood pressure measurements

All office BP measurements were conducted within the first half hour after the participant's arrival. The participants were thoroughly informed of the ensuing BP measurements, and the examinations to come. The circumferences around both mid-upper arms were measured, and the correct cuff-size chosen. If discordance as to which cuff to be used, we used the circumference of their non-dominant arm, since that arm was going to be used for ambulatory BP measurements. After attaching the cuff the participants were instructed to sit comfortably, in silence, without their legs crossed, for 5 minutes, while both the doctor and the assistant were in the room preparing for the ensuing examinations. The assistant measured the BP at least three times, at 30 seconds time intervals. If the first two readings differed by more than 5 mmHg in systolic value, additional measurements were done (mean number of measurements was 3.5). Subsequently the same procedure was done on the other arm, also with 5 minutes of rest after attaching the cuff. Mean BP was calculated after excluding the first measurement. Oscillometric BP was measured with Dinamap CARESCAPE V100 with standard cuff (DURA-CUF 23-33 cm), large cuff (DURA-CUF 31-40 cm) or small cuff (DURA-CUF 17-25 cm). Subsequently, the assistant left the room. The doctor, unaware of the first BP values, then measured BP in both arms with a mercury sphygmomanometer, following the same protocol. HR and BP measured at 0, 60, 90 and 120 minutes of clamping were also measured with Dinamap CARESCAPE V100. Only HR values were used from these measurements. BP values categorizing participants as hypertensives were according to ESH/ESC guidelines; systolic office BP ≥140 mmHg and/or diastolic ≥90 mmHg [74].

Ambulatory blood pressure measurements

Ambulatory BP was measured in the non-dominant arm, or in the arm with persistent BP ≥ 10 mmHg higher than in the other arm (n=1). Oral and written instructions were given. A calibrated and validated BP measuring device (Microlife WatchBP O3, Microlife Health Management Ltd, Cambridge, United Kingdom) was used [75]. Time of application was around 14.30 on the examination day for most of the participants. They were instructed to keep their

arm still during measurements, and asked to report unexpected events or markedly deterioration of sleep. During daytime (06.00-22.00) BP was recorded at 20 minutes intervals and during night (22.00-06.00) at 30 minutes intervals. The recordings took place on a working day, and they were encouraged to maintain normal daily activities, except physical training. Time of awakening and sleeping was assessed in 90% of participants. To avoid any potential confounding from awareness of high BP [76], they were not informed of their office BP until they had completed a successful ambulatory BP measurement. Ambulatory BP values categorising subjects as hypertensives were according to 2007 ESH/ESC guidelines; daytime systolic BP ≥135 mmHg and/or diastolic BP ≥85 mmHg, or night-time systolic BP ≥120 mmHg and/or diastolic BP ≥70 mmHg [74]. Men with office BP of at least 140/90 mmHg, but normal out-of-office BP values, would be labelled as white-coat hypertensives [19]. Men with normal office BP and hypertensive ambulatory BP values were identified as masked hypertensives. If they had hypertensive values in both office and ambulatory BP measurements, they were classified as having sustained HT. All ambulatory BP measurements met the ESH/ESC guidelines recommendations at that time of at least 14 measurements during day, and seven at night [77].

Computed tomography

CT was performed on a different day than the whole-day examination. To assess any significant weight change, the participants were weighed in the same way as on the whole-day examination. Intraclass correlation coefficient (ICC) value between the two weight measurements was 0.98 with 95% CI of 0.97-0.99. CT was performed using a Siemens Somatom Sensation 64 CT Scanner (Erlangen, Germany) with the participant examined in a supine position, arms extended above the head. One single axial scan was performed without intravenous contrast medium, through the mid-abdomen, at the level of $L_{3/4}$. CT parameters were 120 kV, 200 mAs, and slice thickness 5 mm. The dicom images were analysed using Osirix v 5.8.2, 32 bit (Pixmeo, Geneva, Switzerland). The circumferences were tracked for the superficial and deep SAT compartments, divided by a membranous fascia, and for the muscle compartment including the spine (**Figure 4**). The VAT compartment was measured by tracking

the inner abdominal circumference, and calculated by highlighting the pixels containing fat (-30 to -190 Hounsfield Units).
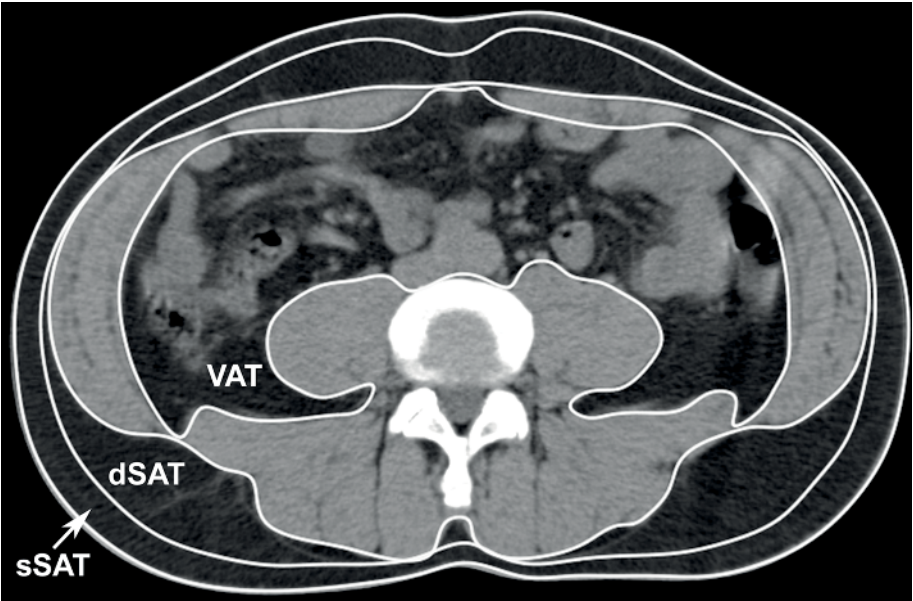
Figure 4. Axial CT scan at level $L_{3/4}$ showing VAT (visceral adipose tissue), dSAT (deep subcutaneous adipose tissue) and sSAT (superficial subcutaneous adipose tissue).

Questionnaire

A validated food questionnaire (SmartDiet) [78, 79] was used to assess dietary habits. It also included a question of frequency of 30 minutes physical activity per week. An extensive questionnaire regarding education, activity and stress related to profession, leisure activity, screen time, family history of disease, own health and use of medication, as well as tobacco and alcohol-habits was answered at the end of the day (**Appendix**, in Norwegian). For validation, 36 participants answered the two questionnaires again after two weeks.

Anthropometric measurements

Waist circumference was measured directly on the skin, midway between the inferior margin of the last rib and the crest of the ileum in the mid-axillary line, with relaxed posture and at the end of normal expiration. Hip circumference was recorded over underwear, at the level of maximum posterior extension of the buttocks. Measurements were recorded to the nearest 0.1 cm and repeated by the assistant (unaware of the first values). If the two measurements disagreed by more than 1 cm, a third measurement was taken. The average values from the (last) two measurements were used.

Height was measured using a KaWe person-check height-measuring device. The participants were measured without shoes, standing right with heels against the wall with the head in Frankfurt horizontal plane. The measurement was performed twice, and with disagreement of more than 0.5 cm, a third time. Recordings were done to the nearest 0.1 cm, and the average values from the (last) two measurements were used.

Weight was measured to the nearest 0.1 kg using a digital scale (OBH Nordica, digital, 150 kg), wearing light indoor clothing, excluding shoes, belt and sweater, and with empty pockets. One kg was subtracted to compensate for clothing.

Statistics

The data were analysed using the statistical software package SPSS for Windows version 20-22 (IBM SPSS, Chicago, IL, USA). Parametric tests were applied for normally distributed data, and non-parametric test for non-normally distributed data. To investigate changes in continuous variables between baseline and follow-up, paired sample t-test or Wilcoxon signed-rank test were used. Independent sample t-test or Mann-Whitney U test were used to compare differences in continuous variables between two groups. One-way analysis of variance (ANOVA) or Kruskal-Wallis test were performed to compare continuous variables between normotensives, masked hypertensives and sustained hypertensives at follow-up in *Paper I*. Further, multiple comparisons were performed using Tukey's test. The chi square test or Fisher's exact test for contingency tables were applied to detect associations between categorical independent variables. In *Paper I*, a multivariable analysis using the logistic regression model was performed to identify independent risk markers of masked HT, using a manual backward elimination procedure. Any variable with $p < 0.25$ from the univariable logistic regression analysis was considered a candidate for the multivariable model. Two-tailed p-values below 0.05 led to rejection of the null hypothesis.

In *Papers II* and *III*, Pearson (r_p) or Spearman (r_s) correlations were applied. Subsequent multiple linear regression analyses with a manual backward elimination procedure was performed including variables correlating with the outcome with p-value < 0.25 from univariable analysis, or being clinically relevant. Variables with more than 15% of the data missing were not considered. The degree of tracking in *Paper II* was assessed by Spearman's rank or Pearson's correlation coefficient between baseline and follow-up measurements [80].

ICC was used to assess concordance between Humalog and Actrapid insulin in *Paper II*, and between weight at the whole-day examination and at the CT-scan in *Paper III*.

SUMMARY OF PAPERS

Paper I: High screening blood pressure at young age predicts future masked hypertension: A 17 year follow-up study

In this long-term follow-up study, we investigated cardiovascular risk markers in 100 healthy young men with high or normal screening BP from the military draft. At follow-up, men with high screening BP had 4.8 times higher likelihood of masked HT, than men with normal screening BP. In addition, only 25% of the 40 men with masked HT had high normal office BP at follow-up, and would thus be recommended ambulatory BP measurement according to guidelines. The remaining 75% would thus, by following the current guidelines, be wrongly labelled as normotensives. Another interesting result was that we observed a reduction in office BP from baseline to follow-up. This finding brings attention to the importance of accuracy in BP measurement.

Paper II: Family history of hypertension and serum triglycerides predict future insulin sensitivity: a 17-year follow-up study of young men

Cardiovascular risk markers, including insulin sensitivity measured by the gold standard method, hyperinsulinaemic isoglycaemic glucose clamp, were examined in 100 men at baseline and at follow-up after mean 17 years. We found that having a first-degree relative with HT and baseline triglycerides were negative predictors of future insulin sensitivity, an effect largely confined to men with a family history of diabetes. Moreover, in contrast to the majority of cardiovascular risk markers, insulin sensitivity measured by glucose clamp was not a long-term stabile feature. Our results indicate that special attention should be paid to individuals with a family history of diabetes or hypertension, despite potentially normal insulin sensitivity at young age.

Paper III: Predictors of abdominal adipose tissue compartments: 18-year follow-up of young men with and without family history of diabetes

This was a mean 18-year follow-up study of 94 men, having measured cardiovascular risk markers at baseline and AAT by CT at follow-up. In multiple regression analyses, baseline BMI and family history of diabetes remained positive predictors of future abdominal superficial and deep SAT, and VAT, while high-density lipoprotein (HDL) cholesterol remained a negative predictor. Baseline risk markers were more strongly associated with future AAT in men with versus without family history of diabetes. In men without a family history of diabetes the amount of AAT seemed predominantly dependent on their current metabolic profile. In addition, family history of diabetes was more positively related to amount of VAT and deep SAT, than to amount of superficial SAT. The increased risk of unfavourable metabolic features associated with family history of diabetes could thus potentially be caused by an impaired ability to store excess fat as superficial SAT.

DISCUSSION

Methodological aspects

All participants were recruited from the military draft procedures in Oslo and Akershus, Norway, and 71% of the men examined at follow-up had high screening BP (≥140/90 mmHg). In 1996, less than 6% (203 of 3415) of men at the military draft had high screening BP. Our main finding in *Paper I*, that high screening BP predicted future masked HT, was a direct result of this selection. We evaluated whether the results in *Papers II* and *III* also could have been influenced by selection. There were no significant differences in insulin sensitivity between the groups with high or normal screening BP. This is in line with the missing association between insulin sensitivity and screening BP found by Moan *et al.* [5]. There was, however, a tendency of lower insulin sensitivity among men with high screening BP (unpublished data). Likewise, amount of AAT was not significantly different between the two groups, but the amount of all three adipose tissue layers was larger among men with high screening BP (unpublished data). They were analysed together, but we can thus not exclude that a higher number of participants could have led to a significant difference in insulin sensitivity and amount of AAT according to screening BP group. All were young Caucasian men, further limiting the generalizability. On the other hand, by examining such a homogenous group, we reduced statistical variance.

Measuring BP at the military draft just once (not three times) is not according to guidelines, and one can assume that for many of the young men, this situation was conceived as stressful. This unstandardized method of BP measurement led to the opportunity to study men with an assumed hyper-reactivity to mental stress [4, 9]. The screening BP can thus in many ways be regarded as a mental stress test. A clear correlation between high screening BP and high response to the laboratory mental stress test supports this [68].

Previously, it has been shown that high screening BP during military draft predicted future persistent BP elevation [81, 82]. However, the BP values were then confirmed before follow-up, and not based on a single measurement like in the present study. Consequently, those results may rather be viewed as tracking, than as an indication of hyper-reactivity being a predictor of future HT. Nevertheless, a meta-analyses from 2010 suggested that a greater

cardiovascular response to acute mental stress has an adverse effect on future cardiovascular risk status, HT in particular [83]. These associations were stronger among men than women, in younger age groups, and in those with longer follow-up periods. In what way hyper-reactivity influences on future amount of AAT or insulin sensitivity is not well described. Our research group has shown that elevated adrenaline response to MST was a negative predictor of e.g. BMI and waist circumference [12], but no significant association was found to future insulin sensitivity [11]. How the associations were according to high or low screening BP was not evaluated in these studies.

Both at baseline and at follow-up, BP measurements were conducted only on one occasion, which is not according to guidelines. Still, in *Paper I* absolute values were not evaluated, only BP groups. And, since only 25% of participants having masked HT displayed pre-hypertensive BP values, we find it unlikely that measurements on additional days would have had a great influence on the results.

The present work is based on five previous studies being conducted by four medical doctors during a time-span of 12 years. Several important baseline examinations are dependent on the examiner. Especially in a cohort with a predominance of men that may be particularly hyper-reactive, different examiners could influence on the results of measurements such as BP, HR, insulin sensitivity measured by glucose clamp, and the MST. As discussed in *Paper I*, different examiners has probably been of importance to baseline BP measurement. Still, our results show that screening BP (*Paper I*), family history of HT, triglycerides (*Paper II*), family history of diabetes, BMI and HDL cholesterol (*Paper III*) predicted future masked HT, insulin sensitivity and AAT, respectively. Except for screening BP, as already discussed, none of those predictors are influenced by the examiner.

The glucose clamp

There were several differences between the baseline and follow-up clamp procedures (**Table 1**). At baseline, 39 men were clamped for only 90 minutes, while the remaining 64 participants were clamped for 120 minutes. In men being subjected to the latter, insulin sensitivity was significantly lower after 90 minutes than after 120 minutes, both at baseline and at follow-up. Therefore, we used only 120 minutes clamp from baseline.

A heating sleeve used to arterialize blood during the glucose clamp was used in all baseline studies except one. Hand-warming has been shown to increase insulin sensitivity [84]. Since a heating sleeve was used in all the 120-minute clamps, hand-warming was of no importance when gathering baseline studies, where the 90-minute clamp was excluded. However, we also assessed tracking of insulin sensitivity, comparing baseline values, measured *with* a heating sleeve, to follow-up values measured *without* a heating sleeve. If insulin sensitivity was artificially increased due to hand-warming at baseline, the tracking coefficient could be underestimated. Still, the value would be considerably lower than for the other cardiovascular risk markers. Moreover, the results are in line with previous studies [37-39], finding low tracking coefficients for insulin sensitivity among young people, again supporting our results.

Another difference between baseline and follow-up glucose clamps was type of insulin used. To explore any potential clinical differences between the two types of insulin, a methodological randomized double-blinded crossover study was performed (unpublished). Fourteen participants (13 men), mean age 38 (± 7) years and mean GDR with Humalog 6.96 (± 3.88) mg/kg body weight/min, were examined 8 (± 2) days apart. With an ICC value of 0.92 (95% CI= 0.74-0.97), we concluded that the two types of insulin could be used interchangeably.

Blood pressure measurements

Another methodological difference between baseline and follow-up examinations was measurement of office BP. As discussed in *Paper I*, the examiners did not abstain from talking with the participants during BP measurements at baseline. Assuming a predominance of hyper-reactive men, this is probably an important reason for 70% of the men having white-coat HT at baseline, and the apparent reduction of office BP between baseline and follow-up. Subsequently, tracking of office BP in *Paper II* must be seen in light of this. We observed a decrease, with tracking coefficient for systolic BP of 0.6, while others have found increase in BP with tracking coefficient between 0.39 and 0.54 [37, 39, 85, 86].

In Norway, prevalence of HT among men aged 30-39 years in 1995-1997 (HUNT 2) was 29.5%, with great variance according to family history of HT and BMI [87]. Finding that 65% of the men with high screening BP later were diagnosed with masked (47%) or sustained (18%) HT

indicates that this is not a representative group regarding BP development. In total, only 14 of 100 had sustained HT at follow-up. However, compared to prevalence in men with approximately the same degree of family history of HT and BMI-level, the numbers are quite similar [87].

Questionnaires

We have no knowledge of the participants' lifestyle between baseline and follow-up. In the questionnaires the answers were only in regard to the last 12 months. However, since the last year's lifestyle to a high degree will be reflected in the variables examined, we believe our results are valid. Another challenge is the use of information on family history of diabetes and HT. First of all, we would prefer to have data on family history collected at baseline, though this may not be of great importance [45]. Secondly, we have no first-hand confirmation, or documentation, on parental disease. Finally, we can assume that not all are aware of their HT or diabetes, given a relatively high number of people being undiagnosed. However, all reports on family history of diabetes were confirmed in the validation questionnaires. Three participants initially answering they had a first-degree relative with HT replied they had none in the validation questionnaire.

Computed tomography

In the Framingham Heart Study the authors showed that CT measurements of SAT and VAT area obtained at level $L_{3/4}$ were most strongly associated with simultaneous assessment of volumes of SAT and VAT. Measurements at this level were also most strongly associated with cardiometabolic risk factors [88]. We therefore chose to measure at level $L_{3/4}$ in our protocol.

There has been confusion around the nomenclature of the layer dividing the superficial and deep layer of the abdominal subcutaneous fat tissue [89]. The most widely used terms are Scarpa's fascia, Colles' fascia, Camper's fascia and the superficial fascia. Different terms are used for the same structure, and *vice versa*. We therefore chose to name it a membranous layer, in accordance with a recent recommendation [89].

Statistics

Due to the relatively low number of participants, interpretation of the analyses should be done with caution. Some baseline variables had missing values mainly due to different protocols between the five studies at baseline. In addition, sub-division of the material (according to screening BP in *Paper I* and to parental diabetes in *Papers II* and *III*) creates even smaller groups, making interpretation even more vulnerable for type II errors. Moreover, a potentially very interesting analysis, multivariable regression analysis in the group with family history of diabetes, could not be performed. This will be further addressed in Discussion of results.

Discussion of results

Masked HT

The causes of masked HT are unclear [20]. However, it is likely that masked and sustained HT have several mechanisms in common, since development of sustained HT often follows masked HT [26, 28, 29, 90]. The central nervous system, the renin-angiotensin-aldosterone system, increased adrenaline sensitivity, inflammation, endothelial dysfunction and arterial stiffness are all suggested to be involved [4, 20, 91].

It also seems that some mechanisms behind masked HT and sustained elevated BP differ. For example, seemingly contradictory, family history of HT, which is well known to increase the risk of sustained HT, is not necessarily closely related to hyper-reactivity [92, 93], and was not related to masked HT (data not shown). On the other hand, 90% of the participants with family history of diabetes had high screening BP (*Paper II*). Moreover, chronic elevation of sympathetic activity has been associated with pre-hypertension and sustained HT [7, 94], while the intermediate elevation, the hyper-reactivity, is more characteristic in those with masked HT.

Having pre-hypertensive BP values is maybe the most established marker for concurrent masked HT [19]. The group with high screening BP had high office BP at baseline, but not at follow-up. The elevated office BP at baseline is interpreted as a consequence of measurement method, as discussed in *Paper I*, and not an indication of masked HT. The question is then why men with masked HT had such low office BP values at follow-up? According to guidelines, these men would not have been recommended ambulatory BP measurements, and thus remained undiagnosed [19]. One reason could be that the group with high screening BP may still have an elevated stress response [13], but in contrast to what has been found in pre-hypertensive men [7, 68, 95], they might not have a high stress level during rest [13]. The fact that we emphasized a relaxed atmosphere during BP measurements may thus have been particularly important in these hyper-reactive men.

There are to our knowledge no prior studies on longitudinal predictors of masked HT. Mental stress, measured as job strain, has been associated with masked HT in cross-sectional studies [20]. In many regards, military screening, consisting of a whole day of physical and

psychological evaluation, can be viewed as a mental stress test. Thus, our results indicate that mental stress also is a long-term predictor of masked HT. Moreover, our research group has previously found that cardiovascular and sympathoadrenal reactivity to mental stress is a rather stable feature [13]. Taken together, this supports the validity of our findings. Our results are also in agreement with the conclusions in a meta-analysis from 2010, where incident HT was predicted by greater stress reactivity [83]. The authors suggested that the hyper-reactive response, with repeated BP elevations, with time could lead to persistent elevation in BP. The BP development will then depend on daily life stress exposure. An alternative, or additional, explanation is that the cardiovascular response is a marker of an underlying process which simultaneously can lead to masked HT. The observed BP development supports the first theory, and as will be addressed later, several of our findings support the suggestion of an underlying process.

There is a cross-sectional association between the level of catecholamines during mental stress and screening BP [4]. One might deduce that the high screening BP is a reflection of the catecholamine level, and hence the driving force behind the high BP the following years. However, one would then expect that not only high screening BP is related to future masked HT, but also the catecholamine level during mental stress. That was not the case in our trial. This brings us back to the theory of an underlying process which gives rise to elevated catecholamines during stress, and in parallel (not necessarily as a consequence of) leads to high screening BP. This process could again partly explain a high prevalence of masked HT. Some of the findings in *Paper III* also support this theory. Adrenaline during MST correlated negatively with future amount of AAT. Still, men with high screening BP had *higher* BMI and *larger* amount of AAT in all three compartments, though the differences did not reach level of significance (unpublished data). This suggests that the high screening BP is not caused by, but rather co-occurs with high levels of catecholamines.

To our surprise, we observed a reduction in office BP between baseline and follow-up examinations. As discussed in *Paper I*, there are several potential explanations. Though the statement by Kaplan is dated back to 1998, it may still be relevant; "that BP measurement is likely the procedure of greatest importance that is performed in the sloppiest manner" [96].

However, performing BP measurements that are *not* according to guidelines may actually reveal information otherwise hidden. These measurements may also be valuable, if correctly interpreted and handled. The importance of measurement methods is emphasized both in major guidelines, and in numerous articles [19, 97, 98]. Interestingly, there have been no studies supporting the recommendation of resting a few minutes prior to office BP measurement [99], which was the main difference between baseline and follow-up measurements in the present study. Possibly, the decrease in BP during rest may be more evident in people prone to high BP. In a study of untreated hypertensive patients, researchers have shown that BP fell progressively during rest (11.6/4.3 mmHg), especially the first 10 minutes [100]. Similarly, BP-lowering was observed after 15 and 30 minutes of rest in men with high screening BP [4]. In a population with mean systolic BP of 135.7 mmHg, the fall in BP was 10.3/0.8 mmHg for men, but whether the reduction was similar in all BP categories is uncertain [101]. In the present study, office BP at baseline was progressively higher in the groups who had normotension, masked HT and sustained HT at follow-up. A BP measured without the 5 minutes of rest may thus tell us more about future BP than a standardized measurement according to guidelines, as indicated before [10]. An important advantage of the recommended rest prior to measurement is of course a greater standardization. Immediate BP measurement, without rest, will probably convey an elevated incidence of white-coat HT and an increased need for out-of-office BP measurements. On the other hand, if the concomitant effect is discovering masked HT, it may be worth considering doing both.

Insulin sensitivity

The sympathetic nervous system has not only been linked to masked HT but also to insulin sensitivity [102]. We have previously observed that the adrenaline level during mental stress is related to insulin sensitivity, but only in cross-sectional studies [5, 103, 104]. When examining whether baseline catecholamines, during rest or mental stress, predicted future insulin sensitivity, we found no association in the present study. This is in line with previous results from our research group, where only catecholamines during the cold pressor test, not during the MST, predicted future insulin sensitivity [11]. As suggested in the previous section, it

seems like an underlying process leads to both high screening BP and low insulin sensitivity, independent of high catecholamines during mental stress.

Most studies have shown that family history of HT has a negative influence on glucose metabolism, [42, 43, 105-108], though not all [109]. Suggested mechanisms are oxidative stress, hypomagnesaemia [105], and low adiponectin level [106, 110]. The latter has in addition been observed among those with a family history of diabetes [111]. Intrauterine environment and adipose tissue dysfunction are other potential explanations for lower insulin sensitivity in diabetic offspring [45, 112]. Nonetheless, a substantial portion of the risk associated with family history of diabetes or HT remains unexplained [45, 105, 113-115]. In our study, family history of HT and family history of diabetes correlated to the same extent with insulin sensitivity at follow-up, though family history of diabetes has been more strongly associated in previous studies [41, 42, 107]. That only family history of HT remained a significant predictor in multivariable regression analysis could be due to the relatively low number of participants.

In men without a family history of diabetes, none of the baseline risk markers remained predictors of future insulin sensitivity in the multivariable linear regression analysis. One interpretation is that their insulin sensitivity is mainly determined by their concomitant lifestyle and metabolic profile. In contrast, baseline risk markers showed a relatively strong correlation with future insulin sensitivity in men having a family history of diabetes. In addition, we confirmed that these men, at an early age, had a worse cardiovascular profile than men without family history of diabetes [116]. Unravelling the causes of DM2 has been a major research focus for decades. Most commonly, it is caused by an unhealthy diet and low physical activity leading to obesity [47, 117], with the subsequent increased risk of DM2 [118]. Our results support the notion that for some individuals, family history of diabetes is mainly accountable for the increased risk of DM2 [45, 119]. In the latter case, DM2 can develop also in lean individuals [112]. Individuals with a family history of diabetes also seem to have a lower "tolerance" to the negative impact from an unhealthy lifestyle [119-121]. Anyhow, the increasing tendency to a sedentary lifestyle unfortunately increases DM2 through both these pathways.

Another potential explanation for the lack of association between baseline risk markers and future insulin sensitivity among men without a family history of diabetes is that we did not

measure the relevant risk markers. In that case, intrauterine factors or birth weight could be potential candidates [44, 122]. Moreover, biochemical markers, like the adipokines leptin and adiponectin, or inflammatory mediators, like interleukin 6 and tumor necrosis factor-α, were not measured [118, 123].

In contrast to our study, insulin resistance has been found to *precede* an adverse cardiovascular risk profile [124]. However, family history was not accounted for, and participants were followed for 6 years from the age of 13, a period where insulin resistance may have a peak [125]. In a study of children with family history of diabetes, the authors suggested that elevated BMI in childhood precedes reduced insulin sensitivity in adolescence, which again precedes dyslipidaemia in adulthood [116]. Again, it is uncertain whether these results are applicable to other age groups. If our results are confirmed, what reasons could there be for men with family history of diabetes to first have a worse cardiovascular risk profile, and subsequently lower insulin sensitivity? One theory is that obesity and the increase in other cardiovascular risk markers causes the low insulin sensitivity through mechanisms including for instance the sympathetic nervous system [46] or adipose tissue dysfunction [54, 126]. The latter could also explain the impaired insulin sensitivity in lean offspring of diabetic parents [53, 112]. Another question then arises; why do men with family history of diabetes have these unfavourable metabolic traits? Whether it is caused by intrauterine factors [122], the sympathetic nervous system [127], adipose tissue dysfunction [53, 54, 112], inflammation [112], or unknown determinants is not clear. Still, it is possible that some of the causal factors also induce the relatively high degree of tracking of cardiovascular risk markers in men with, as compared to without, family history of diabetes.

From cross-sectional studies we know that not only the amount of adipose tissue, but also its distribution, is of importance when assessing cardiovascular risk. Centrally distributed adipose tissue is most strongly associated with low insulin sensitivity [118]. Interestingly, researchers recently observed higher waist-hip-ratio (WHR) and HOMA-IR in persons with, as compared to without, family history of diabetes, despite equal BMI [112]. In our study, both BMI and waist circumference in men with family history of diabetes correlated strongly with

future insulin sensitivity. This suggests an early and important role for adipose tissue, which will be further discussed in the next section.

Abdominal adipose tissue

We know that family history of diabetes is negatively associated with cardiovascular and metabolic features, including obesity [54], though the mechanisms through which this happens remain unclear [45]. The obesity associated with family history of diabetes is primary centrally located, i.e. abdominal adiposity [54, 112, 116], and is suggested to be more associated with VAT than SAT [54]. It is, however, also linked to SAT, but without further subdivision of the SAT compartments [112, 128].

The novelty of our study is that family history of diabetes had a greater impact on the amount of deep SAT, than on superficial SAT. This has to our knowledge not been examined previously. Researchers have found that family history of diabetes is associated with a more dysfunctional AAT, linked to metabolically unfavourable traits [53, 54, 112, 128]. Moreover, in studies where family history is unaccounted for, deep SAT has been found to be metabolically more dysfunctional than superficial SAT [61, 62, 64]. Taken together, these findings increase the plausibility of our results.

There has been increasing attention towards distribution, not only amount, of adipose tissue [52, 129-133]. Our findings support the theory of ectopic fat contributing to the increased risk of DM2 [54, 134]. Individuals prone to DM2 seem to have an impaired capacity to store excess fat in subcutaneous compartments, and rather accumulate visceral fat [134]. Unfortunately, the primary distinction has again been made between VAT and SAT, without further subdivision of SAT. Thus, the increased risk for e.g. diabetes and HT has been attributed to higher VAT, while the role of deep SAT is not particularly appreciated. In a large genetic study, where family history was not accounted for, reduced SAT was suggested to be essential to i.e. DM2 and HT [123]. If family history of diabetes predominantly leads to increased VAT and deep SAT, it could suggest that an impaired ability to store excess fat as *superficial* SAT is one of the mechanisms increasing risk of DM2.

We did not examine the biochemical characteristics of the adipose tissue. However, several recent papers have shown that family history of diabetes is associated with abdominal tissue dysfunction, also in non-obese persons [53, 54, 112, 128]. As the negative impact from having a family history of diabetes apparently starts early, adipose tissue dysfunction may be one explanation to the high degree of tracking of cardiovascular risk markers that we observed in this group (*Paper II*).

A second discovery described in *Paper III* was that in men without a family history of diabetes, the cardiovascular risk profile they had 17 years earlier was of less significance to future AAT, than among men with a family history of diabetes. This is consistent with our findings in *Paper II*, where baseline risk markers correlated much stronger with future insulin sensitivity in men with, as compared to without, a family history of diabetes. It is also in agreement with the findings in a large 7-year follow-up study; that there was no reduced risk of HT in participants being previously lean [135]. Again, our results imply that the current lifestyle (as opposed to their previous lifestyle) has a greater impact on a person's contemporary risk profile among men without a family history of diabetes. A healthy lifestyle is, of course, also important, and probably of even greater importance, when having a family history of diabetes [120, 121]. Diabetes can be prevented with interventions counteracting weight gain, also in diabetic offspring [53, 136]. Whether response to lifestyle interventions in the latter group is more or less effective than among persons without a family history of diabetes, is however not agreed on [137-139]. Unfortunately, it does seem like the unfavourable cardiovascular and metabolic profile is more predestined among persons with a family history of diabetes. This view is supported by studies of adopted children, where no increased risk for DM2 was found when the adoptive parents had DM2. On the other hand, an increased risk was found if their biological parents had DM2 [140].

In addition to family history of diabetes, baseline BMI was a strong predictor of future AAT. As mentioned, the link between distribution of adipose tissue and cardiovascular and metabolic risk [49, 54, 132], even in lean persons [141], is well described. The distribution of adipose tissue may even be of greater importance than obesity *per se* [49, 142]. One could thus argue that using waist circumference, WHR or waist-height ratio (WHtR) would be preferable

over BMI [130, 141-143]. In our material there was a distinction according to family history of diabetes. Without a family history of diabetes, only BMI correlated with future amounts of AAT, and then only the SAT-layers. In men *with* a family history of diabetes, however, BMI correlated with all the AAT layers. WHR did not correlate with any of the layers, while WHtR and waist circumference had correlation coefficients between 0.52-0.67 with all three layers. At follow-up, on the other hand, all four measures correlated cross-sectionally with the AAT compartments, having correlation coefficients between 0.58-0.90, with only minor differences according to hereditably (unpublished data). This may indicate that choice of measurement method depends on whether it is the current or future risk being assessed, and if the person has a family history of diabetes. Differences between different age groups, sexes and ethnicities also need to be taken into account [144].

The men with a family history of diabetes had strong correlation coefficients between baseline variables and future AAT in *Paper III*. With a larger sample size, a multiple regression analysis could have been performed in that group as well. Adrenaline response to mental stress, TGs and having a first-degree relative with HT were all highly correlated with future amount of AAT in men with a family history of diabetes. Their potential as predictors will therefore be discussed below.

First, we observed that baseline adrenaline response to mental stress could be a negative predictor, especially among men with a family history of diabetes. Offspring of patients with DM2 have previously shown an increased resting muscle sympathetic nerve activity (MSNA) [127]. Adrenaline response to mental stress in this group is however unknown. The relationship between obesity and sympathetic nervous system activity is highly complex, and has been investigated for decades [102]. Several follow-up studies have found resting noradrenaline to be positively related to weight gain [145, 146], and adrenaline response to mental stress as a negative predictor of weight gain [12]. Different methods to assess stress, cross-sectional versus longitudinal relationships, resting versus stress-induced and acute versus chronic stress, complicate comparison between different studies. If we focus on the adrenaline response to mental stress, as was assessed in our study, previous results may not be that contradictory after all. In a longitudinal study, adrenaline response during the MST was

negatively associated with change in BMI [12]. In a cross-sectional study, obesity was found to be associated with a blunted neuroendocrine response to acute mental stress [147]. Our research group has in addition found catecholamine response to be a relatively stable feature [13]. Taken together, this suggests that adrenaline response to mental stress could have been a negative predictor of future AAT in a multivariable analysis, at least in men with a family history of diabetes.

Secondly, TGs and having a first degree relative with HT were the two remaining predictors of insulin sensitivity (*Paper II*). A possible mechanism behind this finding could include adiponectin, which has shown to be reduced in persons with a family history of HT [106], and also been associated with increased HDL cholesterol and reduced TGs [148]. It is tempting to speculate that with a larger study than ours, TGs and family history of HT could have been significant predictors of AAT in men with a family history of diabetes.

Concluding remarks and future perspectives

When trying to untangle all the information on what precedes the other, follow-up studies are preferred over cross-sectional studies. However, one type of study falls between the two, namely, cross-sectional studies including participants with a family history of a disease, with the assumption that they eventually will develop the disease. As for those with family history of diabetes and HT, DM2 will occur in 30-70% [54] and HT in around 35-50% [19, 149], respectively. Whether and when the disease develops is influenced by the age of both the affected patient and their relative, the relationship between them, and the number of affected relatives in the family [45, 105]. Then again, this relatively high hereditability underscores the importance of taking family history into account when examining interrelationship and development of cardiovascular and metabolic diseases.

A considerable amount of the associations found in our study seems related to family history of diabetes and HT. It is not unlikely that causal mechanisms are different in persons with and without a family history of diabetes or HT. Hence, it is unfortunate that family history often is unaccounted for.

Family history of HT increases the risk of HT, but is also found to be a risk marker for both overweight and insulin resistance [19, 42, 56, 57, 107]. Several studies find that in persons with a family history of HT, insulin resistance precedes HT [42, 107]. It has been suggested that genes associated with BP regulation might be involved in development of insulin resistance [43]. Further, low level of adiponectin, associated with worse insulin sensitivity, has also been found in normal weight, normotensive men with a family history of HT [110]. It thus seems like factors associated with a family history of HT, and not HT in itself, lead to reduced insulin sensitivity, as previously hypothesized [150].

Overweight and obesity, and especially abdominal fat, is a major cause of DM2 [117, 129]. The reduced insulin sensitivity, and in many cases subsequent DM2, is moreover closely linked to family history of diabetes. In individuals with a family history of diabetes there is a general agreement that adipose tissue dysfunction precedes obesity, or alternatively leads to DM2 independent of obesity [53, 54, 126, 128]. In children/adolescents with a family history of diabetes in the Bogalusa Heart Study, significantly higher level of BMI and subscapular skinfold preceded higher levels of insulin and HOMA-IR, which again preceded dyslipidemia [116]. Adipose tissue (dys)function was not measured in that study. We could not do multivariable regression analysis in men with a family history of DM2, due to limited number of participants. However, in addition to family history of HT, BMI and waist circumference were strongly correlated to future insulin sensitivity, and thus in line with these other studies.

All in all, our results suggest that family history of diabetes is essential. Preferably, we should have had a larger study and higher validity on family history data. Still, it is difficult to disregard its great influence. Ninety per cent of the men with a family history of diabetes had high screening BP, suggesting a potential role in the development of masked HT. None of the baseline risk markers predicted future insulin sensitivity in *Paper II* unless the men had a family history of diabetes. Finally, family history of diabetes had a strong association with future AAT. The latter may be a key to the associations, given the role of adipose tissue dysfunction.

Although adipose tissue (dys)function was not measured in our study, it could potentially be the underlying process explaining nearly all our findings. Many factors are associated with adipose tissue dysfunction, and one of them is of particular interest, namely adiponectin. This

protein, mainly secreted by adipose tissue is highly heritable, and is in addition to the obvious relation to AAT, correlated to insulin sensitivity, HT and dyslipidemia [151-153]. Meta-analyses have shown controversial results as to whether adiponectin level is positively, indifferently or negatively associated with cardiovascular disease [154]. However, in persons without established cardiovascular disease, there is a general agreement on the beneficial role of adiponectin in regard to cardiovascular and metabolic diseases [148, 153, 155].

Some researchers even suggest that adiponectin may be involved in the reduced insulin sensitivity associated with parental diabetes and parental HT [106, 156, 157]. This may thus be a potential explanation to our observed group-differences. Adiponectin is also associated with lower TG level and higher HDL level [123, 148, 158], and could thus partly explain their predictive role on insulin sensitivity and amount of AAT in *Papers II* and *III*, respectively. As presented in *Paper III*, the dysfunctional AAT related to family history of diabetes is probably related to both VAT and deep SAT. Family history of diabetes has been shown to be associated with reduced adiponectin in many [111, 156-160], though not all studies [161, 162]. Further, family history of diabetes is associated with a worse metabolic and cardiovascular profile. Taken together, this supports our finding of family history of DM2 being more strongly associated with the metabolically unfavourable VAT and deep SAT, than to superficial SAT.

It is difficult to deduce which order of appearance the risk markers have from our material. Firstly, because of the methodological challenges related to office BP measurement, and few ambulatory measurements at baseline. Secondly, because our participants are still young, and relatively few have developed HT or insulin resistance. Thirdly, we measured insulin sensitivity by clamp, where there is no consensus on cut off values for insulin resistance [163]. However, only 14 participants had developed sustained HT at follow-up, while insulin sensitivity decreased significantly from baseline, which makes it more likely that insulin resistance precedes HT.

Factors associated with high screening BP, which is different from the adrenaline response to MST, seems to predict both masked HT and reduced insulin sensitivity, in addition to increased amount of AAT. These unfavorable features are also associated with family history of diabetes, and for insulin sensitivity and AAT, with family history of HT as well.

As for uncovering masked HT, it would be interesting to do a large study where BP was measured both with and without the 5 minutes of rest. Thereafter, by means of ambulatory BP measurement, one could evaluate the potential of revealing masked HT by non-resting BP measurement.

There are potentially many ways to slow down, or hopefully turn, the unfortunate increase in cardiovascular and metabolic diseases. However, to do so, it is imperative to know the order of appearance of the different cardiovascular and metabolic risk markers. In addition, creating tools to identify individuals with increased risk at an early age increases the opportunity to start with preventive measures. This is even more important when it comes to risk markers that do not give any symptoms until the disease manifests, or even years later.

Dealing with this complex web of interactions, with many unknown factors, large studies are necessary. In parallel, progressively more advanced methods in genetic studies provide new knowledge. In clinical investigations, it seems appropriate to recommend taking into account both family history of HT and family history of DM2.

CONCLUSIONS

- We found that having high screening blood pressure at the military draft was a strong predictor for future masked hypertension in young men. Catecholamine levels were not associated with future masked hypertension (*Paper I*).

- Baseline triglycerides and family history of hypertension were found to predict future insulin sensitivity, a result mainly driven by men with a family history of diabetes. Baseline body mass index did not predict future insulin sensitivity. Moreover, clamp-derived insulin sensitivity was not a long-term stable feature (*Paper II*).

- Baseline body mass index and family history of diabetes were found to be positive predictors of future amount of abdominal adipose tissue, while HDL cholesterol remained a negative predictor. Baseline risk markers were further found to be stronger associated with amount of abdominal adipose tissue in men with, as compared to without, a family history of diabetes (*Paper III*).

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Spørreskjema om helsetilstand og risikofaktorer for hjerte- og karsykdom

Hensikten med dette spørreskjema er å skaffe informasjon om din helsetilstand og eventuelle risikofaktorer for hjerte- og karsykdom hos deg. Det er viktig at du leser spørsmålene grundig, og svarer på alle spørsmålene (plass til kommentarer på s. 10).

Generell informasjon

1. Hvilken sivilstand har du <u>nå</u>?

Gift/samboer ☐   Separert /skilt ☐

Enkemann ☐   Enslig ☐

Annet ☐ beskriv:_____

Antall barn: _____

2. Hvilken utdannelse har du? *(Sett kun ett kryss for den høyeste utdannelsen du har fullført. Kryss også av for den utdannelsen du eventuelt holder på med.)*

	Fullført	Holder på med
9-årig grunnskole	☐	☐
1-2-årig videregående	☐	☐
Videregående yrkesfaglig	☐	☐
3-årig videregående allmennfaglig, gymnas	☐	☐
Distriktshøyskole, universitet inntil 4 år *(cand. mag., sykepleier, lærer, ingeniør)*	☐	☐
Universitet, høyskole, mer enn 4 år *(hovedfag, embetseksamen)*	☐	☐
Annen utdannelse:_____	☐	☐

Arbeid

3. Er du i inntektsgivende arbeid?

Ja, full tid ☐

Ja, deltid: _____% ☐

Nei ☐

4. Tenk på den virksomhet du har arbeidet i lengst tid siste 12 mnd; hvilket yrke/tittel

   hadde du på dette arbeidsstedet:_____

5. Mottar du for tiden noen av følgende ytelser?

	Ja	Nei	
Sykepenger (er sykemeldt)	☐	☐	Hvis ja, fra dato:_____
Arbeidsavklaringspenger	☐	☐	Hvis ja, fra dato:_____
Uførepensjon	☐	☐	Hvis ja, fra dato:_____
Dagpenger under arbeidsledighet	☐	☐	Hvis ja, fra dato:_____
Sosialhjelp/stønad	☐	☐	Hvis ja, fra dato:_____
Annet, beskriv:_____	☐	☐	Hvis ja, fra dato:_____

	Ja	Nei
6. Har du skiftarbeid, nattarbeid eller går vakter?	☐	☐

7. Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?
   (sett et kryss ved det svaralternativ som passer best)

For det meste stillesittende arbeid? (f.eks. skrivebordsarbeid, studier)	☐
Arbeid som krever at du går mye? (f.eks. ekspeditørarbeid, lett industriarbeid)	☐
Arbeid der du går og løfter mye? (f.eks. postbud, pleier, bygningsarbeid)	☐
Tungt kroppsarbeid? (f.eks. skogsarbeid, jordbruksarbeid, bygningsarbeid)	☐

8. Hvordan stemmer følgende beskrivelser av din arbeidssituasjon. *(Sett kun ett kryss for hver linje.)*

	stemmer	stemmer ganske bra	stemmer ikke særlig bra	stemmer ikke i det hele tatt
Jeg har fysisk tungt arbeid	☐	☐	☐	☐
Jeg har et stressende eller masete arbeid	☐	☐	☐	☐
Jeg lærer mye i arbeidet mitt	☐	☐	☐	☐
Arbeidet innebærer at jeg gjør de samme tingene om og om igjen	☐	☐	☐	☐
Arbeidet mitt krever stor arbeidsinnsats	☐	☐	☐	☐
Jeg har muligheten til selv å bestemme hvordan arbeidet skal utføres	☐	☐	☐	☐
Det er godt samhold på arbeidsplassen	☐	☐	☐	☐
Jeg trives i arbeidet mitt	☐	☐	☐	☐

Fysisk aktivitet

9. Hvor lang tid bruker du til sammen daglig foran dataskjerm?
   (Sett 0 hvis du ikke bruker data)

   I arbeid _____ timer   På fritiden _____ timer

10. Hvor mange timer ser du på TV /DVD/spiller PC-spill daglig?

   < 1 time   ☐   4-6 timer   ☐

   1-3 timer   ☐   > 6 timer   ☐

11. Hvordan har din fysiske aktivitet i **arbeidstiden** vært i det <u>siste året</u>?
(Tenk deg et ukentlig gjennomsnitt for året, ikke regn med arbeidsvei)

Timer per uke

	Ingen	<1 time	1-2 t	3-6 t	7-10 t	11-20 t	>20 t
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐	☐	☐	☐
Moderat aktivitet	☐	☐	☐	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐	☐	☐	☐	☐	☐	☐

12. Hvordan har din fysiske aktivitet i **fritiden** vært det <u>siste året</u>?
(Hvis stor variasjon mellom sommer og vinter, ta et gjennomsnitt, arbeidsvei regnes som fritid)

Timer per uke

	Ingen	<1 time	1-2 t	3-6 t	7-10 t	11-20 t	>20 t
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐	☐	☐	☐
Moderat aktivitet	☐	☐	☐	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐	☐	☐	☐	☐	☐	☐

Sykdommer i din nærmeste familie

13. Kryss av for de slektninger som har eller har hatt noen av sykdommene:

	Mor	Far	Bror	Søster	Ingen	Vet ikke	Hvis ja, alder ved sykdom
Hjerneslag eller hjerneblødning:	☐	☐	☐	☐	☐	☐	_____
Hypertensjon:	☐	☐	☐	☐	☐	☐	_____
Hjerteinfarkt:	☐	☐	☐	☐	☐	☐	_____
Sukkersyke (diabetes):	☐	☐	☐	☐	☐	☐	_____
Blodpropp utenom i hjerte og hjerne. Beskriv nedenfor.	☐	☐	☐	☐	☐	☐	_____
Andre *(f.eks. "røykeben")*: Beskriv nedenfor.	☐	☐	☐	☐	☐	☐	_____

Beskriv: _____

Tidligere sykdommer

14. Har du tidligere fått påvist noen av følgende sykdommer/tilstander?

	Ja	Nei	Usikker (beskriv)

Høyt blodtrykk (hypertensjon): ☐ ☐ ☐

:_____

Hvis ja, når:_____

Sukkersyke (diabetes): ☐ ☐ ☐   :_____

Hvis ja, når:_____

Høyt kolesterol: ☐ ☐ ☐   :_____

Hvis ja, når?_____

15. Har du (hatt) andre langvarige, eller alvorlige tilstander/sykdommer?

Ja ☐   Nei ☐

Hvis du svarte ja; hvilke(n) sykdom(mer) dreier det seg om ?

_____

_____

16. Har du vært innlagt på sykehus?

Ja ☐   Nei ☐

Dersom ja, når og av hvilke grunn?

Beskriv: _____

Aktuelle sykdommer

17. Er du for tiden frisk (bortsett fra eventuelle kroniske tilstander)?

Ja ☐   Nei ☐

Hvis du svarte nei; hva feiler det deg?

Beskriv: _____

Medikamenter

18. Bruker du noen form for medisiner <u>fast</u>?

     Ja ☐   Nei ☐

     Hvis du svarte ja; hvilke(n) medisin(er) bruker du?

Preparat:_____ styrke:_____ antall:_____

Preparat:_____ styrke:_____ antall:_____

Preparat:_____ styrke:_____ antall:_____

                                            Ja   Nei

19. Bruker du andre medisiner <u>av og til</u>?
    (f.eks. Valium, Paracet, Ibux)   ☐   ☐

     Hvis du svarte ja; hvilke(n) medisin(er) bruker du?

	Nesten daglig	Noen ganger i uken	Noen ganger i mnd.	Sjelden
Preparat:_____	☐	☐	☐	☐
Preparat:_____	☐	☐	☐	☐
Preparat:_____	☐	☐	☐	☐

                                        Ja   Nei

20. Har du <u>tidligere</u> brukt andre medisiner i mer enn 3 mnd sam-
menhengende, som du ikke har nevnt ovenfor?   ☐   ☐

     Hvis ja; hvilke(n) medisin(er) brukte du?

Preparat:_____ styrke:_____periode:_____

Preparat:_____ styrke:_____periode:_____

Preparat:_____ styrke:_____periode:_____

21. Har du brukt vitaminer, mineraler, kosttilskud eller helsekost siste året?

	Ja	Nei		Daglig	4-6 x pr.uke	1-3 x pr.uke	<1 x pr. uke
Vitaminer	☐	☐	Hvilke:_____	☐	☐	☐	☐
Mineraler	☐	☐	Hvilke:_____	☐	☐	☐	☐
Kosttilskud (f. eks. tran)	☐	☐	Hvilke:_____	☐	☐	☐	☐
Helsekost	☐	☐	Hvilke:_____	☐	☐	☐	☐

Nytelsesmidler

22. Har du noen gang røykt?   Ja ☐   Nei ☐   Hvis nei, gå til pkt. 29

23. Røyker du nå?   Ja ☐   Nei ☐   Av og til ☐

24. Hvis du helt har sluttet å røyke, hvor gammel var du da du sluttet? :_____år

25. Hvis du røyker fremdeles, hvor mange sigaretter røyker du vanligvis daglig?

1-5 ☐	16-20 ☐	30 + ☐
6-10 ☐	21-25 ☐	
11-15 ☐	26-30 ☐	

Hvis av og til, hvor mange per uke:_____ stk

26. Hvis du har røykt **tidligere**; hvor mange sigaretter røykte du vanligvis daglig?

1-5 ☐	16-20 ☐	30 + ☐
6-10 ☐	21-25 ☐	
11-15 ☐	26-30 ☐	

Hvis av og til, hvor mange per uke:_____ stk

27. Hvor gammel var du da du begynte å røyke?:_____ år

28. Hvor mange år til sammen har du røykt daglig?:_____ år

29. Dersom du røyker, har du da vurdert å slutte? Ja ☐   Nei ☐

30. Hvis du har brukt andre former for nikotin <u>siste året</u> og fremdeles bruker det, kryss
    av for hvilken type:

	Ja	Nei		
Skrå/tyggetobakk/snus	☐	☐	bruker fremdeles	☐
Nikotintyggegummi	☐	☐	bruker fremdeles	☐
Nikotinplaster	☐	☐	bruker fremdeles	☐
Nikotininhalator	☐	☐	bruker fremdeles	☐

31. Drikker du alkohol?

    Ja ☐   Nei ☐   Hvis nei, gå til pkt. 36

32. Hvilken type alkohol drikker du vanligvis? *(Sett eventuelt flere kryss)*

    Lettøl   ☐   Rusbrus   ☐

    Øl   ☐   Hetvin *(sherry, portvin, madeira)*   ☐

    Rødvin   ☐   Brennevin *(vodka, gin, akevitt, cognac, whisky, likør)*   ☐

    Hvitvin   ☐

33. Hvor mange ganger i måneden drikker du vanligvis alkohol?
    (Regn ikke med lettøl. Sett 0 hvis mindre enn 1 i måneden)

    Antall:_____

34. Hvor ofte har du drukket alkohol det siste året?
    (Regn ikke med lettøl og alkoholfritt øl)

    4-7 ganger i uken ☐

    2-3 ganger i uken ☐

    ca. 1 gang i uken ☐

    2-3 ganger i måneden ☐

    ca. 1 gang i måneden ☐

    Noen få ganger siste år ☐

    Ikke siste året ☐

Enheter alkohol
For å sammenligne ulike typer alkohol spør vi etter det vi kaller alkoholenheter
(= 1,5 cl ren alkohol). En alkoholenhet tilsvarer:
1 flaske rusbrus / cider
1 glass (0.33 liter) øl
1 vinglass (12 cl) rød eller hvitvin
1 hetvinsglass (7,5 cl), sherry eller annen hetvin
1 drammeglass (4 cl) brennevin eller likør

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35. Hvor mange enheter drikker du vanligvis når du nyter alkohol?

    10 eller flere ☐

    7-9 ☐

    5-6 ☐

    3-4 ☐

    1-2 ☐

    Færre enn 1 ☐

36. Ca. hvor mange ganger i løpet av det siste året har du drukket så mye som

minst 5 glass og/eller drinker i løpet av et døgn?

Antall:_____

37. Bruker du noen andre rusmidler?

Ja ☐   Nei ☐

Takk for besvarelsen!

Ønsker du å få tilsendt et brev med kort oppsummering av resultatene av undersøkelsene vi har foretatt?

Ja, send kun til meg ☐

Ja, send til meg, samt kopi til fastlege ☐

Nei, ønsker ikke brev tilsendt ☐

Nei, men ønsker brev sendt til fastlege ☐

Hvis man oppdager noe som trenger videre oppfølging, ønskes opplysningene sendt til din fastlege?

Ja ☐   Nei ☐

Navn og adresse på fastlegen:

_____

_____

Eventuelle kommentarer:

_____

_____