Parent-offspring associations in metabolic syndrome and the influence of physical activity: family linkage data within the HUNT Study, Norway

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Abstract

Background: Cardiovascular disease is the leading cause of death worldwide. There are several factors that can increase a person's risk of developing CVD, and many of these may occur simultaneously. A clustering of risk factors for CVD can be defined as metabolic syndrome. Previous studies have shown an intergenerational association for single risk factors for CVD between parents and offspring, but few studies have examined intergenerational association of metabolic syndrome. Moreover, there is evidence that physical activity can decreased the risk of metabolic syndrome, but whether physical activity can modify an intergenerational association in metabolic syndrome is not known. Therefore, the aim of the current study is to prospectively examine the association between parental metabolic syndrome and the risk of metabolic syndrome in their adult offspring. We will also examine the independent effect of offspring physical activity, on risk of metabolic syndrome, as well as the possible modifying role physical activity may have on any intergenerational associations in metabolic syndrome.

Methods: We used data on 7064 father-offspring and 9874 mother-offspring pairs from the two latest survey from the HUNT Study in Norway (HUNT2 1995-97 and HUNT3 2006-08) linked with the Family registry at Statistics Norway. Logistic regression was used to calculate odds ratio (OR) as an estimate of relative risk for metabolic syndrome in offspring, according to metabolic syndrome in their parents, as well as independent and possible modifying effects of offspring physical activity level. All associations were adjusted for offspring age, gender, smoking status and education level.

Results: During the follow-up period, 2684 offspring developed metabolic syndrome. There was a positive association between parental metabolic syndrome and offspring risk of metabolic syndrome (adjusted OR=1.71 (95% CI: 1.51-1.93), if the mother had metabolic syndrome, and adjusted OR=1.50 (95% CI: 1.30-1.72), if father had metabolic syndrome). Offspring physical activity was inversely associated with risk of metabolic syndrome (adjusted OR=0.92 (95% CI: 0.81-1.03), for low level of physical activity, and adjusted OR=0.56 (95% CI: 0.47-0.67) for high level of physical activity). However, stratified analyses and tests for interaction showed no modifying effect of physical activity on the intergenerational association of metabolic syndrome.

Conclusion: This study shows that there is an intergenerational association in metabolic syndrome between parents and their adult offspring. Physical activity can reduce the risk of metabolic syndrome, but do not modify the intergenerational association in risk of metabolic syndrome.

Samandrag

Bakgrunn: Hjarte-karsjukdom er den leiande dødsårsaka på verdsbasis. Det finst fleire risikofaktorar som kan auke eit individs sannsyn for å utvikle hjarte-karsjukdom, og fleire av desse kan opptre samstundes. Ei samling av risikofaktorar for hjarte-karsjukdom kan bli definert som metabolsk syndrom. Tidlegare studiar har vist ein generasjonssamanheng for enkelt risikofaktorar for hjarte-karsjukdom mellom foreldre og avkom, men få studiar har studert generasjonssamanhengar for metabolsk syndrom. Vidare finst det bevis for at fysisk aktivitet kan redusere risikoen for metabolsk syndrom, men om fysisk aktivitet kan modifisere en generasjonssamanheng for metabolsk syndrom er derimot ukjent. Målet med dette studiet er derfor å prospektivt studere samanhengen mellom metabolsk syndrom i foreldre og risikoen for metabolsk syndrom i deira vaksne avkom. Vi vil også studere den uavhengige effekten av fysisk aktivitet hjå avkomma, på risikoen for metabolsk syndrom, så vel som den moglege modifiserande rollen fysisk aktivitet kan ha på visse generasjonssamanhengar for metabolsk syndrom.

Metode: Vi brukte data på 7064 fedre-born og 9874 mødre-born par frå dei to siste HUNT undersøkingane i Noreg (HUNT2 1995-97 og HUNT3 2006-08) som vart kopla saman ved hjelp av Familieregisteret hjå Statistisk sentralbyrå. Logistisk regresjon vart brukt for å kalkulere odds ratio (OR) som eit estimat for relativ risiko for metabolsk syndrom i avkom, som følgje av metabolsk syndrom hos deira foreldre, så vel som den uavhengige og moglege modifiserande effekten av fysisk aktivitets nivå hjå avkom. Alle samanhengar vart justert for avkom sin alder, kjønn, røykestatus og nivå av utdanning.

Resultat: I løpet av oppfølgingstida, utvikla 2684 avkom metabolsk syndrom. Det var ein positiv samanheng mellom metabolsk syndrom i foreldre, og metabolsk syndrom i avkom (justert OR=1.71 (95 % KI: 1.51-1.93), dersom mora hadde metabolsk syndrom, og justert OR=1.50 (95 % KI: 1.30-1.72) dersom far hadde metabolsk syndrom). Fysisk aktivitet hjå avkom var assosiert med motsatt risiko for metabolsk syndrom (juster OR=0.92 (95 % KI: 0.81-1.03), for lågt nivå av fysisk aktivitet, og justert OR=0.56 (95 % KI: 0.47-0.67) for høgt nivå av fysisk aktivitet). Dei stratifiserte analysane og testane for interaksjon viste derimot inga modifiserande effekt av fysisk aktivitet på generasjonssamanhengen for metabolsk syndrom.

Konklusjon: Funna frå dette studiet visar at det føreligg ein generasjonssamanheng for metabolsk syndrom mellom foreldre og avkom. Fysisk aktivitet kan redusere risikoen for metabolsk syndrom, men kan ikkje modifisere generasjonssamanhengen i risikoen for metabolsk syndrom.

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Contents

Introduction

Cardiovascular disease (CVD) is a public health concern worldwide, and according to the World Health Organization (1), 17,5 million deaths each year are caused by CVD, which is more than for any other disease. The Global Burden of Disease (GBD) 2015 Study states that the world as a whole has been undergoing an epidemiological transition, with a shift from a high burden of communicable diseases, to a high burden of non-communicable diseases. This is explained by demographic transitions towards a more developed world, as a whole. Since 1990 this has resulted in an increased ranking of ischemic heart disease (IHD) and CVD, in relation to Years of Life Lost and Disability Adjusted Life Years, and these two diseases have remained the most common causes of death since 1990 to 2015 (2).

CVD is also a common cause for morbidity and mortality in Norway, accounting for 1 in 3 deaths. Even though mortality rates have been decreasing for the last thirty years, it is still the disease group causing the highest number deaths (3). Even if the prognosis is better now than before, CVD is still a big burden for the society (4). In 2014 almost 670 000 persons in Norway had a heart related consultation at their general practitioner, and more than 605 000 had a consultation for hypertension (5). People now live longer and the population of elderly is expected to increase in the future, therefore, the need for treatment will only increase, if nothing is done (6). For this reason, research on how to prevent cardiovascular disease and its risk factors is an important investment in the future.

There are several factors that can increase a person's risk of developing CVD. Most of these stem from lifestyle habits, some are genetic, whilst others might be a combination of the two, influenced by environmental factors (7-10). The most important risk factors for CVD are diabetes, high blood pressure, unfavourable levels of cholesterol, overweight/obesity, family members with cardiovascular disease, lack of physical activity, smoking, alcohol and poor diet (7-10). Several of these risk factors may occur simultaneously, and a clustering of risk factors such as overweight/obesity, high blood pressure, unfavourable levels of cholesterol or triglycerides and impaired glucose tolerance has been labelled the metabolic syndrome (MetS). It is likely that a clustering of these factors have a more detrimental effect on CVD risk than high levels of single factors. Furthermore, the metabolic syndrome has also been associated with other health problems, such as diabetes and stroke (11).

There are several definitions of the metabolic syndrome, and this could influence reported prevalence measures. However, it is estimated that around 20-25% of adults worldwide have metabolic syndrome, and that the prevalence is increasing throughout the world (12). The most important explanation for this is lack of physical activity combined with dietary factors (13). Individuals with the metabolic syndrome are three times as likely to have a heart attack or stroke, and twice as likely to die from it, compared to individuals who do not have metabolic syndrome. They also have a fivefold greater risk of developing type 2 diabetes. For these reasons, the CVD factors clustering together to define metabolic syndrome is now considered to be the driving force for a new CVD epidemic (12).

Few studies have been done on parent-offspring association of metabolic syndrome (14-16), and only one previous study have examined this relationship between parents and their adult offspring (17). The strength and patterns of metabolic syndrome within families could vary according to offspring's age. Younger individuals could be influenced by living in the same household as their parents, and it is important to investigate if the same associations are still present in adult offspring, who is not sharing the same environment. Moreover, unfavourable levels of the risk factors constituting the metabolic syndrome do not usually become manifested until adulthood. Thus, examining parent-offspring associations in children could underestimate the strength of these associations. Recent studies have also shown that there is a heritable component of metabolic syndrome (18-20). Only one of the included studies was a population-based study (20), where the strongest heritable effect was found between twins, both monozygotic and dizygotic, and smaller effects between parents and offspring.

More studies have been done on the intergenerational associations between parents and offspring for individual risk factors of CVD (21-27). However, we do not know whether these associations are of the same strength or pattern as a clustering of these risk factors in the metabolic syndrome.

Previous studies on the association between physical activity and the metabolic syndrome show that both light, moderate and high levels of physical activity reduces a person's risk of getting the metabolic syndrome. Meeting national guidelines, less sitting and more vigorous physical activity and a physically active lifestyle throughout life, has all been associated with a reduced risk of metabolic syndrome (28-31). One hypotheses is that physical activity is beneficial because it has the possibility to improve several of the risk factors included in the

syndrome. This has been shown for blood pressure, blood lipids, glucose tolerance and body fat percentage, in previous studies. (32-36). However, previous studies have either been done on a very small and specific populations, or has looked at future onset of diseases, such as CVD. Furthermore, no previous studies has looked at how physical activity might modify any heritable vulnerability for metabolic syndrome.

Therefore, the main aim of the current study is to prospectively examine the association between parental metabolic syndrome and the risk of metabolic syndrome in their adult offspring. We will also examine the independent effect of offspring physical activity, on risk of metabolic syndrome, as well as the possible modifying role physical activity may have on any intergenerational associations in metabolic syndrome.

Material and methods

Study population

The Nord-Trøndelag Health Study (HUNT) is a large population-based longitudinal study, conducted in three waves of data gathering, the HUNT1 Survey (1984-1986), the HUNT2 Survey (1995-1997) and the HUNT3 Survey (2006-2008). Everyone from the age 20 and up, residing in the county of Nord-Trøndelag, were invited to participate. The population is relatively homogeneous, and stable, with few people moving in or out of the county. The HUNT databank includes a large number of participants. Many of these participated two or three times, resulting in 126 000 unique individuals in the databank. The population is in many regards representative of the whole population of Norway, except for the lack of any big city.

Since the first survey did not obtain information on blood lipid values, the present study includes data from HUNT2 and HUNT3. In HUNT2 93 898 individuals, over the age of 20, were invited of which 65 237 (69,5%) responded. In HUNT3 93 860 individuals, over the age of 20, were invited of which 50 807 (54,1%) responded.

The HUNT Databank includes a large amount of health information for each participant, which is collected through a questionnaire on health and lifestyle factors and medical exams. Information collected through the questionnaire includes, but is not limited to, current CVD, use of blood pressure medication and leisure-time physical activity. At the clinical examination, standardized measures of anthropometry and blood pressure were obtained by trained personal, and non-fasting serum blood-samples were drawn. A more detailed description of procedures and methods can be found at http://www.ntnu.edu/hunt

Record linkage

All Norwegian citizens have been assigned a unique personal identification number, which HUNT use in their record. The number was used to establish a linkage to the Family Registry at Statistics Norway between parents and their biological offspring, who had participated in either HUNT2 or HUNT3. There was a total of 66 000 parent-offspring linkages within the HUNT Study (i.e. offspring and mother and/or father participating in one or more surveys). The parent-offspring linkages were constructed separately for fathers and mothers.

Study design

The study had a prospective design, where we followed offspring without metabolic syndrome in HUNT2 and examined the risk of developing the metabolic syndrome in HUNT3, according to the metabolic syndrome status in their parents in HUNT2, or according to the offspring level of physical activity in HUNT2. Both offspring and parents included in the present study had to have information on all components included in the definition of metabolic syndrome. After excluding offspring with missing data on relevant variables, offspring with prevalent metabolic syndrome at baseline, and offspring without parental data on metabolic syndrome from HUNT2, a total of 7065 father-offspring pairs and 9874 mother-offspring pairs were available for statistical analyses (Fig 1).

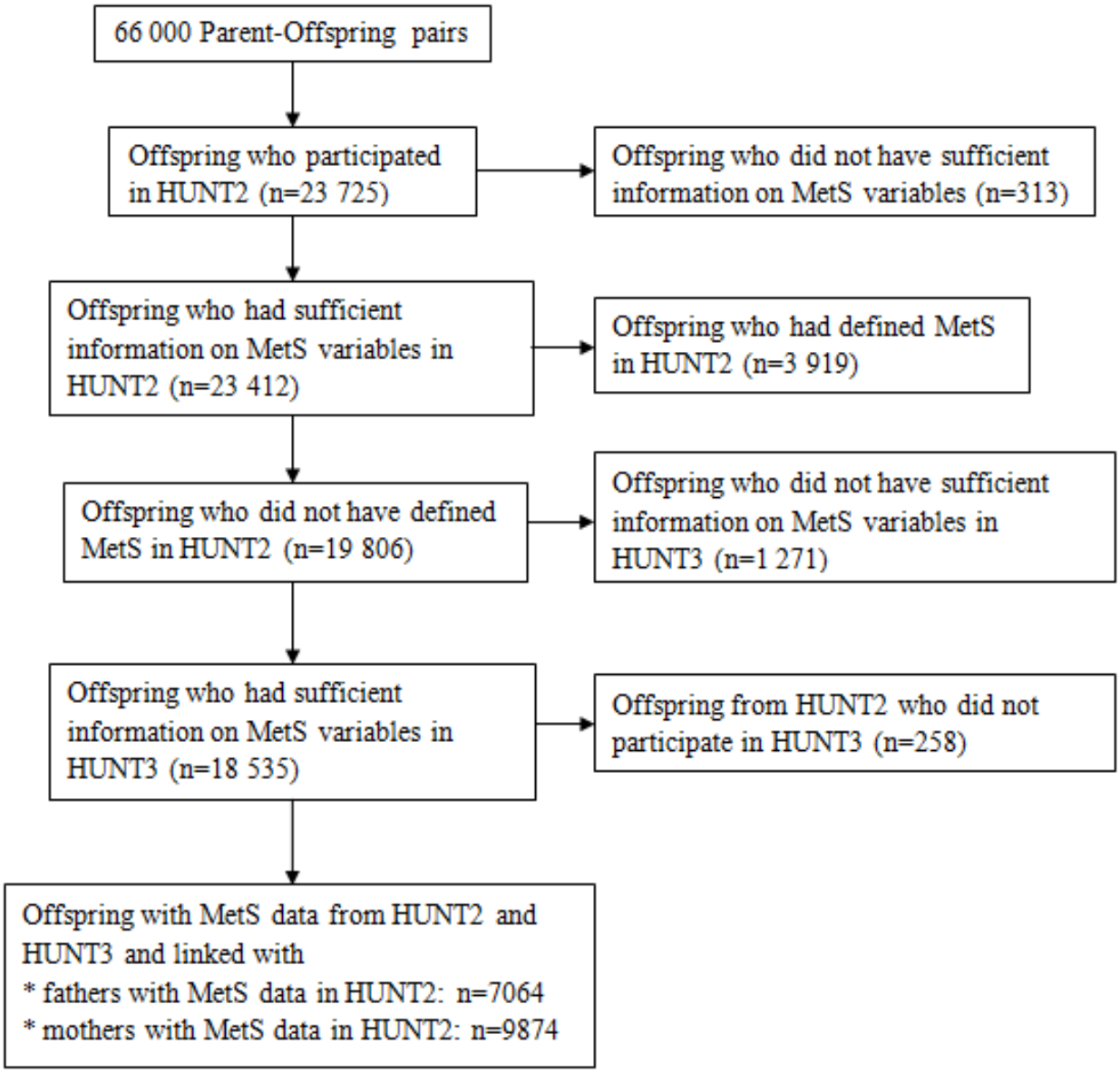

Fig.1: Flowchart of the selection of subjects included in the final analysis (MetS = metabolic syndrome

Study variables

Defining the metabolic syndrome

There are many definitions of metabolic syndrome, but they usually consist of the same risk factors or components (13, 37). The risk factors consist of overweight/obesity, defined either as BMI or abdominal obesity (waist circumference or waist-hip ratio), high blood pressure (differing cut-off points), high cholesterol or unfavourable levels of cholesterol or triglycerides (differing cut-off points) and diabetes (defined either as impaired fasting glucose or glucose tolerance).

For this master thesis the ATP III criteria will be used for defining metabolic syndrome. The risk factors and cut-off points for defining metabolic syndrome using these criteria are as follows: Abdominal obesity, given as waist circumference (men >102 cm, women >88 cm), triglycerides (≥1.7 mmol/L), HDL cholesterol (men <1.04 mmol/L, women <1.03 mmol/L), blood pressure (≥130/≥85 mm Hg) and fasting glucose (≥6.1 mmol/L). The HUNT studies does not include a measurement of fasting glucose, instead they include a measurement of impaired glucose tolerance (≥11.1 mmol/L), which was used in this master thesis, as a substitute for fasting glucose (37, 38)

Metabolic syndrome was defined according to the national Cholesterol Education Programme (38), where three or more of the aforementioned factors had to be present to be defined as having the syndrome. Thus, a combined score of 3 or above, when adding all the factors, was defined as having the metabolic syndrome.

Anthropometric factors

Waist circumference (WC) was measured with the participant standing with the arms hanging relaxed, and measured horizontally at the height of the umbilicus to the nearest 1.0 cm. WC was divided in two by a cutoff point where >102 cm for men and >88 cm for women, was coded as 1, all values below this was coded as 0 (38).

Blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times at 1 min intervals using Dinamap 845XT (Citricon, Tampa, Florida, USA). The mean of the

second and third measures was used in the analyses to avoid an artificially high reading at the first measure. Blood pressure was divided by a cutoff point, where SBP ≥130 mm Hg, and DBP ≥85 mm Hg, for both men and women was coded as 1, and values below this was coded as 0.

Triglycerides, HDL cholesterol and blood glucose

A random blood sample (non-fasting) was drawn from all participants, and serum samples were analysed for glucose and lipid levels. Triglycerides was divided by a cutoff point, where ≥1.7 mmol/L, was coded as 1, values below this was coded as 0. HDL cholesterol was divided by a cutoff point, where <1.03 for men and <1.29 for women, was coded as 1, while values above this was coded as 0. Blood glucose was divided by a cutoff point where >11.1 mmol/l, was coded as 1, values below this was coded as 0.

Leisure time physical activity

Participants were asked about how their physical activity in leisure time had been during the last year. There was one question about average hours of low physical activity per week in the last year, and one about average hours of vigorous physical activity per week in the last year. Both of these questions had four different response alternatives (none, <1, 1-2 and >3 hours). These answers were then recorded into an index variable and classified into four categories; "no activity" (no or <1h light, and no vigorous), "low" (at least 1-2h light and/or <1h vigorous), "medium" (at least ≥3h light and/or 1-2h vigorous) and "high" (any light and ≥ 3h vigorous). For the purpose of the stratified analysis these categories were collapsed into two new categories; inactive ("no activity" and "low) and active ("medium" and "high").

Statistical methods

Logistic regression analyses were used to calculate odds ratio (OR) as estimates of relative risk of metabolic syndrome in offspring, associated with parental metabolic syndrome and offspring physical activity. In these analysis, no metabolic syndrome, or alternatively, no physical activity, was used as the reference group. The possible modifying role of physical activity was examined in analyses stratified on level of physical activity (active and inactive). Statistical interaction was tested by a product term in the regression model. Sensitivity analyses was also done in this regard, were offspring in the lowest and highest levels of physical activity were chosen ("high activity" and "no activity"). All the analyses were

adjusted for offspring age, gender, level of education (<9, 10-12 and >12 years) and smoking status (never, former and current smoker). The precision of the estimated associations was assessed by a 95% confidence interval (CI). All statistical analyses were conducted using SPSS software (version 21; SPSS Institute, Chicago, Illinois, USA).

Results

Table 1 shows baseline characteristics of the study population, consisting of 7064 father-offspring pairs, and 9874 mother-offspring pairs. The mean age of mothers were 65,8 years, for fathers 65,8 years and for offspring 38,3 years at the start of the study. During follow-up 2684 (21%) offspring developed metabolic syndrome.

Table 1 Baseline characteristics* of the study population

	Mother		Father		Offspring	
	MetS	**No MetS**	**MetS**	**No MetS**	**MetS**	**No MetS**
Participants	2425	7449	3144	3920	2684	12757
Female (%)	-	-	-	-	51.3	54.0
Age	67.8 (10.3)	63.8 (11.2)	66.1 (10.5)	65.5 (10.5)	39.3 (9.4)	37.2 (9.5)
WC	94.4 (10.9)	82.6 (9.6)	98.8 (8.6)	90.9 (7.9)	87.4 (9.9)	80.7 (9.7)
BP med. (%)	43.4	21.0	29.7	16.4	5.4	2.6
SBP	158.4 (22.3)	146.9 (24.3)	151.2 (20.5)	145.3 (22.2)	132.5 (15.6)	126.9 (14.3)
DBP	87.1 (13.4)	82.8 (12.5)	88.0 (12.2)	84.7 (12.2)	79.9 (10.8)	75.1 (9.7)
HDL	1.1 (0.3)	1.6 (0.4)	1.0 (0.2)	1.4 (0.3)	1.3 (0.3)	1.5 (0.3)
Triglycerides	2.9 (1.3)	1.6 (0.8)	2.7 (1.3)	1.5 (0.7)	1.8 (1.0)	1.3 (0.7)
Glucose	6.4 (2.7)	5.5 (1.2)	6.2 (2.2)	5.6 (1.3)	5.2 (0.8)	5.1 (1.0)
Education (%) †	70.4	65.0	52.2	49.5	21.4	16.4
Smoking (%)¶	17.1	23.3	22.2	30.8	31.4	26.3
No PA (%)	40.0	29.3	25.5	21.7	24.1	20.5

*Data presented as mean with SD, unless otherwise specified, offspring statistics calculated for offspring linked with mother
MetS; metabolic syndrome, WC; Waist circumference, BP med.; Blood pressure medicine, SBP; Systolic blood pressure, DBP; diastolic blood pressure, HDL; High-density lipoprotein, PA; physical activity
†≤9 years
¶ Current smoker

Table 2 shows the OR for metabolic syndrome in offspring according to status of metabolic syndrome in parents. The analysis show an adjusted OR of 1.71 (95% CI 1.51-1.93) if the mother had metabolic syndrome and 1.50 (95% CI 1.30-1.72) if the father had metabolic syndrome. If one parent had the syndrome (regardless of it being the mother or the father), the adjusted analysis showed an adjusted odds ratio of 1.48 (95% CI 1.25-1.76). If both parents had metabolic syndrome the OR was 3.09 (95% CI 2.46-3.89).

Table 2: OR for MetS in offspring according to MetS in parents.

	No MetS	MetS	OR	OR_{adj} (95%CI)*
Mother (No MetS)	6402	1047	1.00	
Mother (MetS)	1891	534	1.73	1.71 (1.51-1.93)
Father (No MetS)	3401	519	1.00	
Father (MetS)	2590	554	1.40	1.50 (1.30-1.72)
No MetS in parents	2289	300	1.00	
MetS in one parent	2110	371	1.34	1.48 (1.25-1.76)
MetS both parents	523	182	2.66	3.09 (2.46-3.89)

*Adjusted for offspring age(continuous), gender (male, female), level of education (≤9 years, 10-12 years, >12 years and unknown) and smoking status (Never, former, current, unknown). (0); No MetS, (1); MetS

Table 3 shows OR for metabolic syndrome according to level of physical activity, in the offspring, compared to the reference of no activity. The analysis show adjusted ORs of 0.92 (95% CI 0.08-1.03) for offspring in the low activity group, 0.81 (95% CI 0.70-0.93), for offspring in the medium activity group, and 0.56 (95% CI 0.47-0.67) for offspring in the high activity group.

Table 3: OR for MetS in offspring according to level of PA in offspring

	No MetS	MetS	OR	$OR_{adj.}$(95%CI)*
No activity	2000	526	1.00	1.00 (Ref.)
Low	4031	957	0.90	0.92 (0.81-1.03)
Medium	2089	434	0.79	0.81 (0.70-0.93)
High	1493	195	0.50	0.56 (0.47-0.67)

*Adjusted for offspring age (continuous), gender (male, female), level of education (≤9 years, 10-12 years, >12 years and unknown) and smoking status (current, former, never and unknown).

Table 4 shows analyses stratified on offspring level of physical activity. It shows adjusted and unadjusted odd ratios for the interaction between parental metabolic syndrome and offspring level of physical activity, with association to offspring metabolic syndrome. We also did sensitivity analysis in this regard, were the highest and lowest levels of physical activity were examined ("high activity" and "no activity"). The results from these analyses did not show any different results, therefore, they are not presented here. Overall, the results show no

evidence that offspring physical activity modifies the parent-offspring association of metabolic syndrome. The stratified analysis show an adjusted odds ratio of 1.64 (95% CI 1.27-2.12) for physically active offspring, and 1.57 (1.33-1.85) for inactive offspring, if the mother had metabolic syndrome. It shows an adjusted odd ratio of 2.16 (1.64-2.86) for physically active offspring, and 1.33 (95% CI 1.10-1.61) for inactive, if the father had metabolic syndrome. If one parent had the metabolic syndrome (regardless of it being the mother or the father), the stratified analysis of offspring metabolic syndrome shows an adjusted odd ratio of 1.95 (95% CI 1.39-2.75) for physically active offspring, and 1.31 (95% CI 1.03.1.66) for inactive. If both parents had the syndrome the stratified analysis showed an adjusted odd ratio of 5.09 (95% CI 3.21-8.08) for physically active offspring, and 2.39 (1.74-3.27) for inactive. All analysis were adjusted for offspring age, gender, level of education and smoking category. There was no evidence of statistical interaction between parental metabolic syndrome and offspring level of physical activity (all p-values > 0.05).

Table 4 OR for offspring MetS, according to parental MetS, stratified on offspring level of PA

		Active			Inactive			$P\text{-value}_{int}$
		OR	OR_{adj}	95% CI	OR	OR_{adj}	95%CI	
Mother	No MetS	1.00	1.00	Reference	1.00	1.00	Reference	0,84
	MetS	1.66	1.64	1,27-2.12	1.61	1.57	1.33-1.85	
Father	No MetS	1.00	1.00	Reference	1.00	1.00	Reference	0,08
	MetS	1.98	2.16	1.64-2.86	1,29	1.33	1.10-1.61	
Both	No MetS	1.00	1.00	Reference	1.00	1.00	Reference	0.08
	One Parent	1.68	1.95	1.39-2.75	1.24	1.31	1.03-1.66	
	Both Parents	3.84	5.09	3.21-8.08	2.21	2.39	1.74-3.27	

*Adjusted for offspring age, gender (male, female), level of education (≤9 years, 10-12 years, >12 years and unknown) and smoking status (never, current, former, unknown)

Discussion

Main results

The main results from this study shows an increased risk for metabolic syndrome during 10 years of follow-up, in offspring whose parents were classified as having metabolic syndrome, compared to offspring of parents who did not have metabolic syndrome. This study also shows an inverse dose-response relationship between level of physical activity and risk of metabolic syndrome, where offspring who had reported high physical activity had nearly half the risk, compared to those who were inactive. However, there was no clear evidence that offspring physical activity modified the parent-offspring associations in metabolic syndrome, although some of the estimated associations were somewhat stronger among offspring who reported to be physically active.

Comparison with existing literature

To our knowledge, this is one of the few studies to examine the parent-offspring association for metabolic syndrome, in adult offspring. Previous studies have been done on the heritability of the metabolic syndrome, and on the association with parents and young adults/adolescents.

Intergenerational association

Previous studies who have examined young and older offspring also find an intergenerational association for the metabolic syndrome (14, 16), with a stronger association for younger offspring. This stronger association in younger offspring could indicate a stronger effect of shared environment, rather than heritable vulnerability for the metabolic syndrome. However, in both the current study and in a study by Khan, Gebreab (17), who also examined the association in adult offspring, the associations still persist for adult offspring and their parents, indicating the possibility of a heritable vulnerability. However, for the study by Khan, Gebreab (17) this was only the case for the mother-daughter association for the metabolic syndrome.

Both the study of metabolic syndrome independently (as a disorder in itself) and the study of the heritability of the metabolic syndrome is challenging due to several factors. One is the differing definitions of the metabolic syndrome that exists. When comparing previous studies

it is important to have this in mind, because the use of different definitions might affect the prevalence of the metabolic syndrome in the population. In a study by Biino, Concas (19) the prevalence of the metabolic syndrome ranged from 20% - 29% in the population, according to different definitions. Furthermore, the fact that the metabolic syndrome is a clustering of several risk factors (it's a heterogeneous disorder), makes it hard to estimate the heritability. The heritability for the different risk factors may vary considerably between different individuals, even between affected family members.

The effect of physical activity on the metabolic syndrome

To the best of our knowledge no previous studies have examined the possible modifying effect of physical activity on intergenerational association in metabolic syndrome. More studies have been done on the independent preventive effect of physical activity on metabolic syndrome, and on the individual risk factors constituting the metabolic syndrome.

The current study shows that physical activity has the potential to decrease an individuals' risk of developing the metabolic syndrome. This is in line with previous studies. From a meta-analysis by He, Xi (39) high levels of leisure-time physical activity (LTPA) was strongly associated with reduced risk of metabolic syndrome, while moderate LTPA was only weakly associated, compared to being inactive.

Later studies done on the association between physical activity and the metabolic syndrome show both a decreased risk of the metabolic syndrome when meeting the national guidelines (29, 30), and an increased risk of getting the metabolic syndrome when not (28). The strengths of the effect differ somewhat between the studies, but all results are statistically significant.

Several of these studies are cross-sectional, and can therefore not say anything about the cause and effect relationship between physical activity and the metabolic syndrome. The current study adds to this knowledge, because it is prospective in nature. We examined how the level of physical activity in HUNT2, affected the risk of getting the metabolic syndrome in HUNT3. We found the same effect as in previous studies, that there is a preventative effect of physical activity. Furthermore, similar to previous studies we found a dose-response

relationship. The higher the level of physical activity, the larger decrease in the risk of getting metabolic syndrome.

The fact that the metabolic syndrome consists of several risk factors makes it difficult to estimate the heritability, as mentioned earlier, but it also makes it difficult to estimate the role of physical activity. Physical activity could influence the different risk factors of the metabolic syndrome differentially, and the combination of risk factors may vary considerably between different individuals, even between affected family members. Previous studies show that physical activity affects the level of individual risk factors by lowering the blood pressure, LDL cholesterol and triglycerides in the blood, and increasing HDL cholesterol and lean body mass, and decrease the body fat percentage (32, 34, 35). Other mechanisms include reduction of insulin resistance and enhancement of insulin sensitivity and glycemic control (40). They show effect of both aerobic and resistance training, and they show that small doses can decrease the risk for the individual risk factors. Furthermore, they suggest that the factor that might have the biggest impact on reducing the risk is compliance to exercise, and the general improvement in exercise behaviour (32, 34, 35).

The findings from these studies show the vast span of effects for several levels of physical activity, but they also show the importance of adherence to exercise, and at the same time that one can achieve great benefits after only short periods of training (8-12 weeks of intervention).

Possible mechanisms

A population-based study from the Netherlands, using twin and family data, found strong correlations for metabolic traits in monozygotic twins, moderate associations for dizygotic twins, and weaker associations for parents and offspring (20). When examining twin studies we need to keep in mind that monozygotic twins share a 100% of the same DNA, and that this is not the case for parents and offspring. Offspring gets one chromosome from each parent, meaning they share 50% DNA with their mother, and 50% DNA with their father. This means that when studying monozygotic twins, and one can see a stronger correlation in their phenotype (expression of the genes) than for parent and offspring it indicates that this phenotype is influenced by genetic factors. In the study by van Dongen, Willemsen (20) we can see stronger correlations for all factors included in the metabolic syndrome in

monozygotic twins, compared to dizygotic twins, and parent-offspring, suggesting that the phenotype is more influenced by genetic factors than environmental factors. A review by Abou Ziki and Mani (18), present several loci associated with the metabolic syndrome, and there seems to be certain common variants that can increase a person's risk of the metabolic syndrome for one or two metabolic traits.

Intergenerational associations could also be influenced by epigenetic effects. Epigenetics is a change in phenotype, without a change in genotype. Epigenetics involve the chemical tags that turn genes on and off, and these can be influenced by factors including diet, chemical exposure and medication, but also stress or psychosocial factors. It can happen in early or late stages of pregnancy, or even in adulthood. Furthermore, epigenetic changes can be carried on to later generations (41).

Another possible mechanism that could explain the intergenerational association seen in the current and previous studies, is the effect of intrauterine environment on obesity and other metabolic traits. Several studies suggest that maternal obesity, and higher maternal prepregnancy BMI and early-pregnancy weight gain rate affects offspring obesity, and is associated with an adverse adolescent cardio-metabolic profile (42, 43). However, isolating the possible effect of the intrauterine environment is difficult. Metabolic traits seen in the offspring can be the cause of direct transmission from mother to offspring in the uterus, or the effect of lifestyle patterns of the child after birth. In the current study mother-offspring associations were slightly stronger than father-offspring associations in metabolic syndrome. This may point to an effect of the intrauterine environment, although other factors could also explain such differential associations (e.g. mothers more involved in family household and diet, more single-parent children grew up with mothers than fathers, and some of the fathers in the analyses are not necessarily biological fathers (non-paternity effects)). However, the current study stands out from previous studies because the offspring that were analyzed were adults (>20 years), and one can assume that the effect of shared environment is lower than when offspring are children and living together with their parents.

A review article from 2016 explains the relative contributions of genetic predisposition to the metabolic syndrome, and the lifestyle and environmental effects causing epigenetic changes (44). They explain the transgenerational inheritance of metabolic syndrome by two possible modes. One is through intrauterine environment, where the offspring inherits metabolic traits

from the mother, in the uterus. The other is through epigenetics, where the child is affect by reduced supply of oxygen and nutrients. Implying metabolic disorders are subsequently propagated to progeny, endangering generation after generation (44).

We cannot say if the observed intergenerational associations of metabolic syndrome is due to a heritable vulnerability or the cause of shared environment, or a mixture of the two. The study of heritability for the metabolic syndrome is quite a new field of research, with several studies written in the last decade. Furthermore, epigenetics is also a new field of research, and evidence is still a little inconclusive, but it just shows how intricate the symbiosis of nurture vs. nature actually is (44).

To our knowledge this is the first study to examine the possible modifying effect of physical activity on any intergenerational associations for the metabolic syndrome. The results of this current study were somewhat unexpected, with a slightly stronger effect of metabolic syndrome among the most active group of offspring. A possible explanation for this could be that the effect of heritability is stronger if an individual gets the metabolic syndrome, despite being physically active.

If metabolic traits are transmitted through intrauterine environment the health and physical status of the mother is of great importance. Being healthy and physically active before and during pregnancy might help secure the birth of healthy offspring, who are not predisposed for metabolic syndrome, or other metabolic traits. Furthermore, even though the offspring are adults at the time of the study, and it is therefore likely to believe they no longer share environment with their parents, they might still be affected by lifestyle choices they have been accustomed to after sharing household with their parents for several years, like for example dietary habits. This might indicate an importance of environment in the case of diet, and also what is seen as light or vigorous activity. Also, the current study only examines one generation, the results might be different when examining several generations. Physical activity does decrease the risk of the metabolic syndrome, although there was no clear modifying effects. By being physically active early in life, throughout the life time, and through generations, it is reasonable to believe that physical activity might have a bigger impact on the intergenerational associations seen in the metabolic syndrome.

Strengths and limitations

There are several strengths to this study, it is a prospective and population-based study, with a high number of participants, with a wide age range and a long follow-up period. Many of the variables are measured in an objective and standardized way. Information was collected using questionnaires and clinical examinations. Data on family linkages was obtained through the national family register, which made it possible to link offspring and parents who independently reported on lifestyle and health related factors. The analysis show strong associations and have been well adjusted for possible confounders, as well as sensitivity analysis. It is also a strength that the offspring are adults, because unfavourable levels of the risk factors constituting the metabolic syndrome do not usually become manifested until adulthood.

The current study also has some limitations. We had no possibility to distinguish between genetic and environmental effects, and the relative contributions of these, since we had no information on genetic markers. Furthermore, we had no information on whether the offspring actually shared their environment with their biological parents (both or one), neither at the time of study or earlier in life. However, the offspring were adults at the time of the study, so it is reasonable to assume they did not share household environment with their parents at this time. There is also the chance of residual confounding by factors that have not been adjusted for. The most important one of these is diet. Furthermore, previous studies have seen effects of gender on the heritability of certain metabolic traits. This study did not stratify the analysis on offspring gender, because this would have given less statistical strength. Previous studies has also seen a decrease in the correlation between certain metabolic traits with increasing age. The current study did not stratify the analysis on age, because this also would have given less statistical strength

One of the major strengths of the HUNT-surveys is the high participation rate. However, there is a possibility that families, where both parents and offspring contribute, could be more health conscious than the general population. In a non-responder study done after HUNT2 the results showed that non-participants had higher prevalence of cardiovascular disease, diabetes mellitus and psychiatric disorders, lower socioeconomic status and higher mortality than participants (26). Presence of the non-responder group, would most likely not have altered the results largely. Blood lipid and blood glucose levels were only measured in the non-fasting

state, this increases the statistical uncertainty. However, the bias arising from this would also most likely be non-differential.

Another limitation with the current study is that information of physical activity was obtained through a questionnaire, this may result in both subjective interpretation of the questions, and recall bias. Furthermore, physical activity was reported only one time. The seasonal differences in Norway may contribute to differing levels of physical activity throughout the course of one year. However, this is not dependent on parents metabolic syndrome, therefore this would most likely be non-differential bias. Also, the geographical area for the study population did not include any big cities, meaning the results may not be possible to generalize to individuals living in bigger cities. This might also mean that the type of activity the individuals in the study performed might have generally been done outside, we have no way to control for this, since it is not a question included in the questionnaire.

Conclusion

In conclusion we found that there is an increased risk for metabolic syndrome in offspring from parents who have the metabolic syndrome. We saw associations for both mother and father, with somewhat stronger association for mothers. These results may indicate effect of both intrauterine environment, epigenetics, genetic markers and shared environment. For health care personnel it is important to be aware of such familial predispositions and implement preventive measures early to help reduce the risk of developing the metabolic syndrome, in offspring whose parents have metabolic syndrome. We saw an independent dose-response effect between physical activity and reduced risk of metabolic syndrome. However, there was no clear modifying effect of physical activity on the intergenerational associations of metabolic syndrome. Nevertheless, implementations of physical activity throughout the lifetime may have beneficial effect to reduce the risk of metabolic syndrome.

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