

# Fitness in fatness

Associations with cardiovascular risk factors and subclinical disease



Hilde Halland

Thesis for the degree of Philosophiae Doctor (PhD)  
University of Bergen, Norway  
2019

UNIVERSITY OF BERGEN



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Date of defense: 24.05.2019

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Year: 2019

Title: Fitness in fatness

Name: Hilde Halland

Print: Skipnes Kommunikasjon / University of Bergen

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# Contents

1.	Abbreviations.....	8
2.	Scientific environment .....	9
3.	Acknowledgements.....	10
4.	List of Publications .....	12
5.	Abstract .....	13
6.	Introduction .....	14
6.1	<i>Obesity as a global health problem</i> .....	14
6.2	<i>Clustering of cardiovascular risk factors in obesity</i> .....	15
6.3	<i>Subclinical cardiovascular disease</i> .....	17
6.4	<i>Myocardial function in obesity</i> .....	18
7.	Hypothesis and aims .....	20
7.1	<i>Hypothesis</i> .....	20
7.2	<i>Aims</i> .....	20
8.	Methods.....	21
8.1	<i>Study population</i> .....	21
8.2	<i>Cardiovascular risk assessment</i> .....	22
8.2.1	Overweight and obesity.....	22
8.2.2	Clinic and ambulatory blood pressure .....	23
8.2.3	Diabetes .....	24
8.2.4	Metabolic syndrome .....	25
8.2.5	Body composition analysis.....	25
8.2.6	Self-reported health.....	26
8.2.7	Fasting venous blood samples .....	26
8.3	<i>Assessment of subclinical arterial disease</i> .....	26

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8.3.1	Aortic stiffness .....	26
8.3.2	Carotid intima-media thickness .....	28
<b>8.4</b>	<b>Assessment of subclinical cardiac disease .....</b>	<b>29</b>
8.4.1	Echocardiographic imaging and analysis.....	29
8.4.2	Left atrial dilatation.....	30
8.4.3	Left ventricular geometry .....	30
8.4.4	Left ventricular function .....	32
<b>8.5</b>	<b>Exercise testing and fitness .....</b>	<b>32</b>
8.5.1	Exercise testing .....	32
8.5.2	Classification of fitness.....	33
<b>8.6</b>	<b>Statistics.....</b>	<b>34</b>
<b>9.</b>	<b>Summary of results .....</b>	<b>35</b>
<b>9.1</b>	<b>Study 1 .....</b>	<b>35</b>
<b>9.2</b>	<b>Study 2 .....</b>	<b>36</b>
<b>9.3</b>	<b>Study 3 .....</b>	<b>38</b>
<b>10.</b>	<b>Discussion .....</b>	<b>40</b>
<b>10.1</b>	<b>Fitness and cardiovascular risk in obesity.....</b>	<b>40</b>
10.1.1	Hypertension in obesity .....	43
10.1.2	Diabetes .....	45
10.1.3	Metabolic syndrome .....	46
<b>10.2</b>	<b>Subclinical cardiovascular disease .....</b>	<b>47</b>
10.2.1	Subclinical arterial disease.....	47
10.2.2	Left atrial dilatation.....	48
10.2.3	Abnormal left ventricular geometry .....	49
10.2.4	Left ventricular systolic function.....	50

---

<b>10.3</b>	<b><i>Limitations</i></b> .....	<b>52</b>
<b>11.</b>	<b>Future perspectives</b> .....	<b>54</b>
<b>12.</b>	<b>Conclusions</b> .....	<b>55</b>
<b>13.</b>	<b>References</b> .....	<b>57</b>

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## 1. Abbreviations

BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CV	Cardiovascular
FATCOR	FAT associated Cardiovascular dysfunction
GLS	Global longitudinal strain
LA	Left atrial
LV	Left ventricular
OR	Odds ratio
24-h BP	24-hour ambulatory blood pressure

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## 2. Scientific environment

This research project was undertaken in the *Bergen Hypertension and Cardiac Dynamics group* at the Department of Clinical Science, University of Bergen, and supported by the *Norwegian National Advisory Unit on Women's Health*, Oslo University Hospital, Oslo, Norway.

The *Bergen Hypertension and Cardiac Dynamics group* is headed by Professor Eva Gerds. Professor Knut Matre, associate professor Mai Tone Lønnebakken, post-doctoral fellow Helga Midtbø, 4 PhD-fellows, 2 research medical students. Several consultants in cardiology employed at the Department of Heart Disease, Haukeland University Hospital, also work in the group. Our group focuses on non-invasive cardiac imaging methods in clinical and experimental studies. The *Bergen Hypertension and Cardiac Dynamics group* is responsible for the *Echocardiography Research Laboratory*, which is a state-of-the-art core laboratory for echocardiographic image analysis.

The *Bergen Hypertension and Cardiac Dynamics group* has a large network of collaborators, extending both nationally and internationally. Collaborators include Professor Giovanni de Simone (Hypertension Research Centre, Federico II University, Naples, Italy), Professor Richard B. Devereux (Weill Medical College, Cornell University, New York, USA), Professor Vera Regitz-Zagrosek (Institute for Gender Medicine, Charité University, Berlin, Germany), Professor Sverre E. Kjeldsen (University of Oslo, Oslo, Norway), Professor Geir Christensen (University of Oslo, Oslo, Norway), Professor Maja-Lisa Løchen (The Arctic University of Norway, Tromsø, Norway), Professor Kirsti Ytrehus (The Arctic University of Norway, Tromsø, Norway).

The *Norwegian National Advisory Unit on Women's Health* is headed by Professor Siri Vangen and was founded in 2006. The primary aim of this advisory unit is to do research and disseminate knowledge about women's health in a lifetime perspective. The research group includes 4 researchers, 9 post-doctoral fellows and 7 PhD-fellows. The unit's main focus is on reproductive health, but also includes research into cancers that affect women and cardiovascular health.



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### 3. Acknowledgements

This thesis is a story about more than six hundred quite ordinary people, who did something truly extraordinary by volunteering to take part in the FAT associated Cardiovascular dysfunction (FATCOR) study. I am very grateful to all the participants for their time and effort, and I hope they found it a worthwhile experience.

I would like to thank my main supervisor, Professor Eva Gerdts, for being the most amazing supervisor anyone could wish for. Not only is she an excellent scientist, but also gifted in mentoring. Despite a busy schedule, she has always made time for me, and with humor and enthusiasm, willingly shared her vast knowledge with me. She has been a tremendous source of encouragement throughout this project, and has given me inspiration for my future career. I would also like to thank Christian Arvei Moen for advising me to contact Professor Eva Gerdts; this is surely some of the best advice I have ever received.

I thank my co-supervisor Professor Knut Matre for being accessible for all kinds of questions and discussions. I am particularly grateful for the many entertaining conversations totally irrelevant for the PhD, but nevertheless important for happiness and motivation. I thank my co-supervisor Associate Professor Mai Tone Lønnebakken for her kind support, ideas and feedback on papers and presentations.

I am very grateful to my colleagues and co-authors, Helga Midtbø and Sahrai Saeed. They share the ability to give friendly, creative and challenging feedback, which I have been very lucky to benefit from. I also want to thank Eigir Einarsen for all the inspiring and challenging discussions we have had. May they continue in the future! I also owe thanks to all my co-authors for reviewing numerous drafts of my papers, and our research group for providing a good work environment. In particular, I would like to thank Liv Himle, Hilde Jacobsen, Britt Irene Gjellefall, Synnøve Ygre Hauge, Carmenza Ayana Ulveseth and Marina V. Kokorina for their essential contributions in managing the practical aspects of the study, and also for being

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generous and friendly colleagues. I would also like to thank Chandru Punwani and Rigmor Hjørnevik Gjerde for patiently teaching me the basics of echocardiography.

I would also like to thank the Norwegian National Advisory Unit on Women's Health for funding my PhD-fellowship, for constantly inviting me to their events as if my office was just around the corner, and for making me feel truly welcome whenever I visited. On that note, my sincere thanks go to Pernille Frese for taking care of the practical aspects of my employment in Oslo. Her always friendly and very efficient assistance has been very important to me.

I thank the 9<sup>th</sup> floor PhD-fellows for making everyday life in academia both entertaining and interesting. Being a PhD-fellow with you was a privilege, and I will miss you. On several occasions, Aslaug Drotningvik and Johannes Just Hjertaas have come to my rescue when preparing figures. Their contributions have saved me from a great deal of frustration, and I am very grateful for their much needed assistance!

I owe my interest in cardiology to Professor Rune Wiseth and Dr. Morten Slette at St.Olavs Hospital in Trondheim. Several years ago they generously provided me with friendly and enthusiastic guidance in cardiology. Although I was a medical student, and later a recently graduated doctor, they made me feel like their peer. I will always be grateful for that, and I hope our paths will cross again.

Finally, I would like to thank Morten and our little boys, Marius and Aksel, for making life good and amusing. Fortunately, you made it impossible to completely devote life to work, for which I will forever be grateful. I would also like to thank my parents, Arve and Aashild, for their love, support and practical help throughout these years.

Hilde Halland

Bergen, January 2019

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## 4. List of Publications

1. Halland H, Lønnebakken MT, Saeed S, Midtbø H, Cramariuc D, Gerds E. Does fitness improve the cardiovascular risk profile in obese subjects? *Nutr Metab Cardiovasc Dis.* 2017;27:518-24.
2. Halland H, Lønnebakken MT, Pristaj N, Saeed S, Midtbø H, Einarsen E, Gerds E. Sex differences in subclinical cardiac disease in overweight and obesity (the FATCOR study). *Nutr Metab Cardiovasc Dis.* 2018;28:1054-60.
3. Halland H, Matre K, Midtbø H, Saeed S, Pristaj N, Einarsen E, Lønnebakken MT, Gerds E. Effect of fitness on left ventricular systolic myocardial function in overweight and obesity (the FATCOR study). Submitted to *Nutr Metab Cardiovasc Dis.*

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## 5. Abstract

**Background:** Fitness may influence cardiovascular (CV) health in obesity. We explored the impact of fitness on CV risk factors and prevalent subclinical CV disease in overweight and obese women and men without known CV disease.

**Materials and methods:** Clinical and echocardiographic data from the FAT associated CardiovasculaR dysfunction (FATCOR) study was used for analyses of CV risk factors and subclinical CV disease in relation to fitness. Fitness was determined by sex- and age-adjusted peak oxygen uptake on a maximal treadmill test.

**Results:** Hypertension, metabolic syndrome and diabetes were highly and equally prevalent in fit and unfit groups (all  $p > 0.05$ ) (Study 1). In  $>40\%$  of cases, prevalent hypertension and diabetes were diagnosed in-study. Being fit was characterized by lower waist circumference, non-obesity, non-smoking and higher muscle mass (all  $p < 0.05$ ). Women had more subclinical cardiac disease (77% vs. 62%) and left atrial (LA) dilatation (74% vs. 56%) than men, while men had more abnormal left ventricular (LV) geometry (30% vs. 21%, all  $p < 0.05$ ) (Study 2). Female sex more than doubled the risk of prevalent subclinical cardiac disease (95% confidence interval [CI] 1.48-3.22) and LA dilatation (95% CI 1.67-3.49), while male sex doubled the risk of abnormal LV geometry (95% CI 1.30-3.01) (all  $p < 0.05$ ). Fitness was not associated with prevalent subclinical CV disease ( $p > 0.05$ ). Mean global longitudinal strain (GLS) was similar between fit and unfit groups within overweight and obese groups (both  $p > 0.05$ ), while low GLS was more prevalent in the unfit vs. the fit obese group (30% vs. 10%,  $p < 0.05$ ) (Study 3). In obesity, but not overweight, fitness was associated with higher GLS (more negative value) (odds ratio 0.87 [95% CI 0.79-0.99,  $p < 0.05$ ], independent of confounders.

**Conclusion:** The prevalences of major CV risk factors and subclinical cardiac disease were high and uninfluenced by fitness. Despite this, fitness in obesity was associated with improved myocardial function. Our findings indicate that women are at particular risk of subclinical cardiac disease, and that fitness alone cannot compensate for the harmful effects of increased body mass index. Furthermore, our results demonstrate the benefit of a thorough assessment of CV risk in such subjects.

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## 6. Introduction

### 6.1 Obesity as a global health problem

Nowadays, cardiovascular (CV) disease is estimated to be responsible for more than 30% of annual deaths, making CV disease the leading cause of death in the world.<sup>1</sup> At the same time, nearly 2 billion of the world's adult population is overweight, and more than 1/3 of these have developed obesity.<sup>2,3</sup> This obesity epidemic is a driving force for the development of hypertension, and a major risk factor for developing CV disease.<sup>4,5</sup> In fact, in 2015 approximately 4 million deaths globally were attributed to high body mass index (BMI), and more than 2/3 of these deaths were caused by CV disease.<sup>6</sup> Interestingly, almost 40% of reported deaths occurred in overweight subjects,<sup>6</sup> highlighting that overweight is not a benign condition.

Similar to numerous other countries, the obesity epidemic is evident also in Norway. Currently, the average Norwegian adult is overweight, and normal-weight is found in a minority, estimated present in 40% of women and in only 25% of men.<sup>7</sup> The Norwegian Institute of Public Health reports that, in middle-aged subjects, obesity is present in 20% of women and 25% of men.<sup>7</sup> Compared to the global prevalence of obesity, which is estimated to be 15% in women and 11% in men,<sup>2</sup> the prevalence of obesity is higher among middle-aged adults in Norway.<sup>7</sup> Taken together, these data suggest that most Norwegian adults are at increased risk of subclinical and clinical CV disease from overweight and obesity alone.

To combat the obesity pandemic and the large burden of CV disease, physical activity is recommended for the prevention and treatment of both.<sup>8,9</sup> Epidemiological studies have demonstrated that increased physical activity and improved fitness are independently associated with reduced CV morbidity and mortality.<sup>10-14</sup> For instance, a recent prospective cohort study of healthy Norwegians showed that higher peak oxygen uptake reduced the risk of fatal and non-fatal coronary heart disease by 16%.<sup>12</sup> However, as demonstrated in another recent cohort study, being physically active could not overcome negative impact of obesity on risk of myocardial

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infarction.<sup>13</sup> Thus, taken together, the impact of fitness on CV health in obese women and men without known CV disease remains unclear.

## 6.2 Clustering of cardiovascular risk factors in obesity

When overweight or obesity is present, the likelihood of co-presence of other potent CV risk factors increases.<sup>15</sup> The obesity pandemic is considered the driver of the observed increase in incidence of hypertension and type 2 diabetes in the world.<sup>15, 16</sup>

Globally, hypertension is the most important modifiable CV risk factor and a large proportion of the burden of CV disease is attributable to hypertension.<sup>17</sup> It is well documented that the prevalence of hypertension increases in parallel with increasing BMI.<sup>18, 19</sup> Interestingly, the effect of increasing BMI on blood pressure (BP) differs between women and men, and also between non-obese and obese subjects.<sup>19</sup> For a similar increase in BMI in obesity, women experience a larger increase in BP than men.<sup>20</sup> Additionally, the BP increase is larger in obese women compared to non-obese women, while the BP increase associated with weight gain is independent of initial BMI in men.<sup>21</sup>

The impact of fitness on hypertension in overweight and obesity is not fully understood. In a Swedish cohort study including more than 1.5 million male military conscripts, both increased BMI and poor fitness on maximal exercise testing were independently associated with a higher risk of hypertension later in life.<sup>22</sup> A prospective cohort study of Finnish adults tested the single and joint effects of BMI and self-reported physical activity on risk of hypertension in women and men, and found that both lower BMI and higher physical activity were independently associated with a lower risk of developing hypertension regardless of sex.<sup>23</sup> They also showed that the positive impact of physical activity on incident hypertension was present in both women and men with increased BMI.<sup>23</sup> In an American population-based study of 950 women and men, no associations between prevalent hypertension and physical activity or fitness were identified.<sup>24</sup> These previous studies, however, based identification of physical activity and fitness on self-reports and submaximal exercise testing.<sup>23, 24</sup>

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Overweight and obesity are strongly associated with diabetes.<sup>25</sup> When diabetes is present, the risk of CV diseases like stroke and coronary heart disease increases, and the increase in risk is higher in women than in men.<sup>26,27</sup> Additionally, CV morbidity and mortality is increased in subjects with diabetes and poor fitness, independent of abdominal adiposity.<sup>28</sup> Also, a previous population-based study of obese subjects without known CV disease or diabetes, found moderate physical activity to be associated with reduced risk of incident diabetes.<sup>29</sup> Taken together, these findings suggests that fitness may contribute in reducing the risk of incident diabetes in obese women and men, as well as reducing CV complications in subjects with established diabetes.

Metabolic syndrome describes the clustering of CV risk factors like obesity, hypertension, diabetes and atherogenic dyslipidemia.<sup>30</sup> The prevalence of metabolic syndrome sharply increases with increasing BMI,<sup>30-32</sup> and the presence of metabolic syndrome is associated double risk of CV diseases like myocardial infarction and stroke, as well as CV mortality.<sup>33</sup> Several meta-analyses have also found that the increase in CV risk associated with metabolic syndrome is higher in women than in men.<sup>33-35</sup> Cross-sectional population-based studies from Finland have demonstrated that lower self-reported physical activity and poorer peak oxygen uptake on maximal exercise testing is associated with higher prevalence of metabolic syndrome in older subjects and middle-aged men.<sup>36,37</sup> Interestingly, emerging evidence from a recently published study offers an alternative and plausible explanation for the cross-sectional associations between metabolic syndrome and fitness.<sup>38</sup> In that study, which was an exercise intervention study of women and men with metabolic syndrome, exercise-induced weight loss was associated with improvements in the metabolic syndrome Z-score, a continuous metabolic syndrome risk score, but not with increase in peak oxygen uptake.<sup>38</sup> This suggests that the positive impact of fitness on prevalent metabolic syndrome may well be attributable to weight loss. Taken together, there is a need for further studies on the impact of fitness, assessed by directly measured peak oxygen uptake from maximal exercise testing, on the prevalence and clustering of major CV risk factors in subjects with increased BMI.

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## 6.3 Subclinical cardiovascular disease

Following the current paradigm, subclinical CV diseases usually develop following progressive accumulation of CV risk factors like hypertension and obesity, and precede the development of clinical CV diseases like myocardial infarction, heart failure and atrial fibrillation.<sup>9</sup> Therefore, timely identification of CV risk factors and appropriate risk factor management are considered key in both primary and secondary prevention of CV disease.<sup>9</sup> In line with this, identification of subclinical CV disease in hypertensive patients may more accurately identify high risk subjects than the degree of BP elevation.<sup>39</sup>

Subclinical CV disease is defined as structural or functional changes in the heart or in the arteries. Common types of subclinical cardiac disease includes left atrial (LA) dilatation, abnormal left ventricular (LV) geometry or reduced global longitudinal strain (GLS). The term abnormal LV geometry includes distinct phenotypes of LV geometry, defined based on the presence of concentric geometry and/or LV hypertrophy.<sup>40</sup> Subclinical cardiac disease in subject with increased BMI may be induced by both the hemodynamic and non-hemodynamic effects of obesity and influenced by co-presence of other CV risk factors like diabetes or hypertension.<sup>41</sup> In fact, increased BMI is an independent risk factor for both subclinical and clinical CV disease, even after adjustment for other CV risk factors.<sup>5, 15, 21, 42, 43</sup> Other mechanisms explaining the association of increased BMI with subclinical CV disease are related to proinflammatory and pro-fibrotic neuroendocrine activation in visceral fat leading to chronic low-grade CV inflammation<sup>41</sup> as well as peri- and myocardial fat accumulation infiltrating the myocardium, resulting in myocardial steatosis.<sup>44</sup> Studies have shown that the susceptibility both to develop<sup>26, 27, 45-47</sup> and respond to treatment<sup>48, 49</sup> of subclinical cardiac damage may differ by sex. For instance, studies have demonstrated that being female is associated with prevalent LV hypertrophy, particularly when obesity and hypertension are co-present.<sup>21, 50</sup> As obesity and CV disease represent significant burdens for both women and men, this thesis seeks to highlight sex-differences in this



context. Thus, there is a particular need for further data on sex differences in obesity-associated subclinical cardiac disease.

Subclinical cardiac disease is often asymptomatic, but the presence of subclinical cardiac disease is associated with very high risk for subsequent clinical CV disease events.<sup>51-53</sup> For example, LA dilatation is a predictor of atrial fibrillation, stroke and death.<sup>53-55</sup> Further, the presence of LV hypertrophy is associated with increased CV morbidity and mortality, including increased risk of sudden cardiac death.<sup>56,57</sup> Also, even a modest reduction in LV systolic function is a strong predictor of CV events and death.<sup>58</sup>

Subclinical arterial diseases like arterial remodeling and increased arterial stiffness are particularly common among hypertensive subjects and may be assessed by carotid ultrasound and carotid-femoral pulse-wave velocity.<sup>46,59</sup> However, the impact of obesity on subclinical arterial disease is less clear. Some studies suggest a direct association between obesity and subclinical arterial disease, while others indicate that this association is in fact mediated through obesity-associated metabolic abnormalities.<sup>46,60,61</sup> Nevertheless, prevalent subclinical arterial disease is associated with higher risk of CV morbidity and mortality.<sup>62,63</sup> Thus, early detection and appropriate treatment of subclinical CV disease is of utmost importance in order to prevent serious adverse events. However, less is known about the impact of fitness on subclinical CV disease in overweight and obese women and men without known CV disease.

## **6.4 Myocardial function in obesity**

Previous studies have demonstrated that obesity is associated with reduced LV systolic function independent of LV mass, both when measured as LV ejection fraction and midwall shortening.<sup>42,64</sup> Traditionally, LV ejection fraction is the most used measure of LV systolic function. The prognostic value of LV ejection fraction has been established in a variety of study populations,<sup>40,65,66</sup> and LV ejection fraction guides decision-making in clinical practice, ranging from device implantation in heart

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failure to use of cardiotoxic cancer treatment.<sup>67, 68</sup> However, LV ejection fraction may remain normal despite a considerable reduction in myocardial contractility.<sup>69, 70</sup> In assessment of subclinical cardiac disease, more sophisticated measures are now used to allow earlier detection of myocardial dysfunction.<sup>71</sup> In particular, use of speckle tracking echocardiography allows for assessment of LV systolic function by GLS, which in turns enables the detection of reduced LV systolic function at a time when LV ejection fraction is still within normal range.<sup>70, 72-75</sup> Additionally, GLS is an independent and powerful predictor of CV morbidity and mortality.<sup>72, 76</sup> The presence of overweight and obesity has consistently been associated with reduced LV systolic function when assessed by GLS, but inconsistently with reduced LV ejection fraction.<sup>73-75, 77</sup> However, the impact of fitness on GLS in obesity has previously only been assessed in small studies, and with contrasting findings.<sup>78, 79</sup> In a study of 9 obese adolescents, fitness was associated with higher GLS,<sup>79</sup> while no association was found in a study of 39 young females with abdominal adiposity.<sup>78</sup> Thus, further data is needed on the impact of fitness on GLS in subjects with increased BMI.

## 7. Hypothesis and aims

### 7.1 Hypothesis

We hypothesized that fitness was associated with lower prevalences of CV risk factors and subclinical CV disease in overweight and obese women and men without known clinical CV disease

### 7.2 Aims

#### *Main aim*

To determine the impact of fitness on prevalences of CV risk factors and subclinical CV disease in overweight and obese women and men without known clinical CV disease

#### *Specific aims*

*Study 1:* To assess the association of fitness with prevalence of CV risk factors and subclinical arterial disease in overweight and obese women and men without known clinical CV disease

*Study 2:* To assess the association of fitness with subclinical cardiac disease in overweight and obese women and men without known clinical CV disease

*Study 3:* To assess the effect of fitness on LV myocardial function in overweight and obese women and men without known clinical CV disease

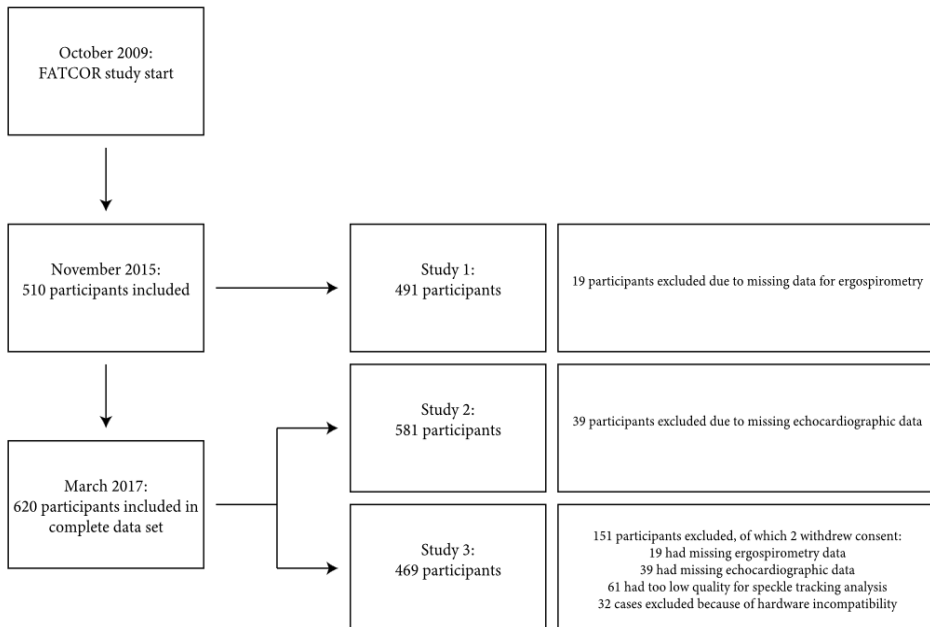
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## 8. Methods

### 8.1 Study population

This thesis was based upon the participants in the FAT associated Cardiovascular dysfunction (FATCOR) study. The FATCOR study is cross-sectional in design, and was performed at the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway. Data collection was initiated in October 2009 and finalized March 2017. AlfaHelse A/S, a collaborating general practice center specializing in the management of overweight and obesity, was responsible for recruitment of participants. In total, 620 women and men were included. Of these, 2 participants later withdrew consent, and subsequently, all data from these were excluded from analyses. Thus, 618 participants were included in the final data set (Figure 1). Inclusion criteria were age 30-65 years and a BMI  $>27$  kg/m<sup>2</sup>. Exclusion criteria were previous myocardial infarction, gastrointestinal disorder, severe psychiatric illness or the inability to understand Norwegian language. Written, informed consent was obtained from all participants prior to inclusion. The FATCOR study was approved by the Western Norway Regional Ethics Committee (approval number 3.2008.1946) and was conducted in accordance with the Declaration of Helsinki.

**Figure 1:** Flow chart of FATCOR study population that was included in Study 1-3



## 8.2 Cardiovascular risk assessment

After inclusion, an initial physical examination at the general practitioner center was performed. This was followed by a rigorous CV evaluation program at the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway.

### 8.2.1 Overweight and obesity

By inclusion criteria, all participants were either overweight or obese. The criteria from the World Health Organization were used to distinguish between overweight, defined as a BMI  $\geq 25.0$  kg/m<sup>2</sup>, and obesity, defined as a BMI  $\geq 30.0$  kg/m<sup>2</sup>.<sup>2</sup>

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## 8.2.2 Clinic and ambulatory blood pressure

Clinic BP was measured, as recommended in the guidelines, by the general practitioner using a standardized procedure and an Omron M4 sphygmomanometer (Omron Healthcare Co. Ltd., Hoofddorp, Netherlands).<sup>17</sup> A cuff appropriate for each participants' arm circumference was used, and the measurement was performed with the participant in the sitting position. After 5 minutes of rest, the BP was measured in triplets with 1-minute intervals. The average of the 2 last measurements was taken as the clinic BP. The BP was considered elevated if systolic BP  $\geq 140$  mmHg and/or diastolic BP  $\geq 90$  mmHg.<sup>17</sup> Pulse pressure was calculated as the difference between the systolic BP and the diastolic BP, and mean BP was calculated as diastolic BP plus 1/3 of the pulse pressure.

The 24-hour blood pressure (24-h BP) monitoring was performed with a Diasys Integra II recorder (Novacor, Cedex, France), in accordance with guidelines.<sup>17</sup> Each participant was fitted with a cuff of appropriate size for their individual arm circumference on the non-dominant arm. The device was programmed to measure the BP twice per hour during the night and three times per hour during the day, which added up to 78 measurements in 24 hours. The 24-h BP was repeated if  $<70\%$  of the measurements were valid. The participants were carefully instructed to keep their arm still during cuff inflation, to adhere to their daily routines, but to avoid hard physical exercise. The 24-h BP was considered elevated if 24-h systolic BP  $\geq 130$  mmHg and/or 24-h diastolic BP  $\geq 80$  mmHg.<sup>17</sup>

By combining the results from clinic BP and 24-h BP, four distinct BP phenotypes were identified (Figure 2).

**Figure 2:** BP phenotypes as determined by clinic BP and 24-h BP in combination.

Clinic blood pressure			
SBP <140 mmHg and DBP <90 mmHg	SBP ≥140 mmHg and/or DBP ≥90 mmHg		
Normotension	White-coat hypertension	SBP <130 mmHg and DBP <80 mmHg	24-hour ambulatory blood pressure
Masked hypertension	Sustained hypertension	SBP ≥130 mmHg and/or DBP ≥80 mmHg	

SBP, systolic blood pressure. DBP, diastolic blood pressure.

We considered hypertension to be present if participants used antihypertensive drugs or if elevated 24-h BP (systolic BP  $\geq 130$  mmHg and/or diastolic BP  $\geq 80$  mmHg) was found. We used the mean systolic BP during daytime and night-time from the 24-h BP monitoring to determine dipping status. If mean systolic BP increased from daytime to night-time, reverse dipping was present. If there was  $<10\%$  reduction in mean systolic BP from daytime to night-time, the participant was classified as a non-dipper.

### 8.2.3 Diabetes

All participants had their fasting blood glucose and HbA<sub>1c</sub> measured after an overnight fast followed by venous blood sampling. In addition, all non-diabetic participants were subjected to a standardized 75 gram oral glucose tolerance test in order to reveal diabetes not identified by fasting blood glucose or HbA<sub>1c</sub>. This was

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followed by blood samples to measure blood glucose two hours after the glucose solution was ingested.

Diabetes in the participants was diagnosed using the criteria from the American Diabetes Association.<sup>80</sup> If fasting blood glucose was  $\geq 7$  mmol/L and/or HbA<sub>1c</sub>  $\geq 6.5\%$  (equal to 48 mmol/mol) and/or the 2-hour blood glucose was  $\geq 11.1$  mmol/L after the 75-gram oral glucose tolerance test, diabetes was diagnosed.<sup>80</sup> When calculating the total prevalence of diabetes in the study population, participants with known diabetes and participants using antidiabetic medication were also included.

Impaired fasting blood glucose was defined as fasting blood glucose 5.6-6.9 mmol/L.<sup>80</sup> Impaired glucose tolerance was present if the 2-hour blood glucose following the oral glucose tolerance test was 7.8-11.0 mmol/L.<sup>80</sup>

#### 8.2.4 Metabolic syndrome

Metabolic syndrome was diagnosed using the criteria from the American Heart Association/National Heart, Lung and Blood Institute.<sup>30</sup> Following these criteria, metabolic syndrome was considered present if 3 out of 5 required criteria were met in the individual participants. The following criteria were applied: 1) Increased waist circumference ( $\geq 88$  cm in women,  $\geq 102$  cm in men), 2) elevated triglycerides  $\geq 1.7$  mmol/L, 3) low high-density lipoprotein cholesterol ( $< 1.3$  mmol/L in women,  $< 1.03$  mmol/L in men), 4) systolic BP  $\geq 130$  mmHg and/or diastolic BP  $\geq 85$  mmHg and/or use of antihypertensive medication, or 5) high fasting blood glucose  $\geq 5.6$  mmol/L and/or use of antidiabetic medication.<sup>30</sup>

#### 8.2.5 Body composition analysis

Body composition analysis was performed by bioelectrical impedance analysis (Tanita TBF-300A, Tanita Corporation of America, Arlington Heights, USA). The device was tetrapolar and measured bioelectrical impedance by a foot-foot system. The bioelectrical impedance analysis estimated fat mass (kg), fat percentage (%), muscle mass (%) and fat-free mass (kg).



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### 8.2.6 Self-reported health

All participants completed a standardized questionnaire on self-reported health. The questionnaire included questions about the participants' general health, medical history, time spent on physical activity per week and use of both prescription and non-prescription medication.

### 8.2.7 Fasting venous blood samples

After an overnight fast, fasting venous blood samples were drawn. The samples were analyzed at validated laboratories using standardized methods and evaluated using standard reference values. Analyses included, but were not limited to, measurement of hemoglobin, glycosylated hemoglobin, fasting blood glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol and triglycerides. In order to calculate estimated glomerular filtration rate, we used the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>81</sup>

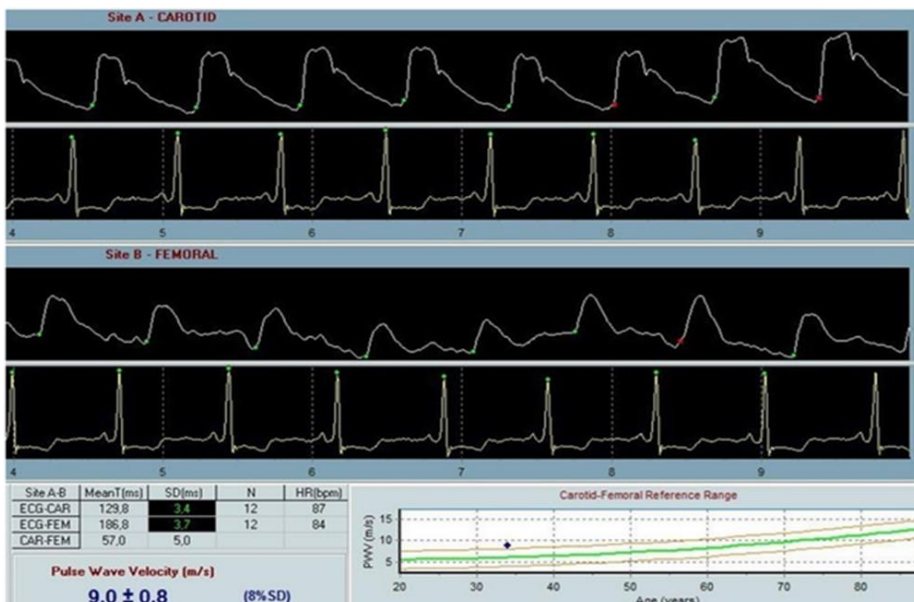
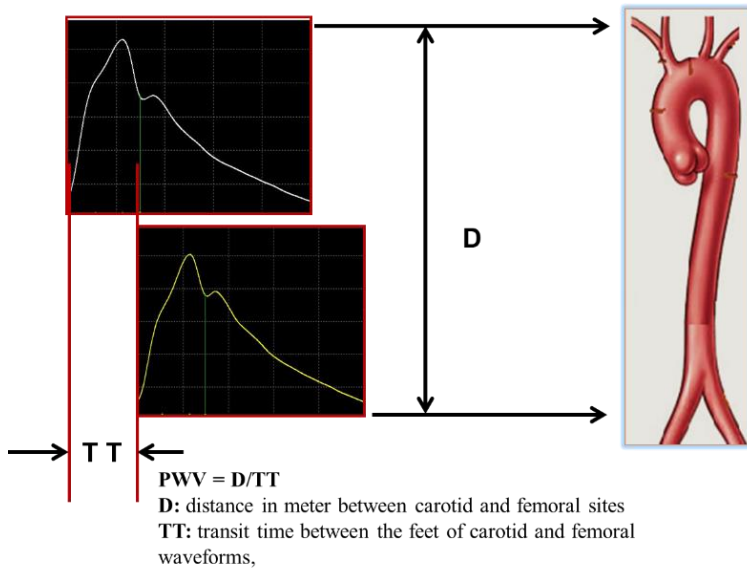
## 8.3 Assessment of subclinical arterial disease

### 8.3.1 Aortic stiffness

Arterial stiffness was assessed from carotid-femoral pulse wave velocity measured by applanation tonometry (SphygmoCor, Atcor Medical, Sydney, West Ryde, Australia) in order to evaluate aortic stiffness. The measurement was performed after the participants had rested for 15 minutes in the supine position. Transcutaneous recordings of pressure pulse waveforms were obtained from the right common carotid artery and the femoral arteries with simultaneous recording of electrocardiogram in order to synchronize carotid- and femoral pulse wave times (Figure 3). The distance between the carotid recording site and the sternal notch (the proximal distance) and the distance between the sternal notch and the femoral recording site (the distal distance) were carefully measured. The carotid-femoral pulse wave velocity was calculated as the distal distance minus the proximal distance, divided by the transit

time, automatically adjusted for mean BP and reported in m/s. As recommended, increased aortic stiffness was considered present if a carotid-femoral pulse wave velocity  $>10$  m/s was found.<sup>17, 82</sup>

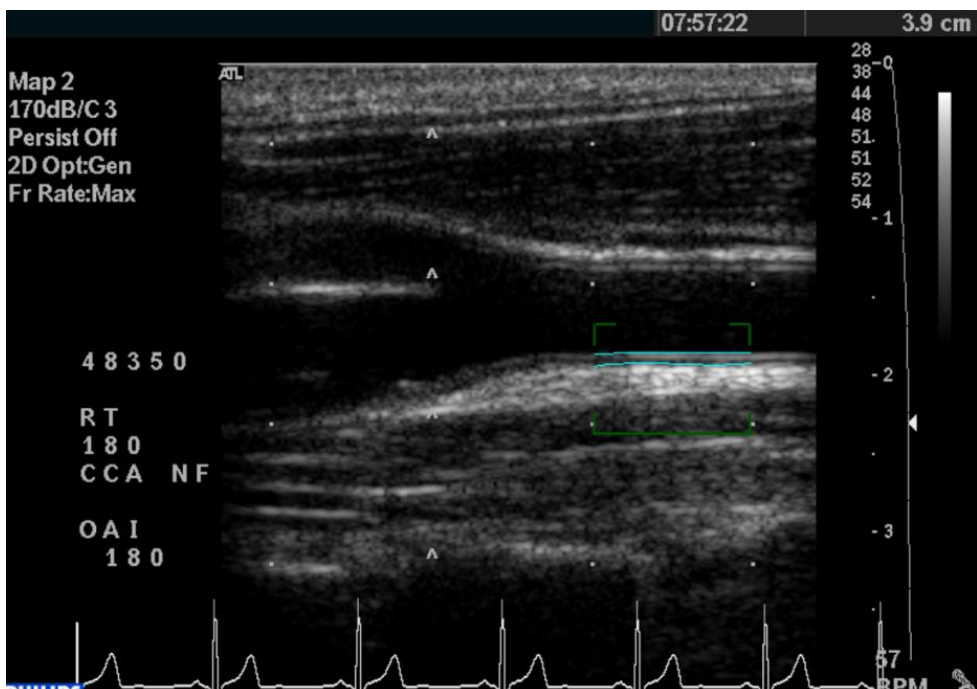
**Figure 3:** Measurement of carotid-femoral pulse wave velocity.



### 8.3.2 Carotid intima-media thickness

Carotid ultrasound (Philips iE33, Philips Healthcare, Best, Netherlands) was used for measuring carotid intima-media thickness. The maximal carotid intima-media thickness in end-diastole was measured following a comprehensive protocol including the near and far wall of the common and internal carotid arteries and the carotid bulb on both the left and right side (Figure 4). In accordance with the guidelines, a mean carotid intima-media thickness  $>0.9$  mm was considered increased, and a focal carotid intima-media thickness  $\geq 1.5$  mm was taken as a carotid plaque.<sup>17</sup>

**Figure 4:** Ultrasound image of the right common carotid artery with bifurcation. The distance the blue lines represent the intima-media thickness.



Courtesy of Halvor Øygarden, MD PhD.

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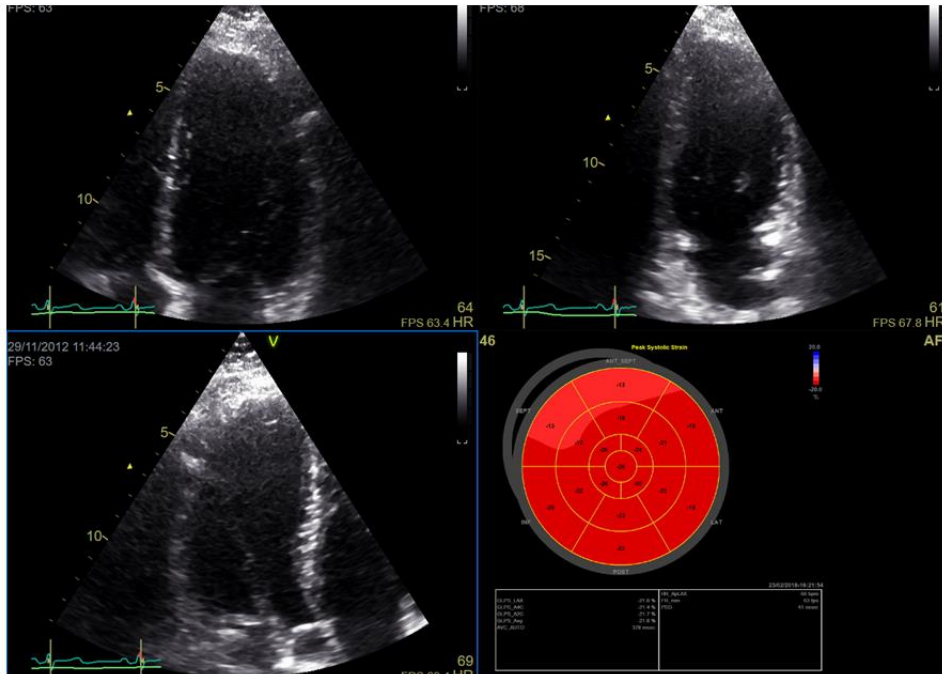
## 8.4 Assessment of subclinical cardiac disease

### 8.4.1 Echocardiographic imaging and analysis

A GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway) (n=549) or a Phillips iE33 (Philips Healthcare, Best, Netherlands) (n=32) scanner was used for echocardiographic examinations. The examination followed a standardized imaging protocol. Image analysis of conventional measures was performed at the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway, on workstations with Image Arena Software version 4.1 (Tomtec Imaging Systems GmbH, Unterschleissheim, Germany), and was done in accordance with the joint guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging on quantitative echocardiography.<sup>40</sup> Junior investigators performed the initial image analysis, and as is recommended for clinical trials, all images were subsequently proofread by a single expert reader (EG).<sup>83</sup> This ensured highly reproducible measurements, as previously published from our Echocardiography Core Laboratory.<sup>84</sup>

EchoPac BT 202 software (GE Vingmed Ultrasound, Horten, Norway) was used for analysis of speckle tracking strain. Thus, analysis of GLS could only be performed in patients where echocardiography was performed by a GE echocardiograph (Figure 1). The analyses were performed by a single investigator (NP), followed by proof-reading by one highly experienced reader (SS). Peak systolic longitudinal strain was assessed in 17 segments of the LV using 4-, 3- and 2-chamber apical views. Automated function imaging with an adequate frame rate (50-70 fps) was used, and the analysis was performed as recommended by the vendor (GE). End-diastole was defined from the electrocardiogram and end-systole was defined from aortic valve closure from a pulsed wave Doppler recording. The endocardial border was then tracked automatically with manual corrections. The quality of the automatic tracking was assessed visually after software processing, and the segment was excluded if the tracking was poor. GLS was calculated as the average of peak systolic longitudinal strain in 17 segments of the LV.

**Figure 5:** Segmental representation of peak systolic GLS from 3 apical views of the LV.



#### 8.4.2 Left atrial dilatation

LA systolic volume was calculated by the area-length method combining apical 2- and 4-chamber views. If LA systolic volume indexed for height<sup>2</sup>  $\geq 16.5$  ml/m<sup>2</sup> in women and  $\geq 18.5$  ml/m<sup>2</sup> in men, LA dilatation was considered present. These sex-specific cut-off values represent the upper 95<sup>th</sup> percentile of LA volume index in healthy European populations.<sup>85</sup>

#### 8.4.3 Left ventricular geometry

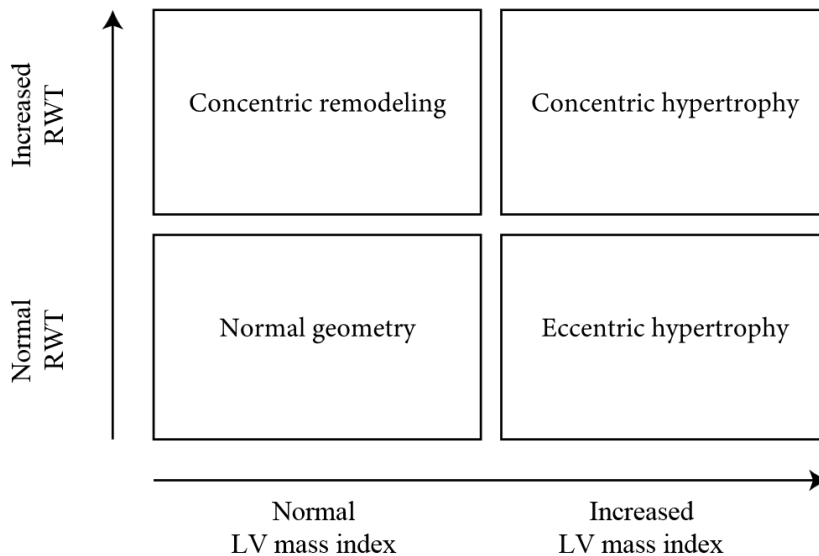
Parasternal long-axis 2-dimensional views were used to measure the wall thicknesses and cavity diameters of the LV. Devereux's validated formula was used for calculating LV mass,<sup>86</sup> and the LV mass was then indexed for height<sup>2.7</sup>. LV hypertrophy was considered present if LV mass index exceeded the prognostically

validated cut-off values of  $>46.7 \text{ g/m}^{2.7}$  in women and  $>49.2 \text{ g/m}^{2.7}$  in men.<sup>45</sup>

Concentric LV geometry was considered present if LV relative wall thickness exceeded the cut-off value of  $\geq 0.43$ , calculated from end-diastolic measurements as  $2 \times$  posterior wall thickness/LV internal diameter.<sup>40</sup>

LV geometric phenotype was determined by combining LV relative wall thickness and LV mass index in the individual participant (Figure 6).<sup>40</sup> Normal geometry was present if both LV mass index and LV relative wall thickness were normal. Eccentric LV hypertrophy was considered present if LV mass index was increased, but LV relative wall thickness was normal. Concentric remodeling was present if LV mass index was normal and LV relative wall thickness increased. Concentric LV hypertrophy was present if both LV mass index and LV relative wall thickness were increased. Concentric LV geometry was considered present if either concentric remodeling or concentric LV hypertrophy was found in the individual participant.

**Figure 6:** LV geometric phenotypes



RWT, relative wall thickness; LV, left ventricular.

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#### 8.4.4 Left ventricular function

LV systolic function was assessed at the endocardial level by LV ejection fraction, which was calculated using modified Simpson's rule (biplane method of discs).<sup>40</sup> As recommended by the current guidelines, the LV ejection fraction was defined as low if <54% in women and if <52% in men.<sup>40</sup>

The LV systolic myocardial function was assessed by peak systolic GLS. GLS is reported as a negative value as the LV shortens in systole. Thus, if the LV shortens less, as in reduced systolic function, the GLS will be a less negative value (closer to zero). Correspondingly, a higher GLS is represented by a more negative value. Based upon data from a healthy European population, investigated by using the same vendor and software as used in the present project, GLS was considered abnormal if >-18.5% in women and if >-16.9 in men.<sup>87</sup>

## 8.5 Exercise testing and fitness

### 8.5.1 Exercise testing

In order to test cardiorespiratory fitness, ergospirometry was performed on a treadmill (Schiller CS-200, Schiller AG, Baar, Switzerland) using a standardized protocol (Chronotropic Assessment Exercise Protocol) particularly suited for overweight and obese subjects. The protocol is incremental both in speed and elevation, but has a longer warm up period than other commonly used ergospirometry protocols. Peak oxygen uptake and respiratory exchange ratio was measured by a breath-to-breath technique. In order to avoid air leakage and to facilitate accurate measurement of peak oxygen uptake, the participants were fitted with a correctly sized face mask, covering both mouth and nose. For continuous heart rate and heart rhythm monitoring, the participants were equipped with electrodes for a 12-lead electrocardiogram. Unless contraindications to further testing arose during the test (such as severe chest pain, severe dyspnea, significant ST-segment depression or -elevation as sign of severe ischemia or ventricular tachycardia detected by

electrocardiogram), all participants were instructed to continue testing until complete exhaustion. Chest pain caused premature abortion of testing in 5 subjects. As all of these reached a high respiratory exchange ratio (at least 1.2), indicating sufficient effort, and therefore remained included in the analyses.

**8.5.2 Classification of fitness** Directly measured peak oxygen uptake under a maximal ergospirometry test, the gold standard for exercise testing, was used for evaluation of fitness in the FATCOR study. As peak oxygen uptake varies with sex and age, a sex- and age-adjusted classification system of cardiorespiratory fitness was used.<sup>88</sup> Using this classification system, the participants were grouped into very poor, poor, fair, average, good, very good and excellent cardiorespiratory fitness.<sup>88</sup> We defined the participants as fit if they reached at least a good level of fitness, and as unfit if a lower level of fitness was achieved (Table 1).

**Table 1:** Sex-and age-adjusted cut-off values for peak oxygen uptake

<b>Age range (years)</b>	<b>Cut-off peak oxygen uptake for fit women (ml/kg/min)</b>	<b>Cut-off peak oxygen uptake for fit men (ml/kg/min)</b>
30-34	NA	>49.6
35-39	>38.2	>51.4
40-44	>37.2	>46.7
45-49	>34.2	>43.3
50-54	>33.8	>40.2
55-59	>30.8	>39.0
60-65	>27.8	>38.6

NA, not applicable.



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## 8.6 Statistics

The Statistical Package for Social Sciences software versions 23-25 (IBM, Armonk, New York, USA) was used for both data management and statistical analysis. All data were plotted manually by a technician, and then proof-read by a second person to ensure accuracy. Continuous variables were presented as mean $\pm$ standard deviation, and categorical variables as percentages.

When comparing two groups, Student's T-test was used for continuous variables and Chi-square test for categorical variables. When comparing four groups, a general linear model with Scheffe's or Sidak's post hoc test was used for comparison of categorical variables, and one-way analysis of variance with Sidak's post hoc test was used for comparison of continuous variables.

Uni- and multivariable logistic regression analyses were used to identify covariables of fitness (study 1), LA dilatation/concentric LV geometry/abnormal LV geometry/subclinical cardiac disease (study 2) and fitness in overweight and obese groups separately (study 3). Only variables with a p-value  $<0.01$  in univariable logistic regression analyses were included in multivariable logistic regression analyses. The results from these analyses were reported as odds ratio (OR) with their 95% confidence intervals (CI).

The intraclass correlation coefficient was calculated to assess the interobserver variability of GLS measurements. The threshold for statistical significance was set to  $p<0.05$  for all analyses.

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## 9. Summary of results

### 9.1 Study 1

Halland H, Lønnebakken MT, Saeed S, Midtbø H, Cramariuc D, Gerds E. **Does fitness improve the cardiovascular risk profile in obese subjects?** *Nutr Metab Cardiovasc Dis.* 2017;27:518-24.

The aim of study 1 was to assess the association of fitness with prevalence of CV risk factors and subclinical arterial disease in overweight and obese women and men without known clinical CV disease. At the time of study, data collection was still ongoing, and the 491 participants who had completed study examinations including ergospirometry testing per November 2015 were included in the study. These participants were on average 48 years old, 60% were women and 28% were classified as fit.

Despite lower 24-h systolic BP and mean BP in the fit group (both  $p < 0.05$ ), the prevalences of hypertension (63% in unfit vs. 58% in fit) did not differ between the groups ( $p > 0.05$ ). Similarly, the prevalences of different BP categories did not differ between fit and unfit groups (all  $p > 0.05$ ). There were no significant differences in average fasting blood glucose or the prevalences of impaired fasting glucose, impaired glucose tolerance or diabetes between the fit and unfit groups (all  $p > 0.05$ ). The prevalence of MetS was high (45%), and did not differ between the groups ( $p > 0.05$ ). When studying the five qualifying criteria for MetS, there were no significant differences in the prevalence of these between the fit and unfit groups. Prevalence of subclinical arterial disease was unexpectedly low, and did not differ between fit and unfit groups. The prevalence of carotid plaques was higher in men than women (26% vs. 17%,  $p < 0.05$ ).

Fitness was characterized by absence of obesity, lower waist circumference, non-smoking, lower fat mass, lower daytime mean BP, higher self-reported physical activity and higher muscle mass (all  $p < 0.05$ ) in univariable logistic regression analyses. After adjusting for confounders in multivariable logistic regression analysis,

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fitness was independently associated with having a lower waist circumference, absence of obesity, non-smoking and a higher muscle mass (all  $p < 0.05$ ).

## 9.2 Study 2

Halland H, Lønnebakken MT, Pristaj N, Saeed S, Midtbø H, Einarsen E, Gerdtts E. **Sex differences in subclinical cardiac disease in overweight and obesity (the FATCOR study).** *Nutr Metab Cardiovasc Dis.* 2018;28:1054-60.

The aim of study 2 was to assess the impact of fitness on prevalence of subclinical cardiac disease in overweight and obese women and men without known clinical CV disease. Subclinical cardiac disease was defined as presence of LA dilatation and/or abnormal LV geometry. Readable echocardiograms were obtained in 581 participants, and these were included in the study. These participants were on average 48 years old and 60 % were women.

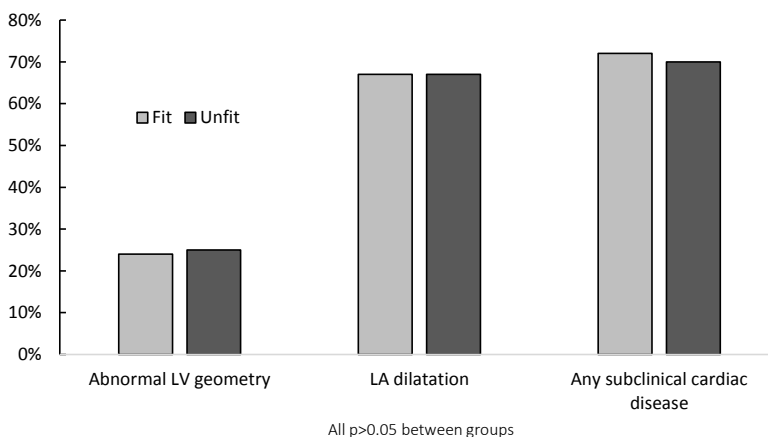
No association of fitness with prevalent subclinical cardiac disease was found (70% in unfit group vs. 72% in fit group,  $p > 0.05$ ) (Figure 7). However, interesting sex differences in prevalences and types of subclinical cardiac disease were identified during data analysis. Helped by reviewers, we re-focused the paper. LA dilatation was highly prevalent in the total study population (67%), and more common in women than men (74% vs. 56%,  $p < 0.05$ ). The prevalences of LA dilatation, abnormal LV geometry and concentric LV geometry did not differ between fit and unfit groups (all  $p > 0.05$ ). In multivariable logistic regression analysis in the total study population, female sex was independently associated with a 2-fold (OR 2.42 [95% CI 1.67-3.49]) higher prevalence of LA dilatation independent of a significant association with higher pulse pressure (OR 1.02 per 1 mmHg [95% CI 1.00-1.04]).

On average every fourth participant had abnormal LV geometry, and this was more common in men than women (30% vs. 21%,  $p < 0.05$ ). Women and men had similar prevalences of eccentric LV hypertrophy and concentric LV remodeling ( $p > 0.05$ ), but men had more concentric LV hypertrophy ( $p < 0.05$ ). In the total study population, male sex was associated with a near 2-fold (OR 1.81 [95% CI 1.19-2.78]),

$p < 0.05$ ) higher risk of having abnormal LV geometry in multivariable logistic regression analysis, independent of higher pulse pressure (OR 1.02 per 1 mmHg [95% CI 1.00-1.04]), higher BMI (OR 1.12 per  $\text{kg}/\text{m}^2$  [95% CI 1.06-1.17]) and higher age (OR 1.04 per year [95% CI 1.02-1.07]) (all  $p < 0.05$ ).

Grouping any presence of subclinical cardiac disease (dilated LA and abnormal LV geometry together), the majority (71%) of the participants had subclinical cardiac disease, and this was even more prevalent in women compared to men (77% vs. 62%,  $p < 0.05$ ). In the total study population, female sex was associated with a 2-fold (OR 2.19 [95% CI 1.48-3.22]) higher risk of any subclinical cardiac disease independent higher pulse pressure (OR 1.03 per 1 mmHg [95% CI 1.01-1.05]) and higher BMI (OR 1.06 per 1  $\text{kg}/\text{m}^2$  [95% CI 1.01-1.12]) (all  $p < 0.05$ ) in multivariable logistic regression analysis. In sex-specific, multivariable logistic analysis, presence of any subclinical cardiac disease was independently associated with higher pulse pressure in women (OR 1.06 per 1 mmHg [95% CI 1.00-1.16]), while in men, higher 24-h pulse pressure (OR 1.04 per 1 mmHg [95% CI 1.00-1.17]) and higher fat free mass (OR 1.04 per 1 kg [95% CI 1.00-1.08]) were both independent covariables of prevalent subclinical cardiac disease (all  $p < 0.05$ ).

**Figure 7:** Prevalence of types of subclinical cardiac disease in fit and unfit groups.



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### 9.3 Study 3

Halland H, Matre K, Midtbø H, Saaed S, Pristaj N, Einarsen E, Lønnebakken MT, Gerdt E. **Effect of fitness on left ventricular systolic myocardial function in overweight and obesity (the FATCOR study)**. Submitted to Nutr Metab Cardiovasc Dis.

The aim of study 3 was to assess the effect of fitness on LV myocardial function in the FATCOR population. Data on both ergospirometry and speckle tracking echocardiography was required for this study, and this was available in 469 of the participants (76% of the total FATCOR population). These participants were on average 47 years old, 60% were women and mean BMI was 32.0 kg/m<sup>2</sup>. Within the overweight and obese groups, the prevalences of hypertension, diabetes and metabolic syndrome did not differ between fit and unfit subgroups of participants.

GLS and LV ejection fraction did not differ between fit and unfit groups among overweight subjects (both  $p > 0.05$ ). Among obese subjects, LV ejection fraction was higher and abnormal GLS was less common in the fit group (both  $p < 0.05$ ), although mean GLS was similar and within normal range both in fit and unfit groups ( $p > 0.05$ ). The obese unfit group had lower (less negative) GLS than the overweight unfit group ( $p < 0.05$ ).

In univariable logistic regression analyses in the overweight group, no significant associations were found between fitness and measures of LV systolic function. In multivariable logistic regression analysis, fitness in the overweight group was independently associated with lower serum triglycerides (OR 0.50 per 1 mmol/L [95% CI 0.30-0.84]) and lower body fat percentage (OR 0.96 per 1 % [95% CI 0.92-1.00]) (both  $p < 0.05$ ).

In univariable logistic regression analyses in the obese group, fitness was associated with higher GLS, LV ejection fraction, pulse pressure and LV mass index and with lower body fat percentage (all  $p < 0.05$ ). After adjusting for confounders in multivariable logistic regression analysis, the association between fitness and higher (more negative) GLS (OR 0.87 per % [95% CI 0.77-0.99],  $p < 0.05$ ) remained statistically significant.

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Reproducibility of peak systolic GLS measurements was evaluated in 26 randomly selected patients with excellent intraclass correlation coefficient (0.96 [95% CI 0.95-0.98]) for interobserver measurements.

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## 10. Discussion

This PhD-project studied the impact of cardiorespiratory fitness on CV risk factors and prevalent subclinical CV disease in overweight and obese women and men without known clinical CV disease participating in the cross-sectional FATCOR study. A number of clinically important findings were identified in the project: Firstly, we demonstrated that CV risk factors are highly prevalent in overweight and obesity, and to the same extent in fit and unfit subjects. The presence of CV risk factors was frequently unknown to the participants, emphasizing the importance of a thorough CV risk assessment in overweight and obese subjects. Secondly, we showed that subclinical cardiac disease was present in the majority of the participants, and that obesity-related subclinical cardiac disease disproportionately affected women, while subclinical arterial disease was found in a minority, and more common in men. Further, prevalent subclinical CV disease was not influenced by fitness. Taken together these findings suggest that use of echocardiography ideally should be performed routinely in subjects with increased BMI to detect individuals at high or very high risk of CV events reflected by the presence of subclinical cardiac disease. Thirdly, we demonstrated that although fitness did not impact the prevalence of subclinical cardiac disease, fitness was associated with better LV systolic myocardial function in obese subjects, but not in overweight subjects. Thus, our findings highlight the negative impact of overweight and obesity on cardiac health and emphasize the importance of a thorough evaluation of CV risk factors. Optimally, such evaluation in overweight and obese subjects should include ambulatory BP monitoring, oral glucose tolerance testing and advanced echocardiography to optimize CV disease prevention regardless of fitness status.

### 10.1 Fitness and cardiovascular risk in obesity

The total burden of CV risk factors in the FATCOR population was high. By design, the FATCOR study included subjects at increased risk for clustering of cardiometabolic risk factors, and subsequently, for the development of subclinical

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and clinical CV disease.<sup>4, 5, 15</sup> As reported by the Norwegian Institute of Public Health, only 25% of Norwegian men and 40% of Norwegian women are estimated to have a normal BMI.<sup>7</sup> Considering that most Norwegians adults are either overweight or obese,<sup>7</sup> the FATCOR cohort can therefore provide valuable insights relevant for the average Norwegian adult.

More than 2/3 of the FATCOR participants were unfit, and therefore at increased risk of CV disease and death according to previous reports.<sup>10, 12-14</sup> The association between physical activity and CV disease and mortality was first documented in 1953 by Morris et al.<sup>14</sup> In that study sedentary bus drivers had an increased incidence of coronary heart disease and death compared to the more active conductors on double-decker buses.<sup>14</sup> Later studies have confirmed this association in larger samples, with more precise measures of physical activity and fitness, and for several CV outcomes.<sup>10, 12, 13</sup> In a prospective study, more than 9700 American men underwent maximal exercise testing twice to investigate the relationship between changes in fitness and CV- and all-cause mortality.<sup>10</sup> They found that the persistently fit men had the lowest risk of all-cause- and CV death, while the highest risk was found in the persistently unfit men.<sup>10</sup> In addition, they found that, compared to their persistently unfit counterparts, men that progressed from being unfit to fit, had a 44% and 52% lower risk for age-adjusted all-cause and CV mortality, respectively.<sup>10</sup> Regrettably, the study did not include enough women to report results for women, and despite their use of maximal exercise testing, their definition of fitness relied on exercise duration, rather than directly measured peak oxygen uptake.<sup>10</sup>

Similarly, an inverse and independent association between fitness and mortality was demonstrated in randomly selected sample of 1294 Finnish men in the population-based Kuopio Ischaemic Heart Disease study.<sup>89</sup> In fit men, the risk of all-cause and CV mortality was reduced regardless of whether fitness was quantified as exercise duration or directly measured peak oxygen uptake from maximal exercise testing.<sup>89</sup> Furthermore, the association between higher fitness and lower risk of fatal and non-fatal coronary heart disease was preserved in both women and men in a fit, and on average overweight and middle-aged Norwegian population, with a low



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prevalence of clustering of CV risk factors.<sup>12</sup> The latter study, based upon the Nord-Trøndelag Health Study, could however not show that higher fitness reduced all-cause mortality.<sup>12</sup> Taken together, these studies provide convincing arguments for the positive impact of fitness on risk of clinical CV morbidity and mortality.

The relationship between fitness and CV health in obesity has been investigated in several studies, and the fat-but-fit paradigm arose following publications from the Aerobics Center Longitudinal Study.<sup>90,91</sup> In short, these studies showed that fit obese men had lower risk of CV mortality than unfit overweight or unfit normal-weight men, suggesting that fitness could eliminate or neutralize the negative impact of obesity.<sup>90,91</sup> In the Nurses' Health study, which explored the joint effects of BMI and physical activity on mortality, they found that the physically active obese women had a lower risk of CV- and all-cause mortality than inactive obese women.<sup>92</sup> They did not, however, find that a high level of physical activity was able to fully compensate for the increased risk of CV- and all-cause mortality associated with obesity, nor could leanness compensate for negative effects of low physical activity.<sup>92</sup> Other large cohorts have also found that physical activity can attenuate, but not eliminate the increased risk associated with obesity.<sup>93-95</sup> A recent publication from the population-based Tromsø Study, found that higher level of self-reported physical activity reduced, but did not eliminate, the increased risk of having a myocardial infarction associated with increased BMI.<sup>13</sup> Together, these results indicate that CV risk in obesity may be reduced by physical activity and fitness, but the fact that these study results relied on self-reported physical activity rather than exercise testing, which is known to be more strongly associated with all-cause mortality, represents a weakness in study design that may have impacted the results.<sup>96</sup> The caveats of using self-reported physical activity were highlighted in a large prospective cohort study comparing the impact of self-reported physical activity and fitness on all-cause mortality in women and men.<sup>96</sup> In that study they found that fitness quantified by exercise testing was associated with reduced mortality in both women and men, and interestingly, that there was no association between mortality and self-reported physical activity in women.<sup>96</sup>

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In the FATCOR project we found that fit subjects had a lower prevalence of obesity and lower waist circumference, reflecting less abdominal obesity, but despite this, we could not find that fitness was associated with a lower prevalence of major CV risk factors like hypertension, diabetes or metabolic syndrome. This is in contradiction to the cross-sectional FINRISK-study, which found that fitness had a positive impact on CV risk factor profile regardless of abdominal adiposity.<sup>97</sup> Two important differences in population characteristics and study methods may account for the divergent findings. Compared to the FATCOR cohort, the participants in the FINRISK study were leaner with an average BMI <27 kg/m<sup>2</sup> compared to the average BMI of 32 kg/m<sup>2</sup> in the FATCOR cohort. Furthermore, in FINRISK fitness was estimated from a non-exercise aerobic fitness test, in contrast to being directly measured from a maximal exercise test in the FATCOR-study.<sup>97</sup> Our findings indicate that, in FATCOR subjects, obesity had a more powerful impact on CV risk factor profile than fitness.

#### 10.1.1 Hypertension in obesity

The overall prevalence of hypertension in the FATCOR cohort was 60%, which is much higher than the prevalence reported for general population of similar age in Norway in the Nord-Trøndelag Health Study.<sup>98</sup> In that population based study 30% of women and 50% of men had hypertension.<sup>98</sup> In comparison, in study 2, we demonstrated that 53% of women and 72% of men had hypertension. Thus, higher prevalence of hypertension was observed both among FATCOR women and men compared to general Norwegian population, but hypertension remained more common in men, reflecting the known sex difference in prevalent hypertension with age.<sup>99</sup> Given the established association between obesity and hypertension, the high prevalence of hypertension in the FATCOR cohort is likely a consequence of increased BMI.<sup>19</sup> In addition, the FATCOR participants were examined with 24-h BP, and it is possible that this more sensitive method enabled a more accurate identification of hypertension.<sup>100</sup> However, the low prevalences of white-coat hypertension and masked hypertension in the FATCOR population suggests that the use of 24-h BP alone cannot account for the high prevalence of hypertension in the present study

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population. Another possible contributing factor to the high prevalence of hypertension in our cohort, is that we had some publicity from a major local newspaper during the recruitment period of the participants. The newspaper article focused on obesity-associated CV risk, and this may have motivated obese subjects with other known CV risk factors like hypertension to participate.

Although the fit group in study 1 had lower 24-h systolic BP, the prevalence of antihypertensive treatment, hypertension and hypertension subtypes did not differ between fit and unfit groups. We expanded these findings in study 3 by demonstrating that the 24-h systolic BP and prevalences of hypertension also did not differ by fitness within the overweight and obese groups, but rather by absence or presence of obesity. These findings are in agreement with reports from the National Health and Nutrition Survey, in which no association between hypertension and peak oxygen uptake or self-reported physical activity was found.<sup>24</sup> However, in that study peak oxygen uptake was estimated from submaximal exercise testing. Thus, the present study adds to previous knowledge by showing even that when the gold standard of direct measurement of peak oxygen uptake during maximal exercise testing was utilized, fitness still did not impact hypertension prevalence. Taken together, these results suggest that fitness alone is unable to attenuate the negative impact of excess body fat on BP. However, a prospective study design with serial assessment of fitness and associated changes in CV risk factor burden and body composition would be needed to confirm this hypothesis.

Another important finding in study 1 was that 46% of all cases of hypertension in the FATCOR study were identified as a result of the diagnostic work-up in the study. At the same time, less than 60% of subjects with known hypertension used antihypertensive treatment. These findings suggest that hypertension is underdiagnosed and undertreated in overweight and obese subjects. It is, however, possible that the relatively low prevalence of antihypertensive drug treatment in our cohort could reflect that participants were attempting to implement lifestyle change with weight loss prior to initiating antihypertensive drug treatment. The current guidelines for management of arterial hypertension suggests that this can be an

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adequate strategy in some subjects, in particular in those with mild hypertension and few other CV risk factors, reflecting mild-moderately increased over-all risk for clinical CV disease. However, ultimately drug treatment is necessary in most subjects with hypertension, and weight loss is often unsustainable in the long term.<sup>39</sup> Thus, antihypertensive treatment should probably have been initiated in the vast majority of the hypertensive FATCOR participants.<sup>39</sup> Previously, the Framingham Heart Study showed that a 5% increase in body weight was associated with a 20-30% higher incidence of hypertension,<sup>101</sup> and the Harvard Male Alumni study found that a weight gain of 25 pounds (~ 12.5 kg) was associated with a 60% increase in hypertension incidence.<sup>102</sup> The presence of higher BMI and hypertension has further clinical implications, as illustrated in a pooled analysis of 97 prospective cohort studies of 1.8 million adults without previous stroke or coronary heart disease.<sup>103</sup> That meta-analysis showed that for each 5-unit increase in BMI, the risk of stroke increases by 18% and the risk of coronary heart disease increases by 27%.<sup>103</sup> Interestingly, they found that 1/3 of the increased risk of coronary heart disease and 2/3 of the increased risk stroke associated with increased BMI, was mediated by BP.<sup>103</sup> Altogether, our results and current knowledge emphasize that vigilance is required in detection and treatment of hypertension in overweight and obese subjects.

### 10.1.2 Diabetes

Diabetes was present in 12% of the total study population, which is about 3 times higher compared to the general population in Norway, estimated by the Norwegian Institute of Public Health based on data from the Norwegian Prescription Database.<sup>104</sup> As the entire FATCOR cohort is overweight and obese, the higher prevalence may well reflect the known association between increased BMI and higher incidence and prevalence of type 2 diabetes.<sup>25</sup> The risk of clinical CV disease is increased in diabetes, and furthermore, the impact of diabetes on risk of CV disease differs by sex.<sup>26, 27</sup> In a meta-analysis of more than 800,000 individuals, women with diabetes had a nearly 3-fold higher risk of coronary heart disease compared to women without diabetes.<sup>26</sup> In men with diabetes, the risk was 2-fold compared to men free from diabetes.<sup>26</sup> Furthermore, the evidence suggests that when diabetes is present, women

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have more than 40% higher risk of coronary heart disease than men.<sup>26</sup>

Similarly, the presence of diabetes considerably increases the risk of stroke, and more so in women than men.<sup>27</sup>

Previous studies have indicated that fitness can attenuate the increased risk of diabetes associated with overweight and obesity.<sup>20, 105</sup> For example, a prospective study of >6000 American women suggested that, in overweight and obesity, unfit women had a 40% higher risk of incident diabetes than fit women.<sup>105</sup> When compared to lean women, in which risk of incident diabetes remained unchanged by fitness, the risk of incident diabetes was 2-fold in overweight and obese women.<sup>105</sup> Similarly, a prospective study of >3,500 American men, showed that fit obese men had nearly 50% lower risk of incident diabetes compared to unfit obese men, but the risk was still 3-fold compared to normal-weight fit men.<sup>20</sup> Although these studies defined fitness from exercise duration of a maximal exercise test, and not from directly measured peak oxygen uptake, their results indicate that fitness can attenuate, but not eliminate, the increased risk of diabetes associated with increased BMI.<sup>20, 105</sup> In contrast, in the current FATCOR population, the prevalence of diabetes did not differ by fitness, sex or presence of obesity.

Of note, 42% of all cases of diabetes in the FATCOR study were diagnosed through the study work up, and additionally 1/5 had impaired fasting blood glucose, indicating particularly high risk of developing diabetes.<sup>106</sup> When the prevalences of diabetes and impaired fasting blood glucose were grouped, there were no differences between overweight and obese subjects. Again, as indicated above, it is possible that our study attracted a subgroup of individuals with increased BMI that already were aware of having additional CV risk factors, and this may influenced our results. However, our findings show that the presence of diabetes in overweight and obese subjects is largely unknown to both patient and physician, and that fitness may not protect from diabetes in all populations.

### 10.1.3 Metabolic syndrome

Metabolic syndrome was highly prevalent in the FATCOR cohort, and present in 45% of the participants. In a population based cohort of Norwegians of similar age,

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prevalent metabolic syndrome was reported in 28% of women and in 22% of men.<sup>107</sup> Given the known association between increased BMI and metabolic syndrome, the observed discrepancy in prevalence is likely caused by more abdominal obesity and hypertension in our study population.<sup>30-32</sup> As shown in the present project, the prevalence of metabolic syndrome did not differ by fitness or sex, but rather by obesity. This is in contrast to several other cross-sectional studies that have identified an inverse association between metabolic syndrome and fitness.<sup>36, 37.</sup><sup>108</sup> In a recently published study, subjects with metabolic syndrome were randomized to a systematic exercise program or to retain their habitual, sedentary lifestyle.<sup>38</sup> The effect on a composite score for metabolic syndrome components was analyzed, and the study concluded that improvement of metabolic syndrome components was caused by the weight loss associated with the exercise program, and not by the achieved increase in peak oxygen uptake,<sup>38</sup> which may explain the findings in the FATCOR study.

## **10.2 Subclinical cardiovascular disease**

### **10.2.1 Subclinical arterial disease**

While subclinical cardiac disease was highly prevalent in the FATCOR cohort, subclinical arterial disease was not despite the high prevalence of hypertension. Our findings contrast previous observations in the Campania Salute Network project, a large prospective registry of treated hypertensive women and men of similar age in the Italian region of Campania.<sup>46</sup> In that study, carotid plaques were more than twice as common as in the FATCOR study, with a prevalence of 45% and 48% in overweight and obese patients, respectively.<sup>46</sup> Prevalent obesity was associated with 17% higher prevalence of carotid plaque after adjustment for confounders like BP, age and sex, but the association of obesity with carotid plaques was offset after further adjustment for serum triglycerides and presence of diabetes.<sup>46</sup> Additionally, they found that women had a 40% lower prevalence of carotid plaques than men.<sup>46</sup> This sex-difference has previously been documented,<sup>109</sup> and is also present in the

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FATCOR cohort. Compared to the FATCOR study, which included 60% women, a lower prevalence of women was included in the study by Mancusi et al., in which 36% of the overweight patients and 44% of the obese patients were women.<sup>46</sup> Considering the aforementioned sex-difference in prevalence of carotid plaque, it is likely that our higher prevalence of women could have contributed to the lower observed prevalence of carotid plaque.

The average pulse wave velocity in the FATCOR population was within normal range and did not differ by fitness. Studies on pulse wave velocity in relation to fitness in adults with increased BMI are scarce, but a study of 166 sedentary, middle-aged, obese subjects indicated that higher fitness, quantified by maximal exercise testing, was associated with lower pulse wave velocity.<sup>110</sup> Generalization of those results to our population is complicated by the fact that brachial-ankle pulse wave velocity was used in that study, which is not in line with current guideline recommendations on how to assess arterial stiffness.<sup>82</sup> Furthermore, their study population included a high prevalence of diabetes, which may have influenced their results, and also reduce the generalizability of the results.<sup>110</sup> Thus, further studies are needed to ascertain the impact of fitness on pulse wave velocity in obesity.

### 10.2.2 Left atrial dilatation

The total prevalence of LA dilatation was 67%, and it was the most common type of subclinical cardiac disease in the FATCOR population. That LA dilatation was present in the majority in our overweight and obese cohort may partly be explained by the LA's vulnerability to increased pressure- and volume overload,<sup>111</sup> as is the case in subjects with increased BMI.<sup>41</sup> The independent association between increasing BMI and prevalent LA dilatation has previously been established in hypertensive patients with electrocardiographic signs of LV hypertrophy<sup>53, 112</sup> and in the general population.<sup>43</sup> For example, in a population-based cohort from Germany, results from 10 years of follow-up showed that, apart from aging, obesity was the most powerful predictor of incident LA dilatation in women and men.<sup>43</sup> Additionally, both hypertension and obesity were identified as independent predictors of incident LA dilatation, and interestingly, the joint effects on these differed by sex.<sup>43</sup>

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Normotensive, obese women and men had similar prevalences of LA dilatation, but in co-presence of hypertension, the prevalence of LA dilatation was 2-fold in women compared to men.<sup>43</sup> Similarly, women had a higher prevalence of LA dilatation than men in an elderly population with LV hypertrophy and hypertension.<sup>113</sup> The present results add to current knowledge by showing that LA dilatation is highly prevalent in middle-aged overweight and obese subject without known CV disease. Further, our results demonstrated that although the prevalence of obesity did not differ by sex, and despite that hypertension was more common in men, overweight and obese women had a more than 2-fold risk of prevalent LA dilatation compared to men. The presence of LA dilatation is clinically important as it is a predictor of CV morbidities such as atrial fibrillation and stroke.<sup>53-55</sup> In addition, the risk of CV mortality is particularly high if LA dilatation is present in elderly women with atrial fibrillation.<sup>55</sup> Studies have also shown that prevalent LA dilatation is more common in elderly women with LV hypertrophy and in obese, hypertensive women compared to their male counterparts.<sup>43, 113</sup>

### 10.2.3 Abnormal left ventricular geometry

In the FATCOR project, abnormal LV geometry was present in 25% of the participants. Obesity is known to cause LV remodeling in both women and men,<sup>114</sup> and the risk is demonstrated to be higher in obese women,<sup>21</sup> especially if hypertension is co-present.<sup>50</sup> In a cohort of adult Americans, the prevalence of LV hypertrophy in hypertensive subjects was tripled in obese women compared to lean women, while the prevalence was doubled in obese men compared to lean men.<sup>50</sup> The Strong Heart Study, a population based study in free-living North American Indians, also demonstrated that women were at particular risk of obesity-associated LV remodeling, and that this persisted after adjustment of known CV risk factors like history of hypertension, actual systolic BP and age.<sup>21</sup> In the Strong Heart Study they also found that high LV mass in women was particularly associated with other indicators of obesity, such as body fat mass and waist-to-hip ratio.<sup>21</sup> In contrast, in the FATCOR cohort, we found that men had a higher prevalence of abnormal geometry,



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and also higher prevalences of LV hypertrophy and concentric LV geometry. Furthermore, the presence of abnormal LV geometry was not associated with any other indicators of obesity in the FATCOR cohort, neither among women nor among men. Compared to the current study, in which obesity did not differ by sex and the co-presence of obesity and hypertension was more common in men, the Strong Heart Study had a much higher prevalence of obese, hypertensive women.<sup>21</sup> It is possible that these differences in population characteristics can contribute to explaining the diverging results. The powerful impact of co-presence of hypertension and obesity on LV geometry has previously been demonstrated in the prospective Campania Salute Network registry, which found that obese, hypertensive subjects had a 7-fold higher prevalence of LV hypertrophy compared to normal-weight, hypertensive subjects.<sup>46</sup>

Although the mechanisms are unclear, current knowledge suggests that obesity is associated with a higher prevalence of concentric LV geometry.<sup>41</sup> In the current study we could not find that prevalent concentric LV geometry was associated with any measures of body composition or BP, but rather that the only factor retaining significance in multivariable analysis in the total study population was higher age. This is in contrast to the Multi-Ethnic Study of Atherosclerosis, which in more than 5,000 adults found that obesity was associated with prevalent concentric LV geometry.<sup>115</sup> The much larger and older sample in that study, combined with the use of cardiac magnetic resonance imaging, may help explain the differing results.

#### 10.2.4 Left ventricular systolic function

In hypertension, overweight and obesity have been associated with reduced LV systolic function measured by LV ejection fraction and stress-corrected midwall shortening.<sup>42</sup> In a healthy population-based cohort, every 5 unit increase in BMI was associated with 5% reduction of GLS.<sup>75</sup> In the FATCOR population, LV systolic function evaluated by LV ejection fraction and GLS was on average normal. However, when analyzing the prevalences of abnormal LV systolic function after applying sex-specific cut-offs,<sup>40, 87</sup> we found that the prevalences of abnormal GLS were much higher than the prevalences of abnormal LV ejection fraction. This is in

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accordance with previous studies that have demonstrated that GLS is a more sensitive method to detect reduction in LV systolic function than LV ejection fraction.<sup>72, 73</sup> For example, the prevalence of abnormal GLS was 4 times as high as the prevalence of abnormal LV ejection fraction in an American population-based study of 708 middle-aged and elderly subjects without known coronary heart disease.<sup>72</sup> These findings were expanded in another publication from the same cohort, in which they explored the impact of general obesity, assessed by BMI, and of abdominal adiposity, assessed by waist-hip ratio and waist circumference, on LV systolic function.<sup>116</sup> In that study they found that increased waist-hip ratio and waist circumference were independently associated with reduced GLS but not with reduced LV ejection fraction in both non-obese and obese subjects.<sup>116</sup> Furthermore, they found no association between BMI and GLS, but that increasing BMI was associated with higher LV ejection fraction.<sup>116</sup> In line with this, we found the lowest average GLS and the highest prevalence of abnormal GLS in the unfit obese group, which was the group with highest waist circumference. The obese subjects had higher LV ejection fraction than overweight subjects.

In the FATCOR cohort, fitness was independently associated with higher GLS in obese subjects, but not in overweight subjects. Previously, an univariable association between fitness and lower GLS was reported in a small cross-sectional study of 9 obese adolescents.<sup>79</sup> Unfortunately this association could not be examined in multivariable analyses in their study due to too few observations.<sup>79</sup> In contrast, in a cross-sectional study by Share et al. that included 39 obese young females and 33 controls without obesity, no significant association of physical activity with GLS was found.<sup>78</sup> Also, LV myocardial function, assessed by tissue Doppler strain, was negatively associated with BMI in a population of 142 participants with increased BMI without known diabetes or hypertension.<sup>117</sup> In that population there was no association between LV myocardial function and peak oxygen uptake obtained by exercise testing.<sup>117</sup> The present project adds to current knowledge by showing that the negative impact of increased BMI on LV systolic function can be demonstrated in obesity, but not in overweight subjects, and although fitness did not impact prevalent abnormal LV geometry, a positive association between being fit and a more negative

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GLS was identified. Our findings suggest that a reduction in body fat mass percentage through physical activity resulting in higher fitness may result in improved LV systolic function in obesity. However, this remains to be tested in a prospective study with repeated measures of exercise capacity, LV systolic function and body composition.

### **10.3 Limitations**

The present project has some important limitations. The FATCOR study was cross-sectional in design, thus cause-effect relationships could not be documented. The FATCOR cohort was characterized by middle-age, obesity and absence of known clinical CV disease. Extrapolation of results from this cohort to other populations must therefore be done with caution. Also, we did not have information about duration of obesity or current fitness level, and it is possible that this information would have added to our results.

Another limitation is that some data was missing in all studies. This was caused by participants not showing for ergospirometry testing despite repeated invitations or due to poor echocardiographic imaging quality. Furthermore, we decided to analyze GLS using speckle tracking echocardiography and the EchoPac algorithm, which limited the study population in the 3<sup>rd</sup> study to those that had echocardiography performed by a GE machine. Potentially, these factors may have introduced selection biases to the substudies. However, the excluded participants did not differ significantly by age or BMI to the included participants. Obesity is often associated with reduced echocardiographic image quality. However, only 6.7% of patients had image quality too low for quantification of LV geometry, and another 10.5% had image quality too low for speckle tracking echocardiographic analysis of GLS. The use of a high-quality core laboratory for all echocardiographic analyses contributed to reproducible and high quality image analyses, and follows recommendations for echocardiography in clinical studies, strengthening the study design.

Finally, the bioelectrical impedance analysis was performed by a tetrapolar device with a foot-foot system. Compared with a hand-foot system, this method can somewhat underestimate lean body mass, as well as overestimate fat mass in women and underestimate fat mass in men. Another potential limitation is that we did not scale peak oxygen uptake for body composition. Optimally we should have provided both scaled and unscaled results, as both methods are associated with their own sets of misclassifications.<sup>118</sup> However, this recently published information was not available to us when the FATCOR project started in 2009.

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## 11. Future perspectives

The present project demonstrated that CV risk factors were highly prevalent in the FATCOR cohort, and that these were often unknown both to the patient and to the attending general practitioner. This observation suggests that subjects with increased BMI should be recommended thorough evaluation of CV risk organized by the primary health care physician, and that general practitioners should be reminded that targeted more in-depth CV risk assessment, like 24-h BP monitoring and oral glucose tolerance testing, may be necessary even in apparently healthy, middle-aged obese subjects without obvious CV disease. The present results also demonstrated that subclinical cardiac disease was highly prevalent in middle-aged subjects with increased BMI. Considering the prognostic implications of prevalent subclinical cardiac disease, our results point to the benefit of integration of echocardiography in CV risk assessment in subjects with increased BMI.

Prospective studies including frequent and repeated measures of exercise capacity, body composition and CV imaging should be conducted to further explore the impact of duration of fitness and fatness on CV health. Knowledge from randomized-controlled exercise and weight loss intervention studies with CV imaging could provide information on how to best prevent and treat subclinical CV disease in overweight and obese women and men.

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## 12. Conclusions

We hypothesized that fitness was associated with lower prevalences of CV risk factors and subclinical CV disease in overweight and obese women and men without known clinical CV disease. As demonstrated in this thesis, fitness was not associated with lower prevalences of CV risk factors and subclinical disease, but fitness was, associated with better LV systolic myocardial function in obese subjects.

### Study 1

**The purpose of study 1 was to assess the association of fitness with prevalence of CV risk factors and subclinical arterial disease in overweight and obese women and men without known clinical CV disease.**

**Conclusion:** Fitness status did not impact the prevalence of major CV risk factors like hypertension, metabolic syndrome and diabetes, or subclinical arterial disease. Prevalent carotid plaque was more common in men than in women.

### Study 2

**The purpose of study 2 was to assess the association of fitness with subclinical cardiac disease in overweight and obese women and men without known clinical CV disease.**

**Conclusion:** Fitness was not associated with lower prevalence of subclinical cardiac disease. The majority of the participants in the FATCOR study had subclinical cardiac disease. LA dilatation was the most common type of subclinical cardiac disease. Women had a 2-fold higher risk of subclinical cardiac disease, in particular LA dilatation, while men had a 2-fold higher risk of abnormal LV geometry.

### Study 3

**The purpose of study 3 was to assess the effect of fitness on LV myocardial function in overweight and obese women and men without known clinical CV disease.**

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**Conclusion:** In obese subjects, fitness was associated with better LV systolic myocardial function assessed by GLS. Fitness did not impact LV systolic myocardial function in overweight subjects. By adding GLS to evaluation of LV systolic function, detection of LV systolic dysfunction was improved.

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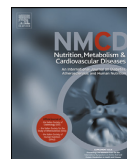
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## Does fitness improve the cardiovascular risk profile in obese subjects?☆



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Received 25 January 2017; received in revised form 11 April 2017; accepted 19 April 2017

Available online 26 April 2017

### KEYWORDS

Cardiorespiratory  
fitness;  
Obesity;  
Hypertension;  
Metabolic syndrome

**Abstract** *Background and aims:* Good cardiorespiratory fitness has been suggested to reduce the risk of cardiovascular disease in obesity. We explored the association of fitness with the prevalences of major cardiovascular risk factor like hypertension (HT), diabetes and metabolic syndrome (MetS) in overweight and obese subjects.

*Methods and results:* Clinical data from 491 participants in the FAT associated Cardiovascular dysfunction (FATCOR) study were analyzed. Physical fitness was assessed by ergospirometry, and subjects with at least good level of performance for age and sex were classified as fit. HT subtypes were identified from clinic and 24-h ambulatory blood pressure in combination. Diabetes was diagnosed by oral glucose tolerance test. MetS was defined by the American Heart Association and National Heart, Lung and Blood Institute criteria. The participants were on average 48 years old (60% women), and mean body mass index (BMI) was 32 kg/m<sup>2</sup>. 28% of study participants were classified as fit. Fitness was not associated with lower prevalences of HT or HT subtypes, diabetes, MetS or individual MetS components (all  $p > 0.05$ ). In multivariable regression analysis, being fit was characterized by lower waist circumference, BMI < 30 kg/m<sup>2</sup>, non-smoking and a higher muscle mass (all  $p < 0.05$ ).

*Conclusion:* In the FATCOR population, fitness was not associated with a lower prevalence of major cardiovascular risk factors like HT, diabetes or MetS. Given the strong association of cardiovascular risk factor burden with risk of clinical cardiovascular disease, these findings challenge the notion that fitness alone is associated with lower risk of cardiovascular disease in obesity.

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### Introduction

Physical inactivity and poor cardiorespiratory fitness are considered independent risk factors for cardiovascular

(CV) disease [1]. Cross-sectional data from the FINRISK study indicate that fitness is associated with a healthier CV risk profile independent of the level of abdominal adiposity [2]. The Nurses' Health Study and the Aerobics Center Longitudinal Study comparing CV outcomes between fit obese subjects and unfit obese subjects, found lower CV morbidity and mortality in the fit group [3–6]. From this it may be suggested that the increased CV risk posed by obesity may be reduced by improving cardiorespiratory fitness [1].

☆ Clinical trial registration: URL: <http://www.clinicaltrials.gov> NCT02805478.

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Despite the large amount of evidence from population-based studies supporting the importance of maintaining fitness for CV health, few clinical studies in obese subjects have tested the relationship between cardiopulmonary fitness measured by maximal oxygen uptake and CV risk factors, and inconsistent results have been reported [7,8]. In the present study, we tested the hypothesis that good cardiorespiratory fitness is associated with an improved CV risk factor profile in an overweight and obese cohort. In particular, the influence of cardiorespiratory fitness on the prevalence of major CV risk factors like hypertension (HT), diabetes and metabolic syndrome (MetS) was targeted.

## Methods

### Study population

Clinical data were collected from the ongoing FAT associated CardioVasculaR dysfunction (FATCOR) study at Haukeland University Hospital in Bergen, Norway. The study included women and men aged 30–65 years old with a body mass index (BMI)  $> 27$  kg/m<sup>2</sup>. Exclusion criteria were previous myocardial infarction, gastrointestinal disorder, severe psychiatric illness or the inability to understand Norwegian language. Inclusion into the study was performed at a collaborating general practice center specializing in management of obesity. A total of 510 participants were recruited from October 2009 to November 2015. Of these, 491 participants had completed ergospirometry and were included in the present analysis. The FATCOR study was conducted in accordance with the Declaration of Helsinki from 1983 and with approval from the Regional Ethics Committee. Written informed consent was signed by all participants.

### Cardiovascular risk assessment

Following inclusion, all participants underwent a clinical examination at the general practitioner center. Clinic blood pressure (BP) was measured using appropriate cuff-size (Omron M4 sphygmomanometer, Omron Healthcare Co. Ltd., Hoofddorp, Netherlands) in accordance with current guidelines [9]. Bioelectrical impedance analysis (Tanita-TBF-300A, Tanita Corporation of America, Arlington Heights, USA) was used for body composition analysis. Blood glucose and lipid profile were measured in fasting, venous blood samples [10]. An oral glucose tolerance test was performed in all participants without known diabetes and fasting blood glucose  $< 7.0$  mmol/L. The participants' self-reported general health was recorded using a standardized questionnaire, which also included declaration of hours of physical activity per week and use of any medication.

The World Health Organization definition was used for identification of overweight and obesity [11]. The American Heart Association/National Heart, Lung and Blood Institute criteria were used to identify MetS [12]. MetS was diagnosed if at least three of the following five criteria were present in the individual participant: 1) waist circumference  $\geq 88$  cm (women) and  $\geq 102$  cm (men),

2) triglycerides  $\geq 1.7$  mmol/L, 3) high-density lipoprotein (HDL) cholesterol  $< 1.3$  mmol/L (women) and  $< 1.03$  mmol/L (men), 4) systolic BP  $\geq 130$  mmHg and/or diastolic BP  $\geq 85$  mmHg and/or antihypertensive treatment or 5) fasting blood glucose  $\geq 5.6$  mmol/L and/or drug treatment for elevated blood glucose. Diabetes was considered present if history of diabetes, fasting blood glucose  $\geq 7$  mmol/L, glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>)  $\geq 6.5\%$  or 2-h blood glucose  $\geq 11.1$  mmol/L after oral glucose tolerance testing was found [13]. A fasting blood glucose between 5.6 and 6.9 mmol/L was recognized as impaired fasting blood glucose (IFG) and a 2-h blood glucose 7.8–11.0 mmol/L was recognized as impaired glucose tolerance (IGT) [13].

### 24-h ambulatory BP recording

The participants underwent a 24-h ambulatory BP (24-h BP) recording (Diasys Integra II, Novacor, Cedex, France) as previously described [14]. An appropriately sized cuff was placed on the non-dominant arm. The equipment was set to perform BP measurement every 20 min during day-time and every 30 min during night-time. The participants were instructed to adhere to their daily routines, apart from abstaining from strenuous exercise, and to relax their arm during measurements. If  $< 70\%$  of the measurements were valid, the 24-h BP recording was repeated. In accordance with the current guidelines for management of arterial HT [9], the results from measurement of clinic BP and 24-h BP recording were used for identifying normotension (NT), white-coat hypertension (WCHT), masked hypertension (MHT) and sustained hypertension (SHT). NT was defined as clinic BP  $< 140/90$  mmHg and 24-h BP  $< 130/80$  mmHg. WCHT was considered present if elevated clinic, but normal 24-h BP was found, and MHT if normal clinic, but elevated 24-h BP was found. SHT was considered present if both clinic and 24-h BP was elevated. Patients treated with antihypertensive drugs were classified as SHT irrespective of actual BP measurements.

### Subclinical arterial disease

Aortic stiffness was measured with applanation tonometry (SphygmoCor, AtCor Medical, Sydney, West Ryde, Australia), derived from carotid-femoral pulse wave velocity (PWV), as previously described [15]. In accordance with current guidelines [9], PWV  $> 10$  m/s was taken as increased aortic stiffness. Carotid intima-media thickness (cIMT) was measured by ultrasound (Phillips iE33, Phillips Healthcare, Best, Netherlands) and considered increased if mean cIMT  $> 0.9$  mm. Carotid plaque was considered present if focal cIMT  $\geq 1.5$  mm [9].

### Exercise capacity and fitness

Peak oxygen uptake ( $VO_{2max}$ ) was measured by ergospirometry using a treadmill (Schiller CS-200, Schiller AG, Baar, Switzerland) and a standardized protocol (Chronotropic Assessment Exercise Protocol) in all participants [16]. The respiratory exchange ratio was measured by breath-to-

breath technique. The participants were encouraged to continue the test until volitional exertion. The classification by Shvartz and Reibold for sex- and age specific identification of cardiorespiratory fitness based upon peak  $VO_{2max}$  was used to identify fit and unfit participants [17]. Based upon peak  $VO_{2max}$  cardiopulmonary fitness was rated as very poor, poor, fair, average, good, and very good to excellent. We classified the participants as fit if they achieved at least good peak  $VO_{2max}$  for sex and age (Table 1).

### Statistics

Data management and statistical analyses were performed using the IBM SPSS Statistics software version 22 (IBM, Armonk, New York, USA). The study population was grouped into fit and unfit groups. Data are presented as mean  $\pm$  standard deviation (SD) for the continuous variables and as percentages for categorical variables. Groups were compared with Chi-square test for categorical variables and with unpaired Student's *t*-test for continuous variables. A general linear model with Scheffe's post-hoc test was used for comparison between BP categories. Uni- and multivariable logistic regression analyses were used to identify covariables of being fit in the study population. Important covariables from univariable analyses were selected for the multivariable model. The results are presented as odds ratio (OR) with 95% confidence intervals (CI). A *p*-value of  $<0.05$  was taken as statistical significance in all analyses.

### Results

#### Total study population

The 491 FATCOR participants were on average  $48 \pm 9$  years old, 60% were women and the average BMI was  $32 \pm 4$  kg/m<sup>2</sup> (Table 1). Of these, 28% of the participants were classified as fit.

#### Comparison of fit and unfit subjects

The fit and unfit groups had comparable prevalence of HT ( $p > 0.05$ ). Use of antihypertensive treatment was comparable between fit and unfit groups (Table 2), and the prevalences of different HT subtypes did not differ (both  $p > 0.05$ ) (Fig. 1). The prevalence of newly diagnosed HT in the study was high (30% in unfit vs. 33% in fit groups ( $p = 0.57$ )). Both 24-h systolic and mean BP were higher in the unfit group ( $p < 0.05$ ), while clinic BP did not differ (Table 3).

**Table 2** Cardiovascular risk factors in the total study population, fit and unfit groups.

Variable	All ( <i>n</i> = 491)	Unfit ( <i>n</i> = 355)	Fit ( <i>n</i> = 136)	<i>p</i> -Value
Women, %	60	59	60	0.92
Age, years	$48 \pm 9$	$47 \pm 9$	$51 \pm 9$	$<0.001$
$VO_{2max}$ , ml/kg/min	$31 \pm 7$	$29 \pm 6$	$37 \pm 8$	
Body weight, kg	$96 \pm 16$	$99 \pm 17$	$86 \pm 11$	$<0.001$
BMI, kg/m <sup>2</sup>	$32 \pm 4$	$33 \pm 4$	$30 \pm 2$	$<0.001$
Waist circumference, cm	$108 \pm 11$	$110 \pm 11$	$102 \pm 9$	$<0.001$
Hip circumference, cm	$116 \pm 12$	$117 \pm 12$	$111 \pm 10$	$<0.001$
Fat mass, kg	$36 \pm 11$	$38 \pm 11$	$30 \pm 7$	$<0.001$
Obesity, %	63	73	38	$<0.001$
Physical activity, h/wk	$3.9 \pm 2.7$	$3.6 \pm 2.6$	$4.6 \pm 2.8$	$<0.001$
Current smoking, %	14	15	9	0.07
Self-reported diabetes, %	7	7	5	0.54
In-study diagnosed diabetes, %	5	5	7	0.50
Total diabetes, %	12	12	12	1.00
In-study diagnosed HT, %	28	27	31	0.57
Total HT, %	61	63	58	0.35
Antihypertensive treatment, %	57	59	51	0.45
MetS, %	45	47	39	0.12
Triglycerides, mmol/L	$1.5 \pm 0.8$	$1.5 \pm 0.9$	$1.4 \pm 0.7$	0.07
HDL-cholesterol, mmol/L	$1.3 \pm 0.3$	$1.3 \pm 0.3$	$1.3 \pm 0.3$	0.97
Fasting blood glucose, mmol/L	$5.4 \pm 1$	$5.4 \pm 1$	$5.3 \pm 1$	0.07
Impaired fasting glucose, %	20	21	18	0.61
Impaired glucose tolerance, %	7	7	8	1.00

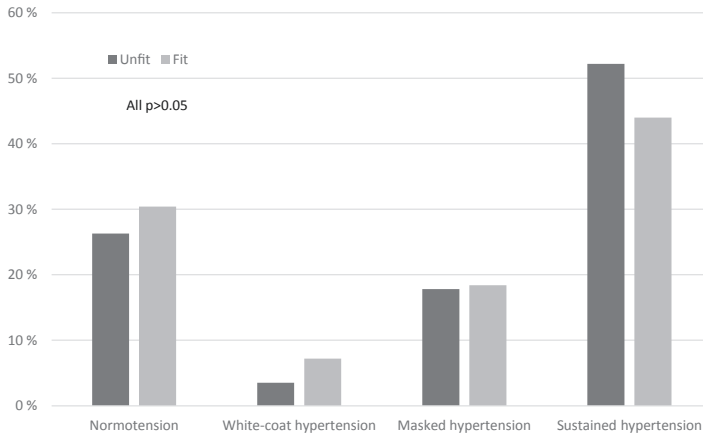
$VO_{2max}$ , peak oxygen uptake; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; MetS, metabolic syndrome; HDL, high-density lipoprotein.

The unfit group had a higher prevalence of obesity and higher fat mass and waist circumference compared to the fit group (all  $p < 0.001$ ), while the prevalence of MetS did not differ between the groups ( $p = 0.12$ ) (Table 2). Also the prevalences of individual components of MetS were similar (all  $p > 0.05$ ) (Fig. 2). Newly diagnosed diabetes in the study was found in 5% of unfit and 7% of fit subjects ( $p = 0.50$ ) (Table 2). Glucose control, evaluated by HbA<sub>1c</sub>, did not differ between fit and unfit diabetic subjects ( $6.1 \pm 1.0$  vs.  $6.1 \pm 0.8$ ,  $p = 0.097$ ).

**Table 1** Identification of fit subjects based upon sex and age specific threshold values for at least good peak O<sub>2</sub> uptake during maximal treadmill testing.

Age groups (years)	30–34	35–39	40–44	45–49	50–54	55–59	60–65
Threshold for fitness in women (ml/kg/min)		$>38.2$	$>37.2$	$>34.2$	$>33.8$	$>30.8$	$>27.8$
Threshold for fitness in men (ml/kg/min)	$>49.6$	$>51.4$	$>46.7$	$>43.3$	$>40.2$	$>39.0$	$>38.6$





**Figure 1** Prevalences of blood pressure categories in fit and unfit groups.

**Table 3** Clinic and 24-h blood pressure and indices of subclinical arterial disease in the total study population, fit and unfit groups.

Variable	All (n = 491)	Unfit (n = 355)	Fit (n = 136)	p-Value
<i>Clinic BP</i>				
Systolic BP, mmHg	130 ± 16	130 ± 16	132 ± 17	0.28
Diastolic BP, mmHg	83 ± 10	83 ± 10	83 ± 9	0.89
Pulse, beats/min	68 ± 10	68 ± 10	66 ± 10	<0.05
<i>24-h BP</i>				
24-h systolic BP, mmHg	122 ± 12	122 ± 13	120 ± 11	<0.05
24-h diastolic BP, mmHg	79 ± 8	80 ± 8	78 ± 7	0.13
24-h mean BP, mmHg	94 ± 8	94 ± 9	92 ± 8	<0.05
Elevated 24-h BP, %	68	70	62	0.14
Day-time systolic BP, mmHg	125 ± 13	126 ± 13	123 ± 12	0.06
Day-time diastolic BP, mmHg	81 ± 8	82 ± 8	81 ± 7	0.13
Day-time mean BP, mmHg	96 ± 9	97 ± 9	95 ± 8	<0.05
Night-time systolic BP, mmHg	109 ± 19	109 ± 13	108 ± 29	0.65
Night-time diastolic BP, mmHg	70 ± 9	71 ± 9	70 ± 8	0.25
Night-time mean BP, mmHg	83 ± 9	84 ± 10	82 ± 8	<0.05
<i>Subclinical arterial disease</i>				
PWV, m/s	7.5 ± 1.7	7.6 ± 1.6	7.4 ± 1.8	0.39
PWV > 10 m/s, %	7	7	7	1.00
Mean cIMT, mm	0.77 ± 0.21	0.78 ± 0.22	0.76 ± 0.17	0.30
Increased cIMT, %	19	20	15	0.23
Carotid plaque, %	21	23	19	0.40

BP, blood pressure; PWV, pulse wave velocity; cIMT, carotid intima-media thickness.

Subclinical arterial disease was rare in the population, and did not differ between fit and unfit groups (Table 3).

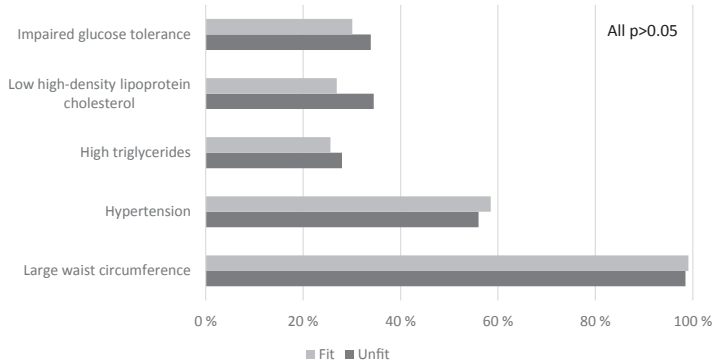
**Covariates of fitness in uni- and multivariable analyses**

In univariable logistic regression higher age, body mass index (BMI) < 30 kg/m<sup>2</sup>, lower waist and hip circumferences, lower fat mass, lower 24-h mean BP, higher self-reported physical activity and a higher muscle mass as percentage of body weight were all associated with being fit (all p < 0.001) (Table 4). In multivariable regression analysis, lower waist circumference, BMI < 30 kg/m<sup>2</sup>,

being a non-smoker and having a higher muscle mass as percentage of body weight were all identified as independent covariables of being fit (all p < 0.05) (Table 4).

**Discussion**

The current study explored if fitness was associated with a more favorable CV risk profile in overweight and obese subjects without known CV disease participating in the FATCOR study. As demonstrated, prevalences of major CV risk factors like HT, MetS and diabetes did not differ between fit and unfit subjects. Furthermore, no difference in



**Figure 2** Prevalences of individual components of metabolic syndrome in fit and unfit groups.

**Table 4** Covariables of being fit in the total study population.

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Non-obesity	4.43	2.92–6.74	<0.001	2.00	1.17–3.41	0.011
Waist circumference, cm	0.93	0.90–0.95	<0.001	0.94	0.92–0.97	<0.001
Hip circumference, cm	0.93	0.90–0.95	<0.001			
Fat mass, kg	0.91	0.88–0.93	<0.001			
BMI, kg/m <sup>2</sup>	0.72	0.66–0.79	<0.001			
Muscle mass, %	1.06	1.03–1.09	<0.001	1.05	1.01–1.08	0.004
Non-smoking	1.91	0.96–3.80	0.06	2.64	1.19–5.86	0.017
Physical activity, h/wk	1.15	1.06–1.24	<0.001			
Day-time mean BP, mmHg	0.97	0.95–1.00	0.04			
Day-time HR, beats/min	0.96	0.93–0.98	<0.001			
Night-time mean BP, mmHg	0.97	0.95–1.00	0.04			

OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; HR, heart rate.

HT subtypes or individual components of MetS was found between the fit and unfit groups, and subclinical arterial disease like increased arterial stiffness or carotid atherosclerosis was uncommon in both groups, despite the high CV risk factor burden.

Our results clearly demonstrate the benefit from thorough and comprehensive CV risk assessment in subjects with increased BMI. A total of 46% of HT and 42% of diabetes cases were diagnosed as a result of the FATCOR study program, pointing to the benefit of systematic use of 24-h BP and oral glucose tolerance test for optimization of CV risk factor identification in overweight and obese subjects. Overall, HT was found in 61% in the current FATCOR population, reflecting the known association between obesity and HT [18]. In comparison, HT was found in 30% of women and in 50% of men of similar age range in a representative subset of general Norwegian population [19]. The higher prevalence of HT in our FATCOR population may be attributed to obesity, but we also used 24-h BP to optimize the detection of HT [20]. However, the prevalences of white-coat and masked hypertension were low in our study population [14,21]. Of note, the fit group had significantly lower 24-h mean BP, despite comparable prevalence of HT and use of antihypertensive drug

treatment. The lack of influence of higher cardiorespiratory fitness on prevalent hypertension was also previously reported from the National Health and Nutrition Survey (NHANES) [7].

The total prevalence of MetS was 45% in the current study population. In comparison, MetS has been reported in 28% of women and 22% of men of similar age in general Norwegian population [22]. A cross-sectional study of healthy police employees in the Netherlands found cardiorespiratory fitness to be associated with less clustering of risk factors [23]. Furthermore, Kouki et al. found that cardiorespiratory fitness was more closely associated with prevalent MetS than diet [8]. However, in the present study, the prevalence of MetS did not differ between fit and unfit groups, despite both BMI and fat mass being significantly lower in the fit group and the independent association of fitness with lower waist circumference in multivariate analysis. In the FINRISK study [2], an association of fitness with lower BP and serum lipid levels was particularly observed in men with the highest waist–hip ratio. However, that study used estimated and not measured cardiorespiratory fitness.

The total prevalence of diabetes in the FATCOR population was 12%, 3-fold higher than in general Norwegian

population, and did not differ between fit and unfit groups [24]. A clinical study of obese subjects with type 2 diabetes found that a low level of cardiorespiratory fitness was associated with a higher risk of all-cause mortality, stroke and myocardial infarction independent of abdominal obesity [25]. Prospective studies in both women and men have found that fitness reduced, but did not fully compensate for the increased risk of diabetes in obesity [26,27]. However, in the Strong Heart Family Study, Fretts et al. found that even a moderate physical activity measured by a pedometer was associated with a 25% reduced risk for incident diabetes in obese subjects [28].

### Study limitations

Given the cross-sectional design of our study, cause–effect relations could not be explored. The majority of the participants were recruited at a general practitioner center that also offered organized weight reduction programs. Since most patients were included without delay, it is possible that the positive effects on CV risk factors exerted by fitness had not yet become evident. The fact that mean 24-h BP was lower in the fit group despite similar prevalences of HT and HT subtypes illustrates this possibility. Unfortunately the duration of the reported level of physical activity was not captured by the questionnaire applied in the FATCOR study. A small study in older obese subjects demonstrated that insulin sensitivity measured by the euglycemic hyperinsulinemic clamp improved by 21% after 16 weeks of moderate exercise training [29]. Since prevalent hypertension increases with age, the age difference between the groups may have contributed to the lack of difference in prevalent hypertension between the groups.

The influence of obesity and MetS on cardiac structure and function is well known, and presence of diastolic dysfunction as well as left ventricular hypertrophy could have influenced  $\text{VO}_{2\text{max}}$  [30]. However, these factors were not assessed in the present study.

### Conclusions

Cardiorespiratory fitness was not associated with a lower burden of major CV risk factors like HT, MetS and diabetes in the overweight and obese FATCOR population. Given the known association of CV risk factor burden with risk for clinical CV disease, these findings challenge the notion that cardiorespiratory fitness alone reduces risk for CV disease in obesity. The benefits from including 24-h ambulatory BP recording and oral glucose tolerance test in a thorough and comprehensive CV risk assessment in subjects with increased BMI were clearly demonstrated.

### Role of the funding source

The FATCOR study was funded by a grant from the Western Norwegian Regional Health Authorities. The funding source did not have any role in study design, in the collection, design and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

### Declaration of interests

The authors have no conflict of interest.

### Acknowledgments

The authors thank the Simon Fougner Hartmanns Family Fund, Oslo, Norway, for donating the SphygmoCor device. We thank Hilde Jacobsen (staff engineer), Marina V. Kokorina (MD), Synnøve Ygre Hauge (RN) and Liv Himle (RN) for technical assistance with data collection, registration, and participant management.

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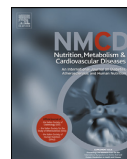
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II





## Sex differences in subclinical cardiac disease in overweight and obesity (the FATCOR study)

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Received 20 March 2018; received in revised form 28 May 2018; accepted 13 June 2018

Handling Editor: F. Galletti

Available online 21 June 2018

### KEYWORDS

Left atrial dilatation;  
Left ventricular hypertrophy;  
Left ventricular geometry;  
Obesity;  
Sex

**Abstract** *Background and aims:* Subclinical cardiac disease, like abnormal left ventricular (LV) geometry or left atrial (LA) dilatation, is common in obesity. Less is known about sex differences in the prevalence and type of subclinical cardiac disease in obesity.

*Methods and results:* Clinical and echocardiographic data from 581 women and men without established cardiovascular disease and body mass index (BMI) > 27.0 kg/m<sup>2</sup> participating in the FAT associated Cardiovascular dysfunction (FATCOR) study was analyzed. LA dilatation was recognized as LA volume indexed for height<sup>2</sup> ≥ 16.5 ml/m<sup>2</sup> in women and ≥ 18.5 ml/m<sup>2</sup> in men, and abnormal LV geometry as LV hypertrophy and/or increased relative wall thickness. On average, the participants were 48 years old, 60% women and mean BMI was 32.1 kg/m<sup>2</sup>. Overall, the prevalence of subclinical cardiac disease was higher in women than men (77% vs. 62%, *p* < 0.001). Women had a higher prevalence of LA dilatation than men (74% vs. 56%, *p* < 0.001), while men had a higher prevalence of abnormal LV geometry (30% vs. 21%, *p* = 0.011). After adjusting for confounders in multivariable logistic regression analysis, female sex was associated with a 2-fold higher risk of subclinical cardiac disease, in particular LA dilatation (confidence interval [CI] 1.67–3.49, *p* < 0.001), while male sex was associated with a 2-fold higher risk of abnormal LV geometry (CI 1.30–3.01, *p* = 0.001).

*Conclusion:* The majority of overweight and obese participants in the FATCOR study had subclinical cardiac disease, which may contribute to the impaired prognosis observed in obesity. Women had a higher prevalence of subclinical cardiac disease than men.

*Clinical trial registration:* URL: <http://www.clinicaltrials.gov> NCT02805478.

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### Introduction

Presence of subclinical cardiac disease like left atrial (LA) dilatation, left ventricular hypertrophy (LVH) and abnormal left ventricular (LV) geometry, is associated with

increased cardiovascular morbidity and mortality in hypertension as well as in the general population [1–3]. Previous publications in hypertension have found subclinical cardiac disease to be more prevalent among women than men, in particular LVH and LA dilatation

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[14,5]. Results from the Campania Salute Network registry demonstrated that in treated hypertensive patients, female sex and obesity was particularly associated with lack of LVH regression independent of blood pressure control [6].

It is well demonstrated that also obesity is associated with increased risk for subclinical cardiac disease [7–10]. In the Strong Heart Study, LVH was particularly prevalent in obese women with low fat-free mass [9]. In a German cohort, Stritzke et al. identified obesity as the main factor associated with age-associated LA dilatation [10], especially in obese women with concomitant hypertension [10]. Furthermore, in older patients with hypertension and LVH, the association of higher pulse pressure, a crude measure of arterial stiffness, with LA dilatation was pointed out [5].

The current study aimed to further explore sex differences in the prevalence and type of subclinical cardiac disease in overweight and obese subjects without known cardiovascular disease.

## Methods

### Study population

The present study is based on the FAT associated Cardiovascular dysfunction (FATCOR) study, which was performed at Haukeland University Hospital, Bergen, Norway, 2009–2017. The study inclusion and exclusion criteria have previously been described [11,12]. In short, the participants were 30–65 years old and had a body mass index (BMI) > 27.0 kg/m<sup>2</sup>. Exclusion criteria were previous myocardial infarction, gastrointestinal disorder, severe psychiatric illness or inability to understand Norwegian language. A collaborating general practice center, with a particular interest in the management of obesity, recruited the participants. In total 620 participants were recruited. Readable echocardiograms were obtained in 581 (94%) of the participants, and these were included in the present analysis. The FATCOR study was approved by the Regional Ethics Committee and adhered to the Declaration of Helsinki. All participants signed written informed consent forms.

### Cardiovascular risk assessment

A standardized questionnaire was used for self-reporting of the participants' general health, including use of any medication. Clinic blood pressure was measured in accordance with current guidelines using an Omron M4 sphygmomanometer (Omron Healthcare Co. Ltd., Hoofddorp, Netherlands) and a cuff of appropriate size for the individual arm circumference [13]. Pulse pressure was calculated from clinic blood pressure as the difference between systolic and diastolic blood pressure. For the 24-h ambulatory blood pressure recordings, a Diasys Integra II apparatus (Novacor, Cedex, France) was used. Blood pressure was recorded every 20 min during daytime and every 30 min during nighttime, using a correctly sized cuff on the non-dominant arm. The participants were

advised to avoid hard exercise and to relax their arm during cuff inflation, but otherwise engage in normal activities [13]. The 24-h blood pressure recording was repeated if <70% of the measurements were valid. Hypertension was considered present if participants used any antihypertensive medication, or if 24-h ambulatory blood pressure was elevated (average systolic 24-h blood pressure ≥130 mmHg and/or average diastolic 24-h blood pressure ≥80 mmHg) [11]. Dipping status was determined from the difference in mean systolic blood pressure between day- and nighttime. Reverse dipping was defined as an increase in mean systolic blood pressure from day-to nighttime and non-dipping as a <10% decrease in mean systolic blood pressure from day-to nighttime.

A 2-h oral glucose tolerance test was performed in all participants without known diabetes mellitus. Diabetes mellitus was diagnosed if presence of history of diabetes mellitus, or a positive 2-h oral glucose tolerance, elevated fasting blood glucose or glycated hemoglobin A<sub>1c</sub> was found, in accordance with the criteria from the American Diabetes Association [14].

Body composition analysis was performed by tetrapolar bioelectrical impedance analysis (Tanita-TBF-300A, Tanita Corporation of America, Arlington Heights, USA). Obesity and overweight in the participants was identified by applying the World Health Organization criteria. Metabolic syndrome was diagnosed by the American Heart Association/National Heart, Lung and Blood Institute definition [15]. The Chronic Kidney Disease Epidemiology Collaboration equation was used for calculating estimated glomerular filtration rate.

### Echocardiography

Echocardiography was performed following a standardized imaging protocol using a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). All images were analyzed in the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway on workstations equipped with Image Arena software version 4.1 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) [16]. Images were first read by junior investigators, and then all proofread by a single expert reader (EG), as recommended for clinical trials [17].

Quantitative echocardiography was performed in accordance with the current guidelines [18]. LA dilatation was defined as LA systolic volume indexed for height<sup>2</sup> ≥16.5 ml/m<sup>2</sup> in women and ≥18.5 ml/m<sup>2</sup> in men, reflecting the upper 95th percentile of LA volume index in healthy European populations [19]. LVH was considered present if LV mass indexed for height<sup>2.7</sup> exceeded the prognostically validated cut-off values of >46.7 g/m<sup>2.7</sup> in women and >49.2 g/m<sup>2.7</sup> in men [20]. Concentric LV geometry was considered present if relative wall thickness ≥0.43 [18]. LV geometry was defined from relative wall thickness and LV mass index in combination [18]. Abnormal LV geometry was considered present if LVH and/or concentric LV geometry was detected. Subclinical

cardiac disease was defined as any presence of LA dilatation and/or abnormal LV geometry.

### Statistics

The IBM SPSS Statistics software version 23 (IBM, Armonk, New York, USA) was used for data management and statistical analysis. To explore sex-differences, data are reported by sex. Data are presented as mean  $\pm$  standard deviation for the continuous variables and as percentages for categorical variables. Group comparison was performed with Student's T-test for continuous variables and Chi-square test for categorical variables. Uni- and multivariable logistic regression analyses were used to identify the covariables of LA dilatation, concentric LV geometry, abnormal LV geometry and subclinical cardiac disease in the FATCOR population, and reported as odds ratio (OR) with 95% confidence intervals (CI). A p-value  $<0.05$  was considered statistical significance in all analyses.

### Results

#### Clinical characteristics

On average, the participants were  $48 \pm 9$  years old, 60% were women and 63% were obese (Table 1). Women had higher fat mass ( $p < 0.001$ ) and higher BMI ( $p = 0.013$ ) than men

(Table 1). Men had higher average clinic and 24-h blood pressure values (all  $p < 0.001$ ), and a higher prevalence of hypertension ( $p < 0.001$ ). The prevalences of obesity, diabetes mellitus and metabolic syndrome were comparable between women and men (all  $p > 0.20$ ) (Table 1).

#### LA dilatation

LA dilatation was the most common type of subclinical cardiac disease, overall present in 67% of the participants (Table 2). Women had a higher prevalence of LA dilatation than men (74% vs. 56%,  $p < 0.001$ ) (Table 2). In women, LA dilatation was particularly associated with higher pulse pressure (OR 1.03 [95% CI 1.01–1.05],  $p = 0.012$ ), while no significant associations with age, BMI, fat mass, systolic blood pressure, waist circumference or serum triglycerides were found (all  $p > 0.11$ ). In men, LA dilatation was associated with higher fat-free mass (OR 1.04 [95% CI 1.00–1.07],  $p = 0.041$ ) and lower serum triglycerides (OR 0.75 [95% CI 0.57–1.00],  $p = 0.046$ ), but no significant association were found with age, BMI, fat mass, waist circumference, systolic blood pressure or pulse pressure (all  $p > 0.06$ ). In univariable logistic regression analyses in the total study population, presence of LA dilatation was associated with female sex (OR 2.20 [95% CI 1.54–3.30],  $p < 0.001$ ), but not with higher pulse pressure, BMI or age, and not with presence of diabetes mellitus or use of antihypertensive treatment (all  $p > 0.11$ ). In multivariable

**Table 1** Clinical characteristics of overweight and obese women and men.

Variable	All (n = 581)	Women (n = 351)	Men (n = 230)	p-value
Women (%)	60			
Age (years)	48 $\pm$ 9	48 $\pm$ 9	47 $\pm$ 9	0.398
Body weight (kg)	96 $\pm$ 16	91 $\pm$ 15	103 $\pm$ 14	<0.001
Height (cm)	172 $\pm$ 9	167 $\pm$ 6	180 $\pm$ 7	<0.001
Body mass index (kg/m <sup>2</sup> )	32.1 $\pm$ 4.1	32.4 $\pm$ 4.5	31.5 $\pm$ 3.6	0.013
Waist circumference (cm)	108 $\pm$ 11	106 $\pm$ 12	110 $\pm$ 10	<0.001
Hip circumference (cm)	116 $\pm$ 111	118 $\pm$ 12	112 $\pm$ 9	<0.001
Fat mass (kg)	36 $\pm$ 11	40 $\pm$ 10	31 $\pm$ 9	<0.001
Obesity (%)	63	64	62	0.517
Current smoking (%)	13	12	14	0.417
Diabetes mellitus (%)	9	11	7	0.199
Clinic SBP (mmHg)	130 $\pm$ 16	127 $\pm$ 17	134 $\pm$ 14	<0.001
Clinic DBP (mmHg)	82 $\pm$ 9	80 $\pm$ 9	85 $\pm$ 10	<0.001
Clinic pulse pressure (mmHg)	48 $\pm$ 11	46 $\pm$ 12	49 $\pm$ 10	0.001
24-h SBP (mmHg)	121 $\pm$ 12	119 $\pm$ 12	124 $\pm$ 11	<0.001
24-h DBP (mmHg)	79 $\pm$ 8	78 $\pm$ 8	82 $\pm$ 7	<0.001
Hypertension (%)	60	53	72	<0.001
Treated hypertensive participants (%)	34	38	30	0.150
SBP daytime (mmHg)	126 $\pm$ 13	123 $\pm$ 13	129 $\pm$ 12	<0.001
SBP nighttime (mmHg)	109 $\pm$ 13	107 $\pm$ 13	111 $\pm$ 13	0.00
Non-dipping (%)	27	27	26	0.832
Reverse dipping (%)	2	3	2	0.866
Fasting blood glucose (mmol/L)	5.3 $\pm$ 0.9	5.2 $\pm$ 0.8	5.5 $\pm$ 1.0	<0.001
HbA <sub>1c</sub> (%)	5.6 $\pm$ 0.5	5.6 $\pm$ 0.5	5.6 $\pm$ 0.6	0.642
Total cholesterol (mmol/L)	5.4 $\pm$ 1.1	5.5 $\pm$ 1.1	5.3 $\pm$ 1.1	0.052
HDL-cholesterol (mmol/L)	1.3 $\pm$ 0.3	1.4 $\pm$ 0.3	1.1 $\pm$ 0.3	<0.001
Triglycerides (mmol/L)	1.5 $\pm$ 1.1	1.4 $\pm$ 1.1	1.7 $\pm$ 1.0	0.004
Creatinine ( $\mu$ mol/l)	73 $\pm$ 13	66 $\pm$ 10	81 $\pm$ 11	<0.001
eGFR (ml/min/1.73 m <sup>2</sup> )	96 $\pm$ 13	95 $\pm$ 14	97 $\pm$ 12	0.105
Metabolic syndrome (%)	48	47	50	0.483

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate.

**Table 2** Echocardiographic characteristics of overweight and obese women and men.

Variable	All (n = 581)	Women (n = 351)	Men (n = 230)	p-value
IVS thickness end-diastole (cm)	1.1 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	<0.001
LV diameter end-diastole (cm)	5.0 ± 0.5	4.8 ± 0.4	5.2 ± 0.5	<0.001
PW thickness end-diastole (cm)	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.2	<0.001
LA volume index (ml/m <sup>2</sup> )	19.9 ± 5.8	20.0 ± 5.6	19.7 ± 6.0	0.520
LA dilatation (%)	67	74	56	<0.001
LV mass index (g/m <sup>2.7</sup> )	39.3 ± 9.0	37.6 ± 7.9	41.8 ± 9.9	<0.001
LV hypertrophy (%)	16	13	20	0.021
Relative wall thickness (ratio)	0.34 ± 0.08	0.33 ± 0.07	0.35 ± 0.08	<0.001
Concentric LV geometry (%)	14	11	18	0.021
Abnormal LV geometry (%)	25	21	30	0.011
Any subclinical cardiac disease (%)	71	77	62	<0.001
Mitral regurgitation (%)	41	40	42	0.604
Grade 1 (%)	38	36	40	0.371
Grade 2 (%)	3	4	2	0.305

IVS, interventricular septum; LV, left ventricular; PW, posterior wall; LA, left atrial; LV, left ventricular.

logistic regression analysis in the total study population, female sex was associated with a 2-fold higher risk of LA dilatation independent of a significant association with higher pulse pressure (Table 3). Adding 24 h mean BP to the model did not change the results.

### Concentric LV geometry

When concentric remodeling and concentric LVH was considered together as concentric LV geometry, the prevalence of LA dilatation did not differ between groups of participants with and without concentric LV geometry (69% vs. 67%,  $p = 0.725$ ). In univariable logistic regression analyses, concentric LV geometry was more prevalent in men (OR 1.74 [95% CI 1.08–2.79],  $p = 0.022$ ) and associated with presence of antihypertensive treatment (OR 2.49 [95% CI 1.48–4.19],  $p = 0.001$ ), higher pulse pressure (OR 1.04 [95% CI 1.01–1.06]) and higher age (OR 1.05 [95% CI 1.02–1.08], both  $p < 0.001$ ). When these covariables were included in a multivariable model, prevalent concentric LV geometry was significantly associated only with higher age (Table 3). Adding 24 h mean BP to the model did not change the results.

In men, concentric LV geometry was associated with use of antihypertensive treatment (OR 3.52 [95% CI 1.66–7.46],  $p = 0.001$ ), but not with prevalent hypertension (OR 1.8 [95% CI 0.74–4.37],  $p = 0.194$ ). In women, concentric LV geometry was associated with presence of hypertension (OR 2.91 [95% CI 1.32–6.43],  $p = 0.008$ ), but not with use of antihypertensive treatment (OR 1.75 [95% CI 0.82–3.72],  $p = 0.146$ ).

### Abnormal LV geometry

Abnormal LV geometry was present in 25% of the study participants and more common in men than in women (30% vs. 21%,  $p = 0.011$ ) (Table 2 and Fig. 1). Men had a higher prevalence of LVH and higher prevalence of concentric LV geometry than women (both  $p = 0.021$ ) (Table 2). Men had more concentric LVH ( $p = 0.016$ ) than women, but the prevalence of concentric LV remodeling ( $p = 0.360$ ) and eccentric LVH ( $p = 0.325$ ) did not differ by sex (Fig. 1). In univariable logistic regression analyses, male sex (OR 1.64 [95% CI 1.12–2.41],  $p = 0.011$ ), higher pulse pressure (OR 1.04 [95% CI 1.02–1.06],  $p < 0.001$ ), higher BMI (OR 1.09 [95% CI 1.01–1.14],  $p < 0.001$ ), higher age (OR 1.05 [95% CI 1.02–1.07],  $p < 0.001$ ) and use of antihypertensive treatment (OR 1.83 [95% CI 1.16–2.86],  $p = 0.009$ ) were all associated with having abnormal LV geometry, while no significant association was found with diabetes mellitus ( $p = 0.12$ ). In multivariable logistic regression analysis, based on the univariable analyses, male sex was associated with a 2-fold higher risk of abnormal LV geometry, independent of significant associations with higher pulse pressure, BMI and age (Table 3). Adding 24 h mean BP to the model did not change the results.

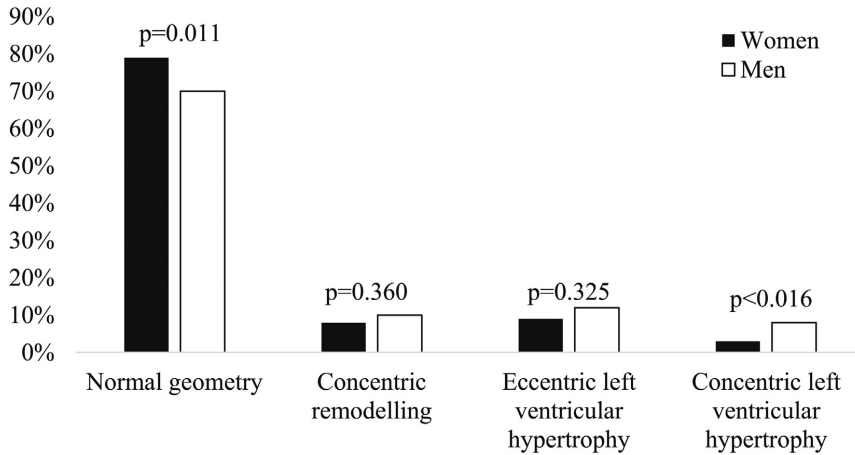
### Any subclinical cardiac disease

When presence of LA dilatation or abnormal LV geometry was considered together, subclinical cardiac disease was found in the majority of the participants (71%). The overall

**Table 3** Associations of LA dilatation, concentric LV geometry, abnormal LV geometry and any subclinical cardiac disease in the total study population in multivariable logistic regression analyses.

Covariables	LA dilatation	Concentric LV geometry	Abnormal LV geometry	Any subclinical cardiac disease
Female sex	2.42 (1.67–3.49) <sup>†</sup>	0.62 (0.38–1.03)	0.55 (0.36–0.84) <sup>*</sup>	2.19 (1.48–3.22) <sup>†</sup>
PP (mmHg)	1.02 (1.00–1.04) <sup>*</sup>	1.02 (1.00–1.04)	1.02 (1.00–1.04) <sup>*</sup>	1.03 (1.01–1.05) <sup>†</sup>
BMI (kg/m <sup>2</sup> )	NA	NA	1.12 (1.06–1.17) <sup>†</sup>	1.06 (1.01–1.12) <sup>*</sup>
Age (years)	NA	1.04 (1.00–1.07) <sup>*</sup>	1.04 (1.02–1.07) <sup>*</sup>	NA
Antihypertensive treatment	NA	1.68 (0.94–2.98)	1.03 (0.61–1.73)	NA

LA, left atrial; LV, left ventricular; PP, pulse pressure; BMI, body mass index; NA, not applicable. \* $P < 0.05$ , <sup>†</sup> $P \leq 0.001$ .



**Figure 1** Left ventricular geometry in overweight and obese women and men.

prevalence of subclinical cardiac disease was higher in women than in men (77% vs. 62%,  $p < 0.001$ ) (Table 2). In univariable logistic regression analyses, female sex (OR 2.03 [95% CI 1.41–2.93],  $p < 0.001$ ), higher pulse pressure (OR 1.03 [95% CI 1.01–1.04],  $p = 0.006$ ) and higher BMI (OR 1.06 [95% CI 1.01–1.11],  $p = 0.017$ ) were all significantly associated with having any subclinical cardiac disease, while no associations were found with age, diabetes mellitus or antihypertensive treatment (all  $p > 0.11$ ). Multivariable logistic regression analysis identified that female sex was associated with a 2-fold higher risk of having any subclinical cardiac disease, independent of significant associations with higher pulse pressure and BMI (Table 3). Adding 24 h mean BP to the model did not change the results. When excluding the participants with diabetes mellitus in a secondary analysis, female sex remained associated with 2-fold higher risk of any subclinical cardiac disease, independent of significant association with higher pulse pressure, while the previous association with higher BMI became insignificant (data not shown).

In sex-specific analyses, systolic blood pressure, pulse pressure and HbA<sub>1c</sub> were identified as covariables of prevalent subclinical cardiac disease in univariable logistic

regression analyses in women, while only pulse pressure retained the independent association in multivariable analysis. The results did not change when hypertension was forced into the model (Table 4). In men, average 24-h pulse pressure and fat-free mass were independent covariables of subclinical cardiac disease both in univariable and multivariable analyses, and the results did not change when antihypertensive treatment was forced into the model (Table 4).

## Discussion

### Sex, obesity and LA dilatation

Previous studies in hypertension have identified higher BMI as an important, blood pressure independent covariable of LA dilatation [15]. Furthermore, a higher prevalence of LA dilatation in women than men has been reported in elderly hypertensive patients with LVH [21]. In a population based German cohort, Stritzke et al. found that obesity was the most important factor associated with increasing LA size with aging. In that population, LA

**Table 4** Associations of subclinical cardiac disease in sex-specific uni- and multivariable logistic regression analyses.

Covariables	Women		Men	
	Univariable	Multivariable	Univariable	Multivariable
Pulse pressure (mmHg)	1.04 (1.02–1.07)*	1.06 (1.00–1.16)*	1.02 (0.99–1.05)	NA
24 h pulse pressure (mmHg)	1.03 (0.99–1.06)	NA	1.04 (1.01–1.08)*	1.04 (1.00–1.07)*
Clinic systolic blood pressure (mmHg)	1.02 (1.01–1.04)*	0.99 (0.95–1.03)	1.02 (1.00–1.04)	NA
Hypertension	1.16 (0.68–1.96)	0.86 (0.45–1.64)	1.49 (0.81–2.71)	NA
Antihypertensive treatment	1.51 (0.74–3.06)	NA	1.09 (0.56–2.10)	1.04 (0.51–2.12)
HbA <sub>1c</sub> (%)	2.08 (1.11–3.88)*	1.71 (0.87–3.39)	1.04 (0.65–1.67)	NA
Diabetes mellitus	1.60 (0.64–3.98)	NA	1.40 (0.47–4.17)	NA
Fat-free mass (kg)	1.00 (0.96–1.04)	NA	1.04 (1.01–1.08)*	1.04 (1.00–1.08)*
Age (years)	1.02 (0.99–1.05)	NA	1.01 (0.98–1.04)	NA

\* $P < 0.05$ .

dilation was equally prevalent among normotensive obese women and men, but twice as prevalent in women when hypertension was co-present [10]. The current study expands these observations by demonstrating that subclinical cardiac disease is highly prevalent also in middle-aged overweight and obese subjects without known cardiovascular disease, found in 71%. Furthermore, LA dilatation was the most prevalent type of subclinical cardiac disease, and particularly common in women.

It is well demonstrated that presence of LA dilatation carries a higher risk for incident clinical cardiovascular events including atrial fibrillation [1,5]. As proof of concept, Proietti et al. noted that LA dilatation was particularly common in elderly women with atrial fibrillation, and also associated with higher cardiovascular mortality in these women [22]. Taken together, these findings suggest that women are at particular risk of developing LA dilatation and associated cardiovascular events when obesity and hypertension are co-present.

### **Sex, obesity and LV geometry**

In a previous study, de Simone et al. found that in hypertension, obese women had a 3-fold higher prevalence of LVH compared to normal weight women, while obese men had a 2-fold increased prevalence LVH compared to their normal weight counterparts [23]. The Strong Heart Study also reported that obesity had a greater adverse effect on LV geometry in women than in men, even after adjustment for important factors like age, systolic blood pressure and hypertension [9]. Furthermore, obesity-related factors like waist-to-hip ratio and adipose mass were particularly associated with higher LV mass in women in the Strong Heart study [9]. In contrast, the present study found abnormal LV geometry, including concentric LV geometry and LV hypertrophy, to be more prevalent in men, and no association between abnormal LV geometry and obesity related measures was demonstrated in either sex. A possible explanation for the diverging findings may be that a disproportionately high prevalence of women had combined obesity and hypertension and associated LV hypertrophy in the study by de Simone et al. [26], while, in the present study population, women and men were equally obese, but combined hypertension and obesity was more prevalent in men. The impact of combined obesity and hypertension on LVH has been well demonstrated by Mancusi et al. who found the prevalence of LVH to increase exponentially with increasing BMI, being seven times more prevalent in obese compared to normal weight subjects with hypertension in the Campania Salute Network registry [24].

Increased pulse pressure, reflecting increased arterial stiffness, has been associated with higher risk of cardiovascular events in several studies [25,26]. The present results add to this by demonstrating that higher pulse pressure was consistently associated with presence of subclinical cardiac disease in the present study, whether assessed by LA dilatation or abnormal LV geometry. Higher pulse pressure is a marker of hypertensive target organ

damage, and particularly prevalent in women and in older age [5,27]. Mancusi et al. found that high pulse pressure >60 mmHg, was more prevalent in women and in patients with diabetes mellitus, and a predictor of cardiovascular events independent of presence of hypertension associated target organ damage like carotid plaque and LVH [27]. Compared to the present study population, the participants in these previous studies were older and had higher prevalences of diabetes mellitus [25–27]. Thus, the present findings add to previous knowledge by demonstrating the important and independent association of higher pulse pressure with prevalent subclinical cardiac disease, also in overweight and obese middle-aged subjects free from clinical cardiovascular disease with a low prevalence of diabetes mellitus. Furthermore, our results show that partly different risk factors for presence of subclinical cardiac disease were identified in obese women and men. This underscores the importance of using a sex-specific approach when evaluating the cardiovascular risk factor profile [28].

### **Study limitations**

The FATCOR study was cross-sectional in design, thus cause-effect relationships could not be established. The FATCOR population was free of known cardiovascular disease, and generalization of the results to less selective obese cohorts should be done with caution. As the FATCOR participants were included by general practitioners with a particular focus on overweight and obesity, it is possible that the participants focused more on improving their health and lifestyle than an unselected population, and that this influenced our findings. Body composition was measured with foot-to-foot bioelectrical impedance. This method can underestimate fat-free mass in obese subjects, and the measurement of body fat may be influenced by sex and age [29,30]. We cannot exclude that this may have influenced findings in the present study population. However, women and men had comparable age.

### **Conclusions**

In the FATCOR population, including overweight and obese subjects without known cardiovascular disease, the majority of participants had prevalent subclinical cardiac disease, which may contribute to explain the impaired prognosis observed in obesity. Women had a higher prevalence of subclinical cardiac disease than men. LA dilatation was particularly common among women, while abnormal LV geometry was more prevalent among men.

### **Role of the funding source**

The FATCOR study was funded by a grant from the Western Norwegian Regional Health Authorities. The funding source did not have any role in study design, in the collection, design and interpretation of data, in the writing

of the report, or in the decision to submit the paper for publication.

### Declarations of interests

The authors have no conflict of interest.

### Acknowledgements

We thank Hilde Jacobsen (staff engineer), Marina V. Kokorina (MD), Synnøve Ygre Hauge (RN) and Liv Himle (RN) for technical assistance with data collection, registration, and participant management.

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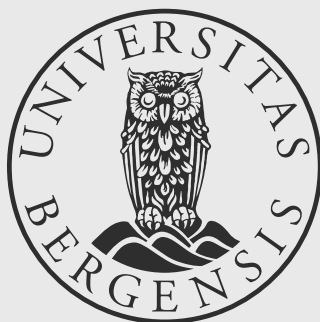








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ISBN: 9788230856536 (print)  
9788230857236 (PDF)