Obesity, Lifestyle and Cardiovascular Risk in Down syndrome, Prader-Willi syndrome and Williams syndrome

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PhD Thesis

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UNIVERSITY OF OSLO

2015

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 2065

ISBN 978-82-8333-084-7

Cover: Hanne Baadsgaard Utigard.
Printed in Norway: AIT Oslo AS.

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Acknowledgements

The work presented in this thesis was performed at Frambu Resource Centre for Rare Disorders and Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, and has been carried out from October 2011 to March 2015. Financial founding was provided by ExtraStiftelsen in collaboration with The Norwegian Association for Persons with Developmental Disabilities (NFU), Frambu Resource Centre for Rare Disorders and Johan Throne Holst Foundation for Nutritional Research.

My deepest gratitude goes to my supervisors, professors Svein O. Kolset and Benedicte Paus for their excellent scientific guidance. Svein, I am especially grateful for your positive attitude and your remarkable efforts to always be available. Benedicte, thank you so much for your always positive remarks, intelligent comments and helpful suggestions.

Special thanks also go to the collaborating patient organizations; NFU, The national network for Down syndrome, The national association for Prader-Willi syndrome and Norwegian Associations for Williams syndrome for their collaboration and support in recruitment of study participants. Great thanks also to Tone Hammerlund at NFU for the cooperation throughout these years.

Gratitude goes to my co-authors Bjørge Herman Hansen, Lene Frost Andersen and Kjetil Retterstøl for providing me with methodological knowledge, scientific experience as well as excellent educational collaboration. Your contributions have been invaluable.

Throughout these years I have enjoyed being part of the scientific network at Department of Nutrition and in the research group of Svein O. Kolset, providing me with good scientific discussions, great laughs and friendships. Admiration and thanks goes especially to; Annicke Stranda, Trine M Reine, Astri J Meen, Ingrid B. Moss Kolseth, Ingunn Narverud, Jackob Juel Christiansen, Anne Juul Skjetne, and Tram Thu Voung,

Warm thanks also go to everybody at Frambu. The former and present leaders, for their facilitation of the project and for their continuous trust in me. To all my present and former inspiring and supportive colleagues especially; Kari Hagen, Kaja Giltvedt, Gro Trae, Sissel W. Berdesen, Eva Næss, Wenche Åstrøm, Lise B Hoxmark, Rita S. Stige, Kari Stenslie, Krister Fjermstad, Stine Borgen, Anders Wold, Simen Aabøe, Rasmus Dinessen, Mona Haug,

Lisen Mohr, Simen Stokke, Kristin Solheim Hustad and Øyvind Kanavin. I would not have been possible without you.

I would also like to express my gratitude to Tove Bergem-Ohr and her skillful colleagues at the Interdisciplinary Medical Laboratory and Medical Biochemistry at Ahus University Hospital.

My deepest thanks also goes to Torgeir Kolset, although I've never personally have meet him, I'm sure his contributions to this work goes beyond my imagination.

Finally, I will thank all my friends and family for their continuous encouragement throughout these years. A special thank goes to Andreas for his patience, support, and doubtless believe in me, and to Gabriel and Dina for the endless joy.

Oslo, March 2015
Marianne Nordstrøm

Summary

Increased risk of obesity has been described for persons with mild to moderate intellectual disability (ID) and unhealthy lifestyle has been documented. However this has not been investigated to any great extent in relation to most specific genetic conditions associated with ID. Moreover, there is a paucity of data describing the risk of developing atherosclerotic cardiovascular disease (CVD) and the association with obesity in subgroups associated with ID. To investigate and explore these perspectives a national cross-sectional study in persons 16-43 years of age with Down syndrome (DS) (n=40), Prader-Willi syndrome (PWS)(n=22) and Williams syndrome (WS) (n=25) was conducted.

Accelerometer-determined physical activity was documented in **paper I**, and we found sedentary lifestyle with low adherence to physical activity recommendations in all three subgroups. Females in all subgroups were found to have especially low levels of physical activity. No association between BMI and overall physical activity was detected, however BMI was strongly associated with reduced physical capacity measured by six-minute walk test.

In **paper II** we used a simplified self-reported food intake frequency assessment in combination with supportive measurements of biomarkers in blood samples. We found that a large proportion of persons with WS and DS living in community residences had low intake frequencies of fruits and vegetables. Low consumption frequency of fish and less use of omega-3 supplementation were also found in a majority of persons with WS.

When investigated in relation to living arrangements, increased food related autonomy was found for persons with DS living in communities when compared to those living with relatives. Furthermore, among the community-dwelling participants a larger proportion frequently used precooked meals. The data also indicate that an increased proportion of participants living in communities had more frequent intake of soft drinks. No other significant differences in proportions with high and low consumptions frequency of the investigated foods were found when participants in the different living arrangements were compared.

Abdominal obesity was prevalent in all three subgroups and associated with increased risk of CVD. Furthermore, diversity in risk of CVD was observed, which may be explained by the

genetic basis of the studied syndromes. As presented in **paper III,** the PWS and WS groups were found to have elevated risks of CVD, whereas DS was associated with low risk. High prevalence of hypertension and type 2 diabetes was described in the PWS group. Similarly, high prevalence of hypertension and clear indication of increased risk of type 2 diabetes was also seen in the WS group but in combination with a more favourable blood lipid profile. In DS low prevalence of hypertension and type 2 diabetes was noted, but with comparable prevalence of metabolic syndrome as in the two other subgroups.

To improve the public health situation there is a need of diagnosis and gender adjusted preventive strategies to promote weight reduction and improvements in lifestyle. Furthermore, development of tailored diagnose-specific health checks is needed to ensure optimal health outcome among adults with these genetic syndromes.

List of scientific papers

I. Nordstrøm M, Hansen BH, Paus B, Kolset SO,. Accelerometer-determined physical activity and walking capacity in persons with Down syndrome, Williams syndrome and Prader-Willi syndrome. Res. Dev. Disabli. 2013:34, 4395-4430.

II. Nordstrøm M, Paus B, Andersen LF, Kolset SO,. Dietary aspects related to health and obesity in in Williams syndrome, Down syndrome and Prader-Willi syndrome. Food Nutr. Res. 2015:59, 25487.

III. Nordstrøm M, Paus B, Retterstøl K, Kolset SO,. The prevalence of metabolic risk factors of atherosclerotic cardiovascular disease in Williams syndrome, Prader-Willi syndrome and Down syndrome. (Revised and resubmitted manuscript)

Abbreviations

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
CVD	Cardiovascular disease
DS	Down syndrome
HDL	High density lipoprotein
ID	Intellectual disability
IQ	Intelligence quotient
LDL	Low density lipoprotein
MVPA	Moderate-to- vigorous physical activity
PWS	Prader-Willi syndrome
RR	Relative risk
SVAS	Supravalvar aortic stenosis
WC	Waist circumference
WS	Williams syndrome

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1 Introduction

1.1 Intellectual disability

Intellectual disability (ID) refers to incomplete development of cognition that cause significant limitations in intellectual functioning, and adaptive behavior, and manifestation of these symptoms before adult age (1). ID can be associated with other clinical findings as part of a syndrome or can occur as an isolated phenotype. *Intellectual disability* is currently the preferred international term (2, 3), although other terms as *mental retardation*, *developmental disabilities* and *learning disabilities* are also being used for categorization of the condition (1), but not always used with equal definitions, leading to some differences in the individuals being included in this group. The continuous use of *mental retardation* has especially been questioned because it implies a static, unchanging condition rather than one that can change over time depending on its etiology and the available environmental support (2, 3). The term ID is used throughout this thesis, regardless of terminology in the sources used for reference.

There are several systems globally for recognition of ID and classification of its severity. The most widely distributed and the one used in Norway is The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD- 10) (4). Chapter V lists ID [mental retardation], and defines ID by intelligence quotient (IQ) below 70, and divides the condition into levels of mild, moderate, severe, profound ID. The level of severity reflects the extent of the intellectual impairment and daily functioning measured by standardized intelligence tests and standardized tests for assessment of adaptive behaviors. The diagnosis and category chosen should be based on global assessment and not on a single or specific impairment in cognition or in behaviors alone. Mild ID is defined by IQ in the range of 50-69, moderate ID by IQ 35-49, severe ID by IQ 20-34, and in profound ID IQ is below 20 (4). The majority of the population with ID falls within the mild ID category with descending occurrence with increase in severity. In persons diagnosed with ID, mild ID, moderate ID, severe ID, and profound ID make up approximately 85 %, 10 %, 3-4 %, and 1-2 %, respectively (3).

The prevalence of ID across the world is about 1 %, however occurrence depend on definition and diagnostic approached used. Furthermore, differences are also found based on age, gender, and socioeconomic status (5-7). Increased prevalence of ID is reported in children and

adolescents compared to adults, more frequently observed in males compared to females, and in low income countries compared to high income countries (5). In Norway, the prevalence of ID is estimated to be 0.44 per 100 inhabitants and with geographic and urban-rural differences in prevalence (8). The prevalence of ID was reported to be 0.62 per 100 in a pediatric cohort born between 1980 and 1985 in Akershus County (9).

1.2 Genetic causes of intellectual disability

There are multiple etiologies of ID, and causes can be classified by different classification systems. Traditionally, causes have been classified based on the timing into; prenatal, perinatal and postnatal causes (3). Others divide causes in to biological and environmental (10). Classifications of etiological causes into a more specific subcategories have also been suggested, such as genetic, acquired (congenital and developmental), environmental and sociocultural, (11).

Genes plays important role in the causation of ID (Goldstein 2005). Although factors like e.g. infection and trauma can result in cognitive impairment, most severe forms of ID have a genetic basis (12, 13). New and improved genome wide diagnostic approaches, like whole-exome sequencing and whole-genome sequencing have resulted in the identification of a large number of etiologic genes and genomic rearrangements involved (12, 14).

Many genetic conditions associated with ID are due to chromosome disorders (12, 15). These conditions are caused by genetic copy number variation due to abnormal chromosome number, e.g. *trisomy*, or structure. In abnormal chromosome structure a part of the chromosome may be extra, a so-called *duplication,* or missing, a so-called *deletion*. Changes in chromosome structure may vary considerably in size, ranging from a kilobase affecting single gene, to several megabases affecting larger segments of DNA. Other genetic mechanisms related to ID include DNA sequence alternation or epigenetic changes where expression of genes is altered without changing the DNA sequence, such as by defects in methylation, turning on or off gene expression, identified in some individuals with ID (16). Currently the understanding of genetics in ID is extensive, but far from complete as the specific etiology remains unknown for a significant proportion of persons with ID (13).

1.3 Health and health inequalities in persons with intellectual disability

Health in persons with ID reflects, as in the general population, complex interactions between biology, behavioral, and environmental factors. In Norway, the health condition in the population is in general good and life expectancies are high, however inequalities in health are observed in relation to socioeconomic status (17). For persons with ID improved health care, medical treatments and better education have resulted in increased life expectancies, greater academic achievements and more fulfilling lives (3, 18-20). Yet, as a group these individuals still experience poorer health and reduced life expectancies compared to the general population (21-23). In a recent investigation from United Kingdom median life expectancies from a cohort of persons with ID was reported to be 64 years. Furthermore, in total 37 % of the deaths in the ID group were reported to be avoidable premature deaths, and much higher compared to the general population where 13 % of the deaths were premature. Females with ID was found to have even more reduced life expectancy compared to males, with a median age of death 63 versus 65. The reduction in life expectancies compared to the general population was 20 years for females and 13 years for males, respectively (24). The difference in health status and life expectancies is to a certain extent avoidable and represent health inequalities. Several key determinants of health inequalities that affect people with ID have been recognized (25, 26). First, persons with ID are more likely to have congenital abnormalities and genetic predispositions to certain health conditions (3, 27-29). Second, persons with ID are exposed to less favorable social circumstances such as unemployment, low economic status, and reduced social network (30). Third, persons with ID have increased risk of unrecognized health needs (31). Underlying features are difficulties in recognition and communication of health problems due to cognitive impairment from the individuals themselves, lack of knowledge and skills to interpret expression of emerging health issues by both careers and health professionals (32, 33). Furthermore, persons with ID take less part in health screening programs (31). Fourth, persons with ID have high risk of unfavorable lifestyle behaviors, especially related to obesity, inactivity and poor diets (34-37). Fifth, compared to the general population less research includes persons with ID, leading to reduced development of knowledge and treatments for these individuals (38).

1.4 Lifestyle related health in persons with intellectual disability

1.4.1 Overweight and obesity

Overweight and obesity can be defined as excess of adipose tissue. Increased body weight is in the general population associated with higher risk of hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome, coronary heart disease, stroke, sleep apnea, and some cancers (39). Obesity is furthermore associated with increased risk of cardiovascular mortality (40). Body mass index (BMI) is a ratio of weight-for-height that is commonly used for classification of overweight and obesity, and is calculated by the formula: Kg/m^2.

Table 1: Overweight and obesity in adults by use of BMI (39):

Normal weight	18.5-24.9
Overweight	25.0-29.9
Obesity	≥ 30.0

Age and gender specific isoBMI-values are used in children less than 18 years of age.

It is well recognized that not only total amount of body fat is of interest, but also the distribution of the adipose tissue. Waist circumference (WC) is a measurement of central obesity and in the general population WC correlates and predicts obesity related cardiometabolic complications better than BMI (41-44).

Table 2: Sex-specific cut points of WC for Caucasians defined by the risk of cardiometabolic complication (39)

	Males	**Females**
Increased	≥ 94 cm	≥ 80 cm
Substantially increased	≥ 102 cm	≥ 88 cm

Overweight and obesity rates have been increasing in most parts of the world including Norway. The most recent report in the Norwegian population found the prevalence of obesity to be about 13 – 14 % for persons 20-29 years. Overweight in the same age-category was found in about 35 % of males and 25 % of females. In the age-group 30-39 years of age about 20 % was obese, 50 % of males and 20 % of females and were overweight, respectively (45). In Norway, higher prevalence of obesity is found among persons with low educational level compared to high educational level (46).

Numerous epidemiological reports over the past years have documented high prevalence of overweight and obesity in persons with ID. Increased prevalence when compared to the general population is found in adolescents, adults and elderly (34, 47-56). The high prevalence of obesity among persons with ID is a major public health concerns as some studies indicate that obesity also for persons with ID are associated with increased risk of secondary health conditions (51, 53).

The prevalence of obesity varies within the ID group. Females are more likely to be obese compared to males (34, 47, 49, 54, 55, 57). The risk of obesity is also increased in persons with mild to moderate ID when compared to severe and profound ID (47, 53, 54, 57). Other determinants associated with high risk of overweight and obesity includes independent living in communities, daily soft drink consumption, use of atypical antipsychotic medication or other medication with risk of weight gain, and reduced level of physical activity (49, 54, 57). Studies also indicate that certain subgroups such as people with Down syndrome (DS), Prader-Willi syndrome (PWS) and autism spectrum disorder may be at particular risk (28, 49, 51, 53, 57).

Underweight is also more common in ID that in the general population, but not as common as obesity and is associated with severe ID (47, 57). Taken together, illustrates the heterogeneity and complexity in weight related health issues for persons with ID.

1.4.2 Physical activity and physical fitness

Physical activity is defined as any bodily movement produced by skeletal muscles that substantially increases energy expenditure (58). It is a complex human behavior carried out for a variety of purposes (59) and differs further in four dimensions; frequency, intensity, duration and the type of activity carried out. Physical fitness refers to a set of attributes that an individual have or achieve and is linked to the person's ability to carry out daily tasks. Health-related components of physical fitness are cardiovascular endurance, muscular endurance and strength, body composition, balance and flexibility (59).

Substantial empirical evidence confirms that regular participation in physical activity has a positive impact on health in individuals of all ages and gender (60, 61). The impact of physical activity shows an inverse dose-dependent relationship with health outcomes and all-cause mortality (61, 62). Even so, numerous studies by use of questionnaires and objective

assessments, have found that people with ID are less likely to engage in physical activity, to be more sedentary, and tend to be less physical fit compared to peers (36, 54, 57, 63-68).

In ID demographic factors such as gender, age, and level of ID have been documented to affect physical activity. Some studies suggest that females are less active compared to males (36, 54, 69, 70). Males were also described to be more interested in trying out new physical activities (69). A decline in level of physical activity associated with ageing has been observed (36, 69, 71), whereas others have not found this association (70). More severe levels of ID correlate with reduced physical activity compared to milder ID phenotype (36).

For persons with ID many of the same barriers to physical activity as for people without disabilities are reported, such as job, lack of necessary financial resources, weather and preference of sedentary activities (72, 73). However unique barriers are also described and include lack of transportation, reduced availability of physical activity resources, and absence of guidance and social support (73-76).There is a particular concern regarding maintaining organized physical activities over time (71). This highlights the necessity of continuity and structured support for physical activity in people with ID (77).

Facilitators of physical activity also exist and have been described to be parents, teachers, caregivers, and organizations that foster interest, social support and development of skills. Moreover, social connections and interactions with other participants performing the activity also seem important for maintenance of activities (77).

In individuals with ID, as in typically developed peers, physical fitness can improve as a result of regular exercise. Studies have shown positive impact on cardiovascular capacity, muscle strength, body composition, and balance after participation in exercise interventions (78-81).

For persons with ID the level of physical activity and physical fitness may also be influenced by physical attributes with the basis in the underlying condition. These features include low muscle mass, reduced muscle tone, balance problems, difficulties in coordination of movements, and impaired mitochondrial function as described in persons with DS (82, 83). Currently such perspectives are less well studied in relation to physical activity. Nevertheless, persons with DS and PWS have been found to engage less in physical activity compared to persons with ID of other etiology (36, 84).

1.4.3 Diet

Food is essential for life and dietary habits are an integrated part of the lives for all people. Over a lifespan the diet consumed can contribute to protect us from developing secondary conditions such as cancer, cardiovascular disease and type 2 diabetes (85, 86).

Precise description of habitual dietary intakes is in general a challenge due to the complex nature of food consumption, and that all traditional dietary assessment methods are associated with different degrees of measurement errors (87). Dietary assessments in adults with ID add even further methodological challenges related to the reduced cognitive functioning, and the lack of validated methods for use in these populations (88).

To date most studies assessing diets in adults with ID have used proxy-assisted or proxy reporters for completion of food frequency questionnaire or food diaries (35, 89-92). Furthermore, observational methods and digital photography of meals alone and in combination with other assessment techniques have also been used (55, 93). Proxy assisted assessment is a method in which a support person, most often staff member, assist a participant in completing the assessment. Proxy reporters implies that a staff member or close family member complete the record or survey without participation by the person with ID. Validations have shown that use of proxy-assisted methods may systematically underestimate intakes (94). In addition, this approach is problematic when assessing diets in persons living mostly independent. The use of photography alone or in combination with other techniques has been shown to be a feasible and promising method for use in community settings for adults, but further validation of these methods is needed (94-97).

Over the past years it has been recognized that nutritional biomarkers may provide more objective indicator of intake. Such a technique has the potential to evaluate more precisely the association between intakes and health outcomes and be of importance for possible confirmation of compliance in dietary intervention studies. Today such biomarkers, although few well documented markers exists, are increasingly being used in studies investigating association with diet and health outcomes (98-102). Even so, these methods have yet not been much used in investigations of adult persons with ID.

Most studies with assessment of diets in adults with ID involve persons with ID of mixed, although a few studies involve persons with DS only (90, 91). The assessments conducted provide indications of adult persons with ID make up a nutritional vulnerable group. Even so,

with exception of PWS and some information about DS, there are in general few studies on diagnose-specific dietary vulnerabilities in adult persons with ID.

High total fat intakes have been suggested by some studies (37), with intakes of saturated fatty acids and polyunsaturated fatty acids above and below recommendations, respectively (89, 91, 92). The studies reporting the actual energy percent from fat, find mean intakes in the range from 31 E % to 35 E % (89, 91, 92), and not all studies report high fat intakes (90, 93). Therefore the evidence of high fat as a major dietary challenge in adults with ID is currently weak. Intakes of fiber below recommendations have been reported indicating high intakes of refined carbohydrates (89-93). Protein intakes were found to be sufficient (89-93). Low intakes of alcohol are reported for the majority (89, 103), but was found to be higher in adults living in less supervised settings in urban areas compared to more supervised and rural living arrangements (57).

With regard to specific food groups and diet patterns, low intakes of fruit and vegetables have consistently been reported for persons with ID (35, 37, 90, 93, 104). Furthermore, increased body weight was associated with reduced consumption of fruit and vegetables in a cohort with overweight and obese individuals (92), whereas this association was not significant in another study comparing participants with normal weight and overweight to participants with obesity (57). Consumption of fish is in general investigated to a limited extent but intakes below recommendations have been described for a majority of the population (104). High intakes of soft drinks have been documented in community-dwelling participants (57, 93). In the report by Hsieh and colleagues nearly 60 % consumed soft drinks daily, and obesity was associated with increased soft drink consumption (57). Eating habits with regular consumption of convenience food, fast food and TV dinners has been reported by managers, support workers and participants with ID themselves (105). Living in less supervised urban settings was associated with higher consumption of fast food compared to other living arrangements (57). A regular meal pattern with high frequency of snacking has also been described (92, 93). Adolfsson et al reported in-between-meals to account for 26 % of all energy consumed. Buns and cakes was the most frequently food items consumed in these meals. For about 30 % of the participants, snacking contributed with more energy than any other meal consumed during the day (93).

1.4.4 Cardiovascular disease

Cardiovascular disease (CVD) covers a wide range of diseases in the heart and vessels. In newborns with genetic conditions associated with ID congenital heart defects is much more common than in healthy newborns, where congenital heart defects affect < 1 % (106). Several chromosomal syndromes such as DS and WS are associated with and show a fixed pattern of congenital heart defects (107, 108). Improvements in cardiac surgery and treatments have resulted in increased survival and better prognosis for the affected individuals (18).

In the general population and now increasingly in persons with ID due to longevity, CVD caused by atherosclerosis is an important cause of morbidity and mortality (24). Atherosclerosis is a complex process where the arteries become narrowed and hardened as a result of an excessive build-up of plaques which can lead to serious cardiovascular complications, such as coronary heart disease and heart failure. Eventually, a rupture in the fibrous cap of the plaque can trigger the formation of blood clots which have the potential to result in a myocardial infarction or stroke. Inflammatory processes are integrated and important elements in all developmental stages of the atherosclerotic process (109).

Atherosclerosis develops though several stages and usually takes decades before symptoms are noted, and for this reason age is an important risk factor. Well known modifiable risk factors include physical inactivity, several dietary factors, hypertension, smoking, high blood cholesterol, especially high levels of low density lipoprotein (LDL) cholesterol, high blood glucose, and obesity (61, 110). Dietary risk factors associated with increased risk of CVD include diets low in fruits and vegetables (111), diets rich in saturated fat (112, 113), those high in sodium (114), and diets rich in processed meat (115). Protective dietary components with the potential to reduce the risk of CVD have also been identified, such as regular whole grain consumption (116), and frequent intakes of nuts (117). Furthermore, long-chained omega-3 fatty acids of marine origin are associated with reduction in deaths from CVD (118).

High prevalence of cardiometabolic risk factors has been described for adolescents, adults and older persons with ID (52, 104, 119, 120). A more recent study in older persons however did not find increased prevalence of metabolic risk factors when compared to the general population (121). Furthermore, for persons with ID 50 years or older similar prevalence as for the general population were reported for coronary heart disease and stroke (122).

Increased prevalence of CVD risk factors has been shown in females, obese individuals and persons with ID living independently in communities (53, 106, 121). A reduced risk of atherosclerotic CVD has been reported for persons with DS (123, 124). DS is associated with high prevalence of obesity and low physical activity, but with low risk of hypertension (125), and few smokers has been reported in this group (126).

1.5 Genetic disorders in this study

1.5.1 Down syndrome

Down syndrome (DS) was named after John Langdon Down who published a phenotype description of individuals with this syndrome in 1866 (127).

There are three different genotypes that all leads to DS (128). Trisomy 21, a condition caused by an extra copy of chromosome 21, is most common affecting about 90-95 % of individuals with DS. Translocation 21, results when a major part of chromosome 21 has been transferred and attached to another chromosome, and DS will result if the offspring inherits the translocation chromosome in addition to the two normal chromosomes 21. Mosaicism occurs when not all of the body's cells display trisomy 21, and is in general associated with a milder phenotype (19, 128).

1.5.1.1 Prevalence of Down syndrome

DS is the most common identifiable genetic cause of ID, occurring in about 1:500 pregnancies, although the live birth prevalence varies between countries depending on the maternal age, utilization of prenatal screening and pregnancy termination (129). In Norway all expecting mothers 38 years or older at expected term are offered ultrasound examination for fetal nuchal translucency. Amniocentesis or chorionic villus biopsy with karyotyping is offered those at increased risk. Prenatal detection rate of DS in Norway was 43 % from 1984 to 2004, and 84 % of the detected cases resulted in pregnancy termination (130).

Based on information from the Norwegian medical birth registry, the prevalence of DS among live births from 2010 to 2012 was about 1:900. In the same time period Trisomy 21 accounted for 20 % of all cases presented to the Committees considering abortions of fetuses more than 12 weeks of gestational age (131). Previous validation has shown that the medical birth

registry holds valid information regarding DS, as only 7.8 % of all diagnosed cases was not recorded in the registry (132).

Life expectancies for persons with DS have increased significantly and have influenced the population prevalence (18, 19, 133). This is illustrated by the positive development documented in Sweden where median age of death for a child with DS was 9.0 years in 1969-1979, which increased to a median age of 54.9 years in 1991-2003 (18). Currently there is no reliable estimate of the number of people living with DS in Norway. Estimates from other countries have reported prevalence in the range from 1:770 to 1:1640 (134, 135).

1.5.1.2 Characteristics of Down syndrome

The syndrome has characteristic physical and dysmorphic features already present at birth which makes it fairly easy to identify, and today diagnosis of DS for the vast majority is made in the neonatal period and confirmed by genetic laboratory analysis (132).

Table 1: Neonatal dysmorphic features in Down syndrome

1. Flat facial profile
2. Slanted palebral fissures
3. Anormalous ears
4. Hypotonia
5. Poor moro reflex
6. Dysplasia of midphalanx of fifth finger
7. Transverse palmar crease
8. Excessive skin at nape of the neck
9. Hyperflexibility of joints
10. Dysplasia of pelvis

Adapted from Ostermaier, 2013 (29).

People with DS may have a variety of birth defects. Congenital heart defects are common and found in about half of the children, with atrioventricular septal defect, secundum atrial septal defect, and ventricular septal defect as the most frequent features (107). Increased risk of congenital gastrointestinal abnormalities are present in about 7 % of the population, and include esophageal atresia, pyloric stenosis, duodenal stenosis or atresia, Hirschsprung disease, and anal atresia (136).

Most individuals with DS have cognitive impairment, although the range is wide. The cognitive profile in DS most often includes language comprehension equal to mental age and delayed development in language production (128). Weakness is described in verbal short-

term memory and explicit long-term memory, whereas visuospatial short-term memory and associative learning are usually preserved (137). Increased response time in shifting, flexibility of thoughts and action, is also described (138). Persons with DS have reduced risk of significant behavioral and emotional problems compared to those with ID of mixed or other etiologies. However rates of adaptive behavioral problems are increased compared to typically developed peers and includes co-occurrence of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (139). In adult age early-onset dementia that resembles Alzheimer's disease is described in relation to DS, with decline in memory, language and cognitive functioning, and individuals with DS over the age of 50 are at substantial risk (137, 140, 141).

At birth weight, length and head circumference are less in children with DS, and growth rate is reduced, resulting in lower final adult height. Diagnose specific growth charts are developed from several national cohorts (142, 143). However, these charts do not include weight for height charts and are therefore inadequate for monitoring of nutritional status.

A high risk of developing obesity is described in individuals with DS (49, 90, 91, 144). Reduced physical activity (36, 63), a reduced basal metabolic rate (145) and increased risk of subclinical hypothyroidism are described as underlying features (146).

Mitochondria are the cell structures that generate most of the cells supply of adenosine triphosphate, used in the cell as a source of energy. Defective mitochondrial function is described in DS, and is currently suspected to be involved in the increased risk of dementia, reduced muscle tone and low level of physical activity (83).

Sensory problems are prevalent in DS, and visual problems that require interventions affect the majority of the individuals (147). Hearing impairments are also common, with high incidence of conductive, mixed and sensorineural hearing loss (148).

DS is associated with a variety of immune deficiencies (149, 150). These are thought to be related to the increased susceptibility to autoimmune disorders such as thyroid autoimmunity manifested as hypothyroidism or Graves' disease, coeliac disease, type 1 diabetes, increased risk of childhood leukemia, and testicular cancer later in life (151-153). In Norway, 4.8 % of the children with DS born from 1999 to 2011 were diagnosed with coeliac disease (154).

The prevalence of atlantoaxial instability, a risk factor of spinal cord compression, is increased in DS and affects about 10 % of the population (155, 156). Participation in ordinary physical activities is not associated with adverse outcome for the affected individuals (157), however currently there is not enough evidence regarding safety of physical activities with high risk of spinal cord injury (158).

1.5.2 Prader-Willi syndrome

The syndrome was first described in 1956 and was originally named Prader-Labhart-Willi syndrome. From the 1990ies and forward most authors use the term Prader-Willi syndrome.

PWS is caused by lack of paternally expression of genes in the 15q11-q13-region. There are three main genetic mechanisms resulting in PWS. These are deletion, maternal uniparental disomy 15 (UPD) or a less common imprinting defect (159). Most cases of PWS result from a *de novo* deletion affecting about 65-75 % of the individuals with PWS (28). The PWS deletion is sometimes described to consist of two subclasses, type 1 and type 2 deletions, depending on the size and chromosomal breakpoint position. Type 1 includes a deletion of four non-imprinted genes that is present in type 2 deletion. More adaptive behavioral problems and obsessive-compulsive behaviors have been described in individuals with type 1 deletion when compared to individuals with type 2 deletions or UPD (160). However, other investigations have questioned if there are clinical differences between individuals with the two deletion types (161). The division of the deletion genotype into two subclasses is therefore currently controversial. UPD, a situation with two chromosome 15 from the mother and none from the father accounts for about 20-30 % of the individuals with PWS (28), and is associated with advanced maternal age (162). There are some known differences between the two main genotypes of the syndrome, where the deletion genotype, compared to UPD, is associated with increased frequency of hypopigmentation, typical facial appearance and skin-picking, higher pain threshold, and better visuo-spatial capacities (162, 163). The UPD genotype is described to have higher average verbal IQ but not performance IQ, less maladaptive behaviors, and increased risk of bipolar disorders, and psychiatric illness (164-167). Lastly, imprinting defect is reported in 1-3 % of the individuals with PWS and is a result of defects in the imprinting center leading to gene silencing in the chromosome 15 region (168).

1.5.2.1 Prevalence of Prader-Willi syndrome

The birth incidence of PWS has been reported to be 1:25.000-1:29.000 (169-171). However, there is a large diversity in studies on population prevalence of this condition. In one region of UK, Whittington and colleagues found a prevalence of 1:52.000 (171). From the Flanders in the Netherlands Vogels and colleagues reported a prevalence of 1:76.600 (170), whereas Grugni et al found a prevalence of 1: 134.000 in a national Italian investigation (172). All authors reported their findings to be minimum prevalence. Few subjects above 30 years of age were described in all reports, probably due to low identification rate in older persons, but also a result of high mortality rate. Increased risk of premature death is reported for persons with PWS, with a relative risk of 3.8 when compared to a multi etiological group of persons with ID (173). Childhood deaths are associated with respiratory infections, while causes of deaths in adults were described to be of mainly of cardiorespiratory origin (170, 172, 173). In Norway to date there has been no systematic investigation of the birth incidence or population prevalence of PWS.

1.5.2.2 Characteristics of Prader-Willi syndrome

PWS is a complex neurodevelopmental disorder. Hypothalamic dysfunction is linked to many of the endocrinological disturbances associated with the condition (174), although changes in other brain areas have also been observed (175).

Main clinical characteristics and clinical criteria previously used for diagnosis are shown in Table 2. Today the clinical criteria are used less rigid as a guide for selection of candidates for genetic investigations (163).

Table 2: Consensus clinical diagnostic criteria for Prader-Willi syndrome

Major criteria

1. Neonatal hypotonia
2. Feeding problems with poor weight gain/failure to thrive
3. Excessive or rapid weight gain or weight-for-length charts after 12 months but before 6 years of age
4. Characteristic facial features with narrow face or bifrontal diameter, almond-shaped eyes, small appearing mouth with thin upper lip and down-turned corners of the mouth
5. Hypogondaism with any of the following depending on age
    a. Genital hypoplasia
    b. Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention
6. Global developmental delay
7. Hyperphagia/obsession with food

Minor criteria

1. Decreased fetal movement or infantile lethargy
2. Characteristic behavioral problems with temper tantrums, violent outbursts and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative and stubborn; stealing or lying
3. Sleep disturbance or sleep apnea
4. Short stature for genetic background
5. Hypopigmentation
6. Small hands < 25^{th} percentile and/or small feet <10^{th} percentile
7. Narrow hands with straight ulnar borders
8. Eye abnormalities
9. Thick viscous salvia with crusting at corners of the mouth
10. Speech articulation defects
11. Skin picking

Supportive criteria

1. High pain threshold
2. Decreased vomiting
3. Temperature instability in infancy or altered temperature sensitivity in older children or adults
4. Scoliosis/kyphosis
5. Early adrenarche
6. Osteoporosis
7. Unusual skill with jigsaw puzzle
8. Normal neuromuscular findings

Adapted from Holm et al 1993 **(176)**

Reduced prenatal fetal activity is common, and hypotonia is a hallmark of the syndrome in the neonatal period. Together with poor suck and neonatal feeding difficulties these findings are important for early recognition and diagnosis of the condition. In a cohort of hypotonic infants 10.7 % was diagnosed with PWS by use of molecular genetic testing (177). Global

developmental delay, affecting both motor milestones and language development is, together with hypotonia, the most sensitive diagnostic criteria affecting >97 % of the children with PWS. The dysmorphological features were the least sensitive, and present in less than half of the persons with molecular verified diagnosis (163).

Most persons with PWS fall within the mild ID category, although some individuals are found with moderate ID, and 7-19 % is reported to have an IQ above 70, but with expressed learning difficulties (167, 178, 179). Relative cognitive strengths are described to be associative long-term memory, visual perception, reading skills, and especially the assembling of jigsaw puzzles. Weaknesses are described in relation to sequential processing, executive functioning, mathematical skills and social cognitive functioning (165, 179-181).

The syndrome is associated with a number of distinct behaviors and is therefore described to have a behavioral phenotype. Behavioral characteristics include a nearly universal excessive interest in food and overeating in the absence of food access restrictions (28). Obsessive traits are common and include hoarding, rigid and repetitive behaviors. Difficulties related to unexpected changes often result in temper tantrums or outbursts, and autism spectrum disorder is present in about a third of persons with PWS. Mood swings and self-harm, especially skin-picking are also frequently observed (161, 180, 182-184).

Persons with PWS have high risk of developing morbid obesity due to hyperphagia and reduced energy expenditure (84, 185, 186). The latter is mainly explained by altered body composition with reduced muscle mass and increased fat mass which leads to a reduced basal metabolic rate (187). Low levels of physical activity has also been recognized (82, 84), which reduce the energy expenditure even further. Fat mass is mainly located subcutaneously and is therefore associated with reduced adverse metabolic effects (188, 189).

The syndrome has traditionally been described to have two nutritional stages; poor feeding in infancy followed by hyperphagia which, in absence of energy restrictions, will lead to excessive weight gain and childhood onset of obesity (176). However more recent examination of the natural history of the condition suggests a more gradual and complex progression through five nutritional phases (190). The first phase is intrauterine with reduced growth and weight status. In the second hypotonic phase, post-delivery, the child has gradually resolving feeding difficulties and is not obese. In the third phase the child increases its interests for food and increase daily caloric intake. If total intake is not controlled, the child

will gain weight such that it crosses standardized weight-for-height percentiles. However in this phase the child is not insatiable and it is easy to control food intakes by use of scheduled meals. The onset of the fourth phase is quite variable and reported from 3 years to as late as 15 years of age. This is the classical phase that most people typically associate with PWS, with food seeking and manipulative behaviors to gain access to food, and with markedly reduced satiety. In the fifth phase, the individual may still have increased appetite but not as aggressively as previously seen. This phase occur only in a subset of individuals typically after 30 years of age.

In PWS, prevention and treatment of obesity is essential. Treatment is supportive and lifelong and includes regular physical activity in combination with a low-energy diet, together with detailed meal plans, rigorous food supervision, and restricted access to food (191, 192).

After birth short stature is present in most individuals with PWS and is due to a relative growth hormone deficiency. Growth hormone deficiency has been reported in 80 % of children with PWS (193). Today, most children with PWS in western-countries receive growth hormone treatment. Growth hormone therapy in PWS improves linear growth and increases final height, but more importantly improves body composition by lowering body fat percentage and increasing lean body mass (194-196). Improved physical functioning by improvements in neuromuscular strengths and motor development are documented effects of this treatment (197, 198). Systematic motor training in combination with growth hormone therapy showed even more pronounced effect on motor development than growth hormone treatment alone (197). There are further preliminary reports of improved cognitive development due to growth hormone treatment (199). Growth hormone treatment appears to change respiratory status in PWS, possible because of growth in tonsils and other lymphoid tissue in the respiratory tract observed shortly after introduction of treatment. Evaluation of sleep-related respiration status is therefore required prior to and shortly after starting treatment due to safety concerns (194). Scoliosis is prevalent in PWS. Currently there is no evidence from controlled investigations that growth hormone treatment increasing the prevalence of scoliosis (198). Monitoring of scoliosis is however recommended for all persons with PWS, regardless of growth hormone treatment (194, 195).

Positive effects is also described by use of growth hormone therapy in adults with improvement in body composition (82, 200), and a more favorable lipoprotein profile; with reduction of total cholesterol and LDL cholesterol, and increase in high density lipoprotein

(HDL) cholesterol (201). Growth hormone may possible have an adverse effect on glucose regulation with increased risk of glucose intolerance in adults (201, 202).

PWS is associated with hypogonadism manifested as genital hypoplasia and without intervention this will lead to incomplete pubertal development (28). Over the past years it has become clear that PWS is also associated with other endocrine disturbances. These include increased risk of hypothyroidism found in about 25 % of children with PWS (193), and increased risk of adrenal insufficiency. The latter was found in 60 % among a randomly selected group of children with PWS, and is possible linked to the increased risk of sudden death during infection-related stress (203, 204).

1.5.3 Williams syndrome

Williams syndrome (WS), or Williams-Beuren syndrome, was named by J. C. P. Williams who first described the syndrome in 1961 (205), and A. J. Beuren who published a report describing three new persons with the same presentation in 1962 (206). In the scientific literature both eponyms are used and imply the same genetic condition.

WS is caused by deletion of 26-28 continuous genes on chromosome 7q11.23 (27, 207). The genetic segment is flanked by genes clusters organized into low-copy repeat blocks, so called *duplicons*, which predisposes to unequal chromosome rearrangements (208).

The microdeletion in WS includes the ELN gene leading to insufficient production of elastin. Haplonsufficiency of elastin is linked to the connective tissue abnormalities and cardiovascular features associated with the syndrome (209). LIM Kinase 1 is another gene located in the critical region and is possibly involved in development of the unique cognitive characteristics (210)

1.5.3.1 The prevalence of Williams syndrome

The population prevalence of WS is in the literature often quoted to be approximately 1: 10.000. Currently there is only one formal investigation of the WS prevalence. Stromme et al found a prevalence of 1:7500, based on identification of four cases with WS in an investigation of children born 1980-1985 in Akershus county in Norway (211).

There is as paucity of data describing life expectancy in WS, although cardiovascular associated premature death is reported (212). One study based on a cohort of 293 persons with WS, found a 25-100 times higher risk of sudden cardiac death in the WS population compared to controls (213).

1.5.3.2 Characteristics of Williams syndrome

Reduced growth rate, developmental delay, combined with distinctive facial appearance, hypercalcemia, and stenosis of medium and large arteries are typical symptoms that can be observed in children with WS (27, 108, 214). Today diagnosis is usually made in infancy or early childhood by recognition of the characteristic features and is based on molecular testing (27).

Table 3: Main characteristic features of Williams syndrome

1. Short stature	Prenatal growth deficiency Failure-to-thrive in infancy Reduced growth rate
2. Connective tissue abnormalities	Typical facial features Hoarse voice Joint laxity early in life followed by joint contractures Premature aging of the skin
3. Intellectual disability	Global developmental delay Unique cognitive profile
4. Cardiovascular disease	Supravalvar aortic stenosis Pulmonary arterial stenosis Ventricular septal defects Hypertension
5. Endocrine alterations	Hypercalcemia Glucose intolerance and type 2 diabetes Hypothyroidism Early puberty

The facial features which ranges from discrete to distinct, consist of broad forehead, flat nasal bridge, short nose with a long philtrum, full lips, and a wide mouth (27). Later, small unusually shaped and missing teeth due to developmental failure may be observed (215).

ID with global developmental delay is observed in early childhood. An average IQ of 50-60 has been described, with an IQ range of 40-100 (216). WS is further described to have a

phenotypic cognitive profile with relative strengths in verbal abilities, especially concrete repetitive and expressive vocabulary, and strengths in facial processing skills combined with weakness in visuospatial construction (216-218).

The personality in WS is described to be friendly, empathic and social, and typically include involvement with unfamiliar people (219). Even so, individuals with WS have difficulties in social judgment, an inflexible and repetitive social repertoire, and therefore difficulties in making and keeping friends (218, 219). In addition, behavioral difficulties coexist and include ADHD found in a majority of children with WS. Hyperactivity is declining in adolescence but attention deficits persist (220). Specific phobias and fears are reported in 35-50 %, and sensitivity to loud, unexpected noises is described as the most frequent spontaneously reported fear (220, 221). Anxiety develops over time and generalized anxiety disorder is frequently observed in adulthood (221). In WS enjoyment and interest for music is nearly universal and increased emotional responsiveness to music is described (216).

Structural congenital cardiovascular abnormalities are found in about 80 % of the population, with the majority of this including some form of arterial stenosis (108, 209, 222). One or more stenosis may occur in numerous locations. The most common location is above the aortic valve, supravalvar aortic stenosis (SVAS) and found in about 70 % of persons with WS (108, 212, 222, 223). The severity of this condition ranges from trivial to severe. Isolated SVAS is a distinct autosomal dominantly inherited in families with point mutations in the gene, ELN. SVAS is rarely seen in persons without genetic mutations or deletions of the ELN gene (27). Pulmonary arterial stenosis is the second most common location of stenosis and is observed in about 40 % of the population (108, 212). In contrast to SVAS, pulmonary aortic stenosis often regresses or resolves with time (212, 223). Other locations of stenosis include aortic arch, coronary and renal arteries. Additional congenital heart abnormalities are also reported and include ventricular septal defects seen in about 5 % of persons with the condition (108, 212).

Increased vascular stiffness is present already in childhood and may lead to development of hypertension which is reported in 40-55 % of adolescents and young adults with WS (224, 225). Elastin insufficiency leads to reduced vessel recoil capability and is linked to vascular stiffness and increased risk of hypertension (226). In contrast, loss in functional copies of the NCF1 gene protects against hypertension, likely through a lifelong reduced angiotensin II mediated oxidative stress (226, 227). NCF1 is one of genes that are variably deleted in WS.

Screening for renal abnormalities is recommended in children with WS, as structural abnormalities of the kidneys and urinary tract are described in about 18 %. A variety of renal system malformation and conditions have been reported (228).

WS is also associated with episodes of hypercalcemia occurring sporadically in 5-50 %, but most frequently observed in infancy. Hypercalcemia is in general mild but can be moderate or severe, especially during infancy (229). Previously suggested, but unconfirmed mechanisms, include increased vitamin D sensitivity and increased 1,25–dihydroxyvitamin D levels (230). However, more recently increased digestive and renal calcium absorption is suggested and linked to the TFII-I gene in the 7q11.23-region (231). Treatment of hypercalcemia includes dietary restrictions of vitamin D and calcium, and some severe cases are treated with intravenous fluid and bisphosphonate administration. Gradual normalization to unrestricted diets is recommended in most cases, when hypercalcemia has been resolved (232).

Impaired glucose tolerance and type 2 diabetes are reported in 63-75 % of adult persons with WS. Even though a high prevalence has been observed in all weight categories increased prevalence was described in obese participants compared to lean participants with WS (229, 233). The syntaxin-1A gene and MLXIPL gene which are located in the critical WS-region is currently suspected to be involved in the abnormal glucose regulation observed (229). Mild thyroid hypoplasia is found in a majority of individuals with WS, and subclinical hypothyroidism is described in 15-30 % (234, 235).

WS is associated with short stature and final adult height is about 15 cm shorter than expected for genetic background (214). Diagnosis-specific growth curves have been developed based on a national cohort in Great Britain (236). At birth mean length is about 3 cm shorter than average. In childhood a 1-2 cm yearly reduced growth rate has been documented, followed by a relative catch up growth, due to early onset of pubertal growth spurt, typically occurring at age 10-11 in boys and age 9-11 for girls.

Increased risk of coeliac disease has been described in WS (27). However, this is controversial, as recent controlled investigations found no evidence of higher prevalence in coeliac disease and other autoimmune diseases (237).

Individuals with WS show mild neurologic dysfunction with delayed motor development and alternations in motor coordination, tone and gait function. Tone abnormalities vary as a function of age, with decreased tone prevailing in younger subjects and increased tone with

rigidity and contractures noted in some adult subjects (238). Later in life mild premature aging in skin and premature graying of hair is observed (27).

1.6 Need of new knowledge

Persons with ID are exposed to health inequality and there are currently few descriptions of the public health challenges related to specific subgroups. Furthermore, there is a paucity of data on lifestyles in subgroups associated with ID from the Norwegian health and support context.

High risk of obesity has been described for persons with mild to moderate ID in general and especially for persons with DS and PWS, but less explored in relation to WS. Physical activity and diet are important lifestyle factors that influence the risk of obesity and have the potential to affect short- and long term health. Currently there are few studies on diet and physical activity in relation to genetic conditions associated with ID.

Moreover, atherosclerotic cardiovascular disease (CVD) has been documented as an important cause of death also for persons with ID. Persons with ID represent a heterogeneous group and possibly also with variability in risk of developing CVD. To date descriptions of established metabolic risk factors of CVD in individuals with genetic syndromes and the possible association with obesity has not been much studied. Such information is valuable for development of tailored health checks and a personalized medicine approach in adult age for these individuals.

2 Study aims

The overall aim of this study was to investigate and describe lifestyle-related health risks in persons with DS, PWS and WS, 16-40 years of age, and by comparing these subgroups describe diagnosis specific vulnerabilities and common challenges.

The specific aims of the separate papers were as follows:

- To describe levels of physical activity and to investigate physical capacity in relation to BMI in the studied subgroups (**paper I**).

- To describe some overall food intake frequency patterns for persons living in community residences and explore this in relation to weight status. Moreover, to explore differences in food related autonomy and food intake frequencies between persons living with relatives and persons living in communities with support (**paper II**).

- To explore and compare the prevalence of metabolic risk factors of CVD, and the association between abdominal obesity and metabolic risk factors in the studied subgroups (**paper III**).

3 Methods

3.1 Ethical aspects and information to the participants

This study involves persons with cognitive impairments which represent vulnerable groups. In planning of the study, scientific methods providing as little discomfort as possible for the participants were selected. Emphasize was put in meeting the participants with respect, adjusted information and means to empower the individuals to be active and contributing in all parts of data collection. All test personnel involved in the study were professionals with experience of working with persons affected by ID.

The ethical approval for this study was granted by The Regional Committee for Medical and Health Research Ethics, Southeast Region. Simplified easy-to-read information about the project was developed for the participants and an ordinary information letter was developed for the parents and legal guardians. Informed written consent to participate was given by the participants and parent/legal guardian. Both versions of the information letter clearly stated that the participants at any time could withdraw from the study. In addition, to ensure that participation was voluntary all test personnel were instructed to respect both oral and physical signs of withdrawal.

In order to ensure that the participants had understood the implication of participating in the study, they were informed again about the methods to be used after arrival at the location, but prior to data collection. This was done in a plenary lecture using photos and demonstrations to explain the data collection procedures. In this session, both participants and their support persons were invited to ask questions. A short resume of the information was repeated by the test personnel for each individual at the beginning of all data collection situations. In addition, how to perform the six-minute walk test was showed in practise for all participants at the first walk test situation.

An individual letter with information about the results obtained from the clinical examinations and regular medical biochemical analysis was developed and sent by mail to all the participants. For participants less than 18 years of age a copy of the letter was sent to the parents, and for adult persons a copy was sent to the legal guardian. In the letter to all

participants with any result out of normal range contact with their general practitioner were recommended.

3.2 Study design and population

The thesis is based on a national descriptive cross-sectional study in persons with DS, PWS and WS. Persons with these diagnoses were from February 2012 to January 2013 invited to participate in the study. A convenient sampling frame was used. The inclusion criteria were diagnosis with DS, PWS or WS verified by standardized clinical methods or by laboratory genetic testing, age 16-45 years and returned consent forms signed by the participant and legal guardian/parent. In addition, to ensure safety and support needs of the participants, all attending participants had to come together with a parent or employed assistant.

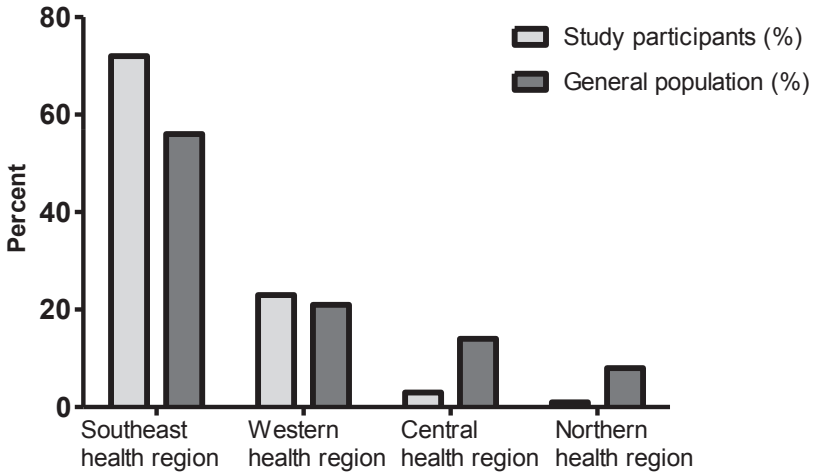
Participants were recruited from all over Norway using information about the study circulated in collaboration with the following nationwide patient organizations: The Norwegian Association for Persons with Developmental Disabilities, The National Association for Prader-Willi Syndrome, The Norwegian Association for Williams Syndrome, and The Norwegian Network for Down Syndrome. These organizations spread information through their information channels such as web-sites, member's bulletins, Facebook groups, and information brochures distributed by letter to members in relevant age-category. A study specific web-site, www.helseibolig.no, was also developed with the purpose of spreading information about the study. Informed consent form was posted and possible to download from the website.

A total of 104 returned a signed consent forms and a total of 96 participants took part in the data collection, after drop-out of four participants with PWS and three participants with DS. In two participants with PWS drop-out was due to withdrawal. In the remaining cases, drop-out was due to difficulties related to finding a support person with possibilities to travel and participate at the courses where data collection was performed.

In persons where molecular testing already had been performed, a copy of laboratory genetic test result was collected from the patient records at the genetic laboratory, and used as verification of the diagnosis. For person with clinical diagnosis and no previous genetic testing, or genetic testing performed with old genetic testing techniques, voluntary molecular testing was offered as part of the study. In the remaining cases with clinical diagnosis,

assessment of standard clinical criteria was used for verification of diagnosis. A total of nine participants were excluded from final analysis due to negative result of genetic testing and not fulfilling clinical criteria, with a result of 87 participants eligible for inclusion in final analysis.

Figure 1: Distribution of the study participants and the general population by health region



Participants from all four health regions in Norway participated in the study. Figure 1 display the proportion of the study participants and the proportion of the general population living in the different health regions (239).

In **paper I** the study population consist of 83 participants in the physical activity assessment and all 87 participants were included in the analysis based on the results of the six-minute walk tests. The drop-out in registration of physical activity was due to refusal to participate in this part of the study by two participants, medical safety concerns for one participant and lack of valid registration of activity in one of the returned accelerometers. In **paper II** the study population consists of 81 persons, as this paper only included persons with PWS and WS living in community residences with support. In **paper III** all participants ≥ 20 years old were included (n= 72). The selection was performed to facilitate a comparison of prevalence rates between the genetic syndromes and the general population. Data form the general population was based on a Norwegian cohort study (HUNT-3) (240).

3.3 Data collection

The data was, with the exception of daily physical activity, collected during seven two-day courses held from October 2012 to February 2013 at Frambu, a national resource centre for rare disorders in Norway. Frambu holds courses on a regular basis for different groups of persons with developmental and intellectual disabilities of all ages, their families and professionals from all parts of Norway. In total 10-15 study participants attended each course where data collection was conducted. The participants attended the courses together with a parent or employed caregiver.

At the courses the participants and their support persons were, in addition to taking part in the study, offered a program with different health, nutrition and activity oriented topics. The participants were invited to try out activities in practise such as; geocaching, fishing, digital photography and sports activities by use of the game console Nintendo Wii. Further, the program contained a voluntary group session lead by a dietitian with information and discussion about how to choose and prepare healthy foods. In this session the participants were invited to share success stories and good ideas with each other. Parallel to the program for the participants, parents and caregivers participated in a program covering relevant health promotion topics such as; medical management and good health support, adequate nutrition, and motivation for lifestyle changes in adult persons with ID. In the evening the participants and support persons were offered a social program with the other participants at the courses.

3.4 Measurements

3.4.1 Assessment of physical activity

Level of physical activity was assessed using the ActiGraph GT3X+ activity monitor (ActiGraph, Pensacola, FL, USA). The devise registers acceleration in units called counts, and samples data at a rate of 30 times per second in sampling intervals (epochs) of 10-seconds. The accelerometers were initialized and downloaded using the ActiLife software provided by the manufacturer of the monitors (ActiGraph, Pensacola, FL, USA).

To facilitate the possibility for comparison of results, the instructed wear time of the accelerometers and data reduction procedure was identical to a Norwegian population study

on physical activity in adults (241). The following outcome variables were derived; counts per minute (CPM), steps per day, minutes of intensity specific physical activity, and used in **paper I**.

The participants and their support person received information about the activity monitors and how to wear them during the courses at Frambu. In a plenary session the participants received a full charged activity monitor in an elastic belt, a prepaid return envelope, activity registration form and two reminder posters. At this session they were showed in practice how to wear the device, and how to take it on and off. They were further instructed to wear the device for seven consecutive days in their home environment during all waken hours, except during swimming or bathing. In this session, photos were used in combination with oral instruction. Parallel to wearing the device they were asked to record on a ready-made form activity during the data collection period involving swimming, bicycling, resistance training or skiing activities. A diary of these activities was chosen as they are frequently conducted activities in the Norwegian population, and if performed regularly and with some duration can lead to underestimation of the physical activity level when assessed by accelerometer registrations. To increase compliance all participants were given two reminder-posters and encouraged to hang them up in visible places in their own homes. The accelerometers were initialized to start recording activity the day after returning back to their home environment. Any wearing of the monitor from receiving the monitor to returning at home environment has therefore not been registered. The accelerometers were returned by mail together with the registration form of activities during the data collection period.

3.4.2 Physical capacity

Physical capacity was assessed by six-minute-walk test. The test was selected as it provides a global assessment of exercise capacity, and has been found to be feasible and reliable when used in individuals with ID (242, 243). The participants performed two six-minute walk-tests during the same day with a break in-between. The first test was regarded as training, and for all participants completing both tests (n=85), the results of the second test was used to determine walking capacity in **paper I**.

3.4.3 Clinical Examination

Body composition was assessed by use of simple clinical standardized direct measurement techniques. BMI was calculated using the standard formula (kg/m^2) and standard definitions was used to define normal weight, overweight and obesity in **paper I and II** (39). For WC, sex-specific cut points for Caucasians proposed by World Health Organizations were used to define increased and substantially increased WC and used as metabolic risk factors of CVD in **paper III** (39). In the study no formal assessment of scoliosis was performed.

Blood pressure readings were performed in accordance to recommendations for blood pressure measurements in research (244). The measures were performed by use of an upper arm automatic blood pressure devise with oscillometric measurement technique (Microlife BP A100 Plus, Microlife, Widnau, Switzerland). The Microlife BP A100 plus measurement device has been clinically tested for its accuracy and passed the validation procedure in accordance with the International protocol of the European Society of Hypertension (245, 246).

A multistep procedure was selected to reduce the possibility of false elevated blood pressure. First, participants were familiarized with blood pressure measurements and screened for differences in blood pressure between the arms on day one of the data collection. The next day, blood pressure was taken three times with one minute intervals in between, after at least ten minutes rest. Information of the prevalence of hypertension in **paper III** was derived with use of recommended definitions and cut-points (247), and was based on measured blood pressure in combination with information about current use of antihypertensive medication.

3.4.4 Questionnaire collected data

An electronic questionnaire was developed using the Questback software (Questback, Oslo, Norway). The questionnaire covered topics like demographic information, living arrangements and hours of support per week, education and main occupation. Medical information was also collected by use of the questionnaire, and questions covered current use of medication, previously diagnosis of cardiovascular diseases, and specific well known medical comorbidities such as type I and type II diabetes, coeliac disease, hypothyroidism, and hyperthyroidism. Furthermore, use of dietary supplements, intake frequency of selected

foods and alcohol, level of food related autonomy and smoking habits were also collected using the questionnaire.

The method was selected and adjusted to facilitate for the participants to be informants. Technical adjustments included; use of one question per screen lay-out, automatic routing through the questionnaire, and when the main theme of the questions changed, this was marked with illustrative pictures to prepare the participants of the new theme of the following questions. During development, the questionnaire was sent to the collaborating parent organisations and they were invited to give feedback about difficulty level of the questions. A justification in the language used in the question asking for the participants level of support was performed as a result of the feedback received form the patient organisations. To explore the feasibility of the electronic questionnaire, two voluntary persons with mild ID were invited to test answering the questionnaire before it was used in data collection. Both participants successfully completed the questionnaire.

In order to increase the reliability for the answers and to reduce the possibility of missing data, the participants and their support persons were prepared of the type of questions and main themes of the questions to be answered. They were also showed in practise who to manoeuvre in the questionnaire. The participants and the support person were specifically asked to bring with them a complete list of all medication used and information about total hour of support received per week, as these questions were regarded to be difficult to answer without specific preparations.

In the data collection session the participants were offered a laptop with the questionnaires directly available. The participants were put in front of the laptop with the support persons sitting beside. The data collection was supervised by one test personnel who assisted all participants with need of technical guidance and with formal or other questions about the survey.

Demographic data were used as background information in **papers I-III**. Moreover, the intake frequencies of foods, use of supplementation and food related autonomy were used in **paper II**. Information about medical use, previous diagnosis of cardiovascular diseases, and relevant comorbidities were together with biochemical and physical measures used to describe the prevalence of metabolic risk factors of CVD in **paper III**.

3.4.5 Biochemical measures

Venous blood sample was collected from the participant in the morning after overnight fasting. All participants were offered local anaesthetic skin treatment with prilocaine before the venous puncture. Tubes for plasma and serum were centrifuged within 2 h.

The specialised analysis of six plasma carotenoids and fatty acids in erythrocyte membranes in **paper II** were performed at a private laboratory with previous experience and standardized routines for performing such analysis (Vita AS, Oslo, Norway).

In **paper III** to describe metabolic risk factors of CVD relevant biochemical measures in blood was analysed. The clinical laboratory of the regional university hospital performed blood analysis in accordance with standard protocols. The prevalence of the metabolic risk factors were determined by use of cut-points and definitions published in clinical guidelines.

3.4.6 Other data

To supplement the data in **paper III**, the study applied for, received data and got permission to publish prevalence data of the metabolic risk factors of CVD from HUNT-3 in a comparable age-range. The HUNT study is a Norwegian longitudinal population health study. The HUNT-3 survey, which is the latest data collection in this study, was started in 2006 and completed in 2008 (240). The prevalence rates of metabolic risk factors of CVD in the included groups were compared to those from the HUNT-3 population, and reported in **paper III**.

3.5 Statistical analyses

In **papers I-III** descriptive statistics were calculated for all demographic variables and presented as mean with standard deviation (SD) or percent of population (%). Initially chi-square, one-way analysis of variance (ANOVA), and independent t-test were used to identify differences between the subgroups with respect to background variables.

In **paper I** linear regressions adjusted for age and BMI, where appropriate, were used to evaluate overall physical activity, intensity specific physical activity and results of the six minute walk test in the different groups.

In **paper II** ordinal categorical variables were dichotomized. Logistic regression models adjusted for BMI were used to investigate the association between proportions with low and high frequency consumers in the different food categories and use of omega-3 supplementation by diagnosis. However due to a zero cell, chi-square tests were used to investigate proportions with low and high intake frequencies of fish by diagnosis. Linear regression adjusted for BMI was used to investigate plasma carotenoids and erythrocyte fatty acids to detect possible differences between the subgroups. Selection of reference group in the linear regression models were based on initial analysis by use of ANOVA with Turkey post hoc test.

Chi-square tests were also used to investigate possible differences by weight status category in proportions with low and high food intake frequencies, and degree of participation in food related tasks. Pearson's correlation test was used to assess the association between BMI and biomarkers in the different genetic syndromes.

Finally, chi-square tests were used to investigate proportions with high- and low-frequency intake of foods, high and low degree of autonomy when living arrangements were compared for persons with DS. Mann-Whitney tests were used to investigate differences in measured biomarkers based on living arrangements.

In **paper III** the measured biochemical and physical values in the subgroups were compared by use of one-way analysis of variance (ANOVA), or, if normality was violated, by use of Kruskal-Wallis test. Chi-square tests were used to investigate differences in prevalence of risk factors between genetic subgroups. However, in prevalence of type 2 diabetes due to low numbers, Fishers exact test was used to compare the WS-group to the PWS-group only. Chi-square tests were also used when the association between abdominal obesity and metabolic risk factors was investigated. To compare the prevalence rates of the metabolic risk factors for the included subgroups to those of the general population, relative risk estimates were calculated for all three subgroups.

In **paper I and II** all statistical analyses were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA), whereas in **paper III** SPSS 22 were used. A p-value of less than 0.05 was regarded as statistical significant.

4 Summary of results

4.1 Characteristics of the participants (Papers I-III)

After evaluations of diagnosis by use of laboratory genetic test result or clinical criteria a total of 87 participants were eligible for inclusion in final analysis and formed the basis for the study populations of **papers I-III**. There is some variance in the total study population used in the separate papers, due to some difference in exclusion criteria. The main characteristics of the total study population are presented in Table 4. More females (n=54) than males (n=33) participated, however no significant difference in age, BMI or living arrangements was detected between the genders.

Table 4: Characteristics of Study Population by Diagnosis

	Down Syndrome (n=40)	Williams Syndrome (n=25)	Prader-Willi Syndrome (n=22)	P-values[b]
Genetically verified diagnosis (%)	80.0	72.0	95.5	0.034*
Age (years)	26.8 (7.5)	31.5 (6.2)	28.1 (7.5)	0.048*
Females (%)	62.5	64.0	59.1	0.94
BMI (Kg/m^2)	31.8 (6.5)	26.6 (6.5)	30.7 (6.2)	0.007*
Smokers (%)	0	4.0	9.1	0.17
Occupation				0.44
Student (%)	15	16	9	
Supported employment (%)	60	68	77	
Daycare attendant (%)	20	4	9	
Unemployed (%)	5	12	5	
Community residence (%)	60.0	84.0	90.9	
Years lived in community residence[a] (years)	7.33 (4.87)	9.38 (5.76)	8.47 (5.51)	0.44
Level of support in community residence[b]				0.020*
0 - 30 hours/week (%)	54.2	47.6	40.0	
31 - 60 hours/week (%)	20.8	23.8	10.0	
More than 60 hours/week (%)	8.3	4.8	45.0	
Level of support unknown (%)	16.7	23.8	5.0	

The data are presented as percentage of the population or as the mean (standard deviation).
[a]Based on community-dwelling participants only, n=32 for DS, n=21 for WS and n=21 for PWS
[b]P-values are derived by comparison of the diagnoses using chi-square tests and one-way analysis of variance (ANOVA).
*P<0.05

4.2 Paper I

In total 83 participants took part in assessment of physical activity and all 87 participants performed at least one six-minute walk test. Participants achieved a mean 6.2 days of valid accelerometer measured activity and a mean wear time of 13.9 h ± 1.4 h per day. On average the participants generated 294 counts per minute (cpm) or 6712 steps per day. Most of the day (63 %) was spent in sedentary activities. No difference in total activity was detected between the diagnoses. However a tendency of reduced activity level in the PWS group was noted, and was related to the reduced time in lifestyle activities observed in this group. Similarly, no difference in walking capacity was detected between the diagnosis groups.

Males were more active than females across all diagnoses, and accumulated a mean of 85 cpm or 2137 steps per day more than females. Furthermore, males walked longer (41.0 m) than females in the standardized six-minute walk test.

Adherence to physical activity recommendation was low, with only 12 % of the total population meeting the recommendations of daily thirty minutes or more of moderate-to-vigorous physical activity (MVPA) in bouts of 8-10 min.

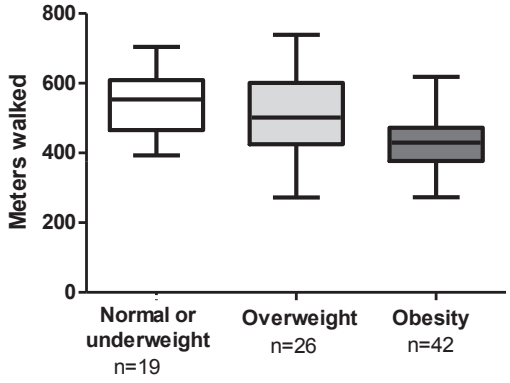
Table 5: Adherence to physical activity recommendations by diagnosis

	Down Syndrome (n=38)	**Williams Syndrome** (n=24)	**Prader-Willi Syndrome** (n=21)
Males (%)	7.1	22.2	25.0
Females (%)	8.3	6.7	15.4

The relation between body weight and physical activity and walking capacity was investigated by the BMI-derived categories; normal or underweight, overweight, and obesity. No association between total physical activity and BMI were detected. However, normal and underweight participants spent more time in sedentary activities, and obese participants engaged less time in MVPA.

The mean distance walked however decreased with increased BMI-category, as shown in Figure 2. Participants with overweight walked an average 33.6 m shorter than normal and underweight participants. Moreover, participants with obesity walked an average of 78.1 m shorter than participants with overweight.

Figure 2: Six-minute walking capacity in relation to body mass index



4.3 Paper II

In the first part, proportions with high and low food intake frequencies and measured biomarkers related to food intakes were investigated and compared among community-dwelling participants with the genetic conditions (n=65), and in relation to weight status. In the second part, food related autonomy, food intake frequencies and measured biomarkers were compared between participants with DS living in community residence (n=24), and participants with DS living with relatives (n=16).

Daily fruit consumption was recorded in 70 % of participants with PWS, 33 % of participants with DS and 15 % of participants with WS. Daily vegetable consumption was found in 85 % of the PWS group, 29 % in the DS group, and 20 % in the WS group. Comparing the diagnoses, a significant larger proportions in the PWS group were high frequency consumers of fruits, and vegetables. Furthermore, higher total carotenoid levels in plasma were measured in the PWS group compared to the WS group and the DS group. In WS, a larger proportion was low frequency consumers of fish, and fewer used omega-3 fatty acid supplements. Supporting these findings reduced contents of long chained omega-3 fatty acids were measured in the erythrocyte membranes of persons with WS compared to the two other groups.

Normal weight- and overweight participants with DS and PWS were more likely to be high frequency consumers of fruits compared to obese peers. In addition, a negative association between BMI and measured total plasma carotenoids were observed in these two subgroups,

however this association was only significant for participants with DS. In contrast, the lowest concentrations of plasma carotenoids were detected in persons being underweight or in the lower end of normal BMI range among participants with WS.

Persons with DS living in communities participated more often in decisions of what to eat, groceries to buy, and preparations of warm meals, when compared to peers living with relatives. No differences in intake frequencies of fruits, vegetables, fish, and use of supplementations or measured biomarkers were detected when persons with DS living in communities were compared to those living with relatives. However, a larger proportion in community residences was found to be high frequency consumers of precooked meals. Moreover, a non-significant tendency towards increased proportion with high frequency consumption of soft-drinks was observed among the community-dwelling participants with DS.

4.4 Paper III

All study participants >20 years of age were included (n=72) and established metabolic risk factors of CVD assessed. The prevalence rates in the included subgroups were compared to those in the general Norwegian population, based on data from about 14.000 participants age 20-43 years in the HUNT-3 study. In addition, the association between abdominal obesity and the CVD risk factors were investigated in the included subgroups.

Hypercholesterolemia determined by use of total cholesterol and LDL cholesterol, was found among 40 % with PWS, 19.4 % with DS and 14.3 % with WS. No differences in increased total cholesterol were detected when compared to the general population. In WS, better blood lipid profile was observed when measured levels of HDL cholesterol, apolipoprotein A1 and apolipoprotein B were compared to those of participants with PWS and WS. Furthermore, no participants with WS were found with total cholesterol: HDL cholesterol ratio > 5, in contrast to 40.0 % in the PWS group, 32.3 % in the DS group and 20.6 % in the general population.

A very high risk of hypertension was observed in the WS group (52.4 %), and with an almost five times higher risk when compared to the general population. High risk of hypertension was also observed in the PWS group (30.0 %), with 2.8 times increased risk compared to the general population. No participants with DS were found with elevated blood pressure.

Metabolic syndrome was observed in 25.0 % with PWS, 19.4 % with DS and 14.3 % with WS. No difference was observed when compared to the general population, where the prevalence rates of metabolic syndrome was 23.2 %.

Type 2 diabetes was found in 15.0 % and 14.3 % with PWS and WS, respectively. The risk of type 2 diabetes was found to be about three times higher in these groups compared to the general population. Low prevalence of type 2 diabetes was recorded in the DS group.

Increased WC was observed in 71.4 % of participants with WS, 80.6 % of participants with DS and 90.0 % of participants with PWS, but only significantly increased among participants with PWS and participants with DS, when compared to the general population. Abdominal obesity was prevalent and increased in all three subgroups when compared to the general population. Abdominal obesity was furthermore associated with increased risk of hypertension and metabolic syndrome. WS was the subgroup with the largest mean increased in systolic and diastolic blood pressure when the persons with abdominal obesity was compared to those with normal and increased WC.

The high risk of hypertension, type 2 diabetes, and abdominal obesity in the PWS and WS groups, provides these subgroups with elevated risk of CVD. In DS, despite the high risk of abdominal obesity, reduced risk of CVD were noted.

5 Discussion

5.1 Methodological considerations

5.1.1 Study populations

In studies with focus on lifestyle related health and open invitations to participate, there is a possibility for selection bias towards participants with higher level of health consciousness and participants living in more health conscious environments. On the other hand, data collection was performed in courses with focus on providing both the participants themselves and their caregivers with information about how to improve lifestyle in these populations. This may have led to recruitment of persons with challenges related to lifestyle. In studies from the general population, information about socio-economical and educational level are demographic variables often used to investigate and describe study populations with regard to overall health status and health consciousness (17). In populations with ID however such approach is invalid, as most persons are offered specialised high school program and thereafter supported employment with disability allowance as their primary source of income. In Norway, the local municipalities are responsible for the disability services as stated in the *Health and Care Service Act*. The national legislation further states that all persons with disabilities have the right to be provided with support services to ensure adequate living situations and health. However, there is variability in how the services are organized and distributed between municipalities. This makes it difficult to find a common robust variable that could imply the overall level of environmental health conscious in-between the participants.

A strength of the study was the national wide recruitment and high participant rate from the known Norwegian population of persons with PWS and WS. Unfortunately, in a national perspective an overrepresentation from the southeast health region combined with underrepresentation of participants from the central and northern part of the country occurred.

No formal assessment of cognitive functioning was performed in this study and is a limitation as this makes it difficult to determine if the participants were representative for their respective diagnosis in cognitive reasoning and overall cognitive functioning. In general, most persons in the study populations cooperated well in all data collection situations. This

observation may at least partly be explained by the repeated adjusted information prior to data collection, but may also indicate reduced levels of adaptive behavioural difficulties in the study populations.

Drop-out in the study was low. A few participants (n=6) had difficulties in finding a support persons with the possibility to accompany them in the travel and data collection. No further investigations of these participants were conducted. In addition, prior to data collection two persons with PWS withdrew from the study. This was not surprisingly as PWS is associated with mood-swings and emotional difficulties related unfamiliar situations (182). Furthermore, lack of valid accelerometer registration in the physical activity assessment was noted in four cases. A part form this, in all other measures complete datasets were obtained.

5.1.2 Study design

The cross-sectional design of the study in this thesis prohibits the possibility to assess causality. Longitudinal studies would be preferable for investigation of the role of different lifestyle factors in relation to relevant health outcomes. However, cross-sectional studies are, if conducted with sufficient accuracy, well suited for descriptive investigations, obtaining prevalence data and for generalization of hypothesis (248).

A major strength of this thesis was that the investigations were performed in specific subgroups rather than studying persons with ID as a homogenous group. Investigations performed on populations of mixed ID, do not take in to account the differences in behaviors and biological basis of the different conditions. For these reasons, investigations of persons with mixed groups of ID likely will face difficulties in identifying health risks associated with the specific conditions. Especially, when the behavioral phenotypes or biological pathways related to the health issue may be changed as a result of the genetic makeup of the syndrome. In this study we observed differences in intake frequency of foods reported in **paper II** that may be related to behavioral phenotype. Moreover, in **paper III** we observed clear differences in cardiovascular risk profile that are likely related to the genotype.

Self-reported methods are in general considered to be associated with bias. Because of the cognitive impairments this is an even larger concern in the present study populations. The use of proxy-reported measures also has important limitations in adult persons with ID living independently in communities and many hours a day without support. For this reasons the use

of objective measures were regarded as preferable when feasible in the study. Furthermore, the participants themselves were selected as informants when self-report measures were used. This decision was based on the assumption that the overall level of ID was similar in the included subgroups and that proxy-report from a mix of parents and employed support persons were especially difficult. Good preparation of the participants with information and training, together with adaptation and simplification of methods were performed to adjust the methods to the abilities in the study population. Even so, the lack of formal investigation of cognitive functioning in the study population is a weakness, as the cognitive abilities may have been different between the compared subgroups. This is a concern in general and especially in **paper II** where self-reported measures of intake frequencies and food related autotomy were used. However, to support these data, biomarkers in blood related to dietary intakes were measured and good agreement between the self-reported intake frequency and measured parameters was obtained. Such a combination of two different methods strengthens the data and facilitates conclusions.

A challenge in studies on subgroups with ID is the use of proper control groups. In all papers, **papers I-III**, the included syndromes were compared with each other without formal control groups. In addition, in **paper I** the results were compared to a recent large Norwegian epidemiological study on physical activity in adults (241). The use of identical study protocols is a strength in this comparison. In **paper III** prevalence data from the HUNT-3 study was used as comparison. Even though there were some differences in available measures and methodology between our study and the HUNT-3, this comparison add important information about the CVD risk profiles in the genetic syndrome. Unfortunately, it was difficult to find relevant and comparable data on the food intake frequency data in **paper II**. The simplified methodology used, to adjust to the cognitive impairments in the included groups, lead to methodological differences and difficulties in comparison of the result from the sturdy population to those in the general population. The results were therefore only discussed in relation to relevant findings from the general population. In addition, to the best of our knowledge, no formal assessment of dietary intakes in adults with ID has previously been conducted in a Norwegian research setting, hampering the possibility to compare the result to a population with ID of mixed etiology. These results must therefore be regarded as preliminary.

5.1.3 Statistical considerations

The insufficient number of participants in this thesis gives the study low statistical power and could have led to erroneous p-values, not detecting differences between the subgroups when there actually is a difference (type II error). In sample size calculations performed as part of preparation to the study at least 120 participants ideally should have been recruited, equally distributed between the diagnoses. However, with a population of only 5.1 million persons to recruit from and working with rare diagnosis with increased mortality rates, we were not able to recruit this number of participants.

Strategies to increase the possibility to describe the differences such as collapse of categories as performed in the ordinal variables **paper II**, led to loss of precision in the measured food intake frequencies and description of food related autonomy.

Moreover, in **papers I-III** normal and underweight participants were collapsed with participants presented with overweight or increased WC and compared to participants with obesity or abdominal obesity, respectively. This analytic strategy were performed due to low number of participants in the normal range, but may have led to an underestimation of the association with excessive body fat mass.

Finally, in **paper III** the analysis comparing the diagnosis groups were not corrected for differences in age and living situations as such statistical correction requires a sufficient number of participants. Even so, the crude description of prevalence rates for the different CVD risk factors likely provides important knowledge of the future risk of CVD in these genetic conditions regardless of the comparison between the diagnosis groups.

5.2 Discussion of results

Unfortunately, persons with ID are often excluded from national surveys and research aiming to describe and improve the public health. The increased longevity in persons with ID (18, 19) warrants increased focus on health promotion also in these groups. To the best of our knowledge the study in this thesis is the first study from a Norwegian health and care context to assess lifestyle and related health issues in specific genetic conditions associated with ID. Thus, the thesis provides new knowledge about lifestyle and related health challenges in the subgroups studied.

5.2.1 Major lifestyle related health risks

It is now well documented from diverse cohorts that overweight and obesity is a major public health concern among persons with ID (34, 47, 55-57). Our study confirms the high risk of obesity as a common health challenge in all three subgroups, and highlights a need for interventions to reduce obesity. It has been recognised that DS and PWS may be at particular risk of obesity (28, 49), but previously not described to any great extent in relation to WS. Interestingly, WS seems to be a condition with a dual situation related to body weight. Obesity was the prevailing problem but underweight was also detected in WS, which fits well with the data providing evidence of increased prevalence of underweight in adult persons with ID compared to the general population (47, 57). No gender differences in overweight and obesity were detected in the study population, and were in contrast to several previous reports where females with ID were found to present higher rates of obesity (54-57).

Diets and physical activity are important in relation to obesity as both factors influence the body's energy balance. More documentation on diets and physical activity, and facilitators and barriers affecting these lifestyles are therefore important for our understanding of why the groups are at particular risk of developing abnormal body weights. The overall physical activity in the study population was lower when compared to the general population, and especially low activity levels were noted in females in the study population compared to females in the general population (241). Reduced levels of physical activities in females with ID when compared to male peers have also been described previously (36, 54, 69, 70). Furthermore, low adherence to physical activity recommendations was detected, indicating sedentary lifestyles for a majority in the included groups, as documented for persons with ID in multiple studies from other countries (36, 54, 66, 249).

The actual level of physical activity is however more difficult to compare between the different studies due to methodological differences also in studies using objective measurement techniques. These include some studies with pedometers (65, 66), whereas others use accelerometers (36, 70), providing differences in outcome measures. Different data processing procedures are also being used making comparisons, for example between our study of physical activity and that of Phillips and colleagues difficult (36). In addition, physical activity recommendation differs between countries and must be kept in mind when comparing the proportions meeting physical activity recommendation in the different studies. Even so, Peterson and colleagues investigated physical activity in community-dwelling

persons with mild to moderate ID, and found a mean of 6508 steps/day among their participants (66). In a Swedish intervention study with aim of promoting healthy lifestyle in a mixed group of persons with ID, a mean of 6296 steps/day was observed in the control group (55). These results were close to the mean of 6712 steps/day observed in our study population. In the intervention group of the Swedish study, a mean of 8042 steps/day was recorded providing promising evidence of increased physical activity after health promoting intervention in persons with ID (55). Other studies in groups of persons with ID have also found that interventions can result in higher levels of physical activity and improved physical fitness (250).

No association between BMI and overall physical activity was detected in our study and this was in contrast to finding from the general population (251). Hence, supporting the notion that unique barriers to physical activity may exists for the included groups (71, 75-77, 252). Even so, reduced time in MVPA was noted in obese participants and in accordance with previous descriptions (70). The reduced time in MVPA also fits well with the reduced physical capacity observed with increased weight. These findings point towards the important discussion about how obesity affects everyday life in persons with ID, and the fact that reduced cardiorespiratory capacity may lead to reduced abilities to participate in society and increased support needs (253). Overall the results warrants increased focus on promoting physical activity in the subgroups, and imply that specific strategies for females are needed.

In general, few descriptions of diets in adult persons with ID living in communities exist, and prior to the dietary assessment performed as part of this thesis, no description of diets involving adult persons with WS were found in the literature. The low numbers of studies are probably related to the lack of validated dietary assessment techniques for use in adult persons with ID living in communities (88). New methods with use of digital photography, use of web-based dietary assessments, as well as the field of nutritional biomarkers are evolving (87, 94, 95, 97, 100). This is promising and has the potential to provide us with more data with improved quality in the future. Even so, these methods still needs further validations before a standardized dietary assessment technique is developed for use in adult persons with limitations in cognitive abilities.

In DS and WS relative few participants consumed fruits and vegetables daily, providing evidence of intakes below recommended levels, and that increased intakes can be

recommended in these subgroups (254). The low intake of fruit and vegetables observed was in line with previous descriptions in persons with ID (35, 37, 90, 92, 93, 104).

In DS, a negative association between BMI and measured total plasma carotenoids was observed. Furthermore, normal weight- and overweight participants with DS and PWS were compared to obese more likely to be high frequency consumers of fruits. From adults with ID high frequency of snack meals has been reported and high intakes of energy were reported in these meals (93). In a recent publication snack meals were the main contributing meal for fruit intakes in the general Norwegian adult population (255). Altogether these findings may indicate that more frequent use of fruits in snack meals could result in reduced energy intake and more favourable weight outcome in adult persons with DS and PWS. Unfortunately, this hypothesis cannot be answered by the data obtained in the study but should be evaluated in future research.

Low intake frequencies of fish was observed in a majority of persons with WS combined with less use of omega-3 fatty acid supplementations, and reduced omega-3 fatty acids found in their erythrocyte membranes. This implies that persons with WS may have an elevated risk of suboptimal intakes of essential omega-3 fatty acids and low dietary intakes of vitamin D. The results obtained indicate a need for further evaluation of nutritional intakes among adults with WS.

It is a paradox that the PWS group, the subgroup with the best described and well known dietary challenges (191), was found to present the most favourable dietary intake pattern. The findings illustrate the importance of good descriptions of dietary vulnerabilities associated with specific subgroups and the use of targeted methods, management and support to achieve defined goals.

It has been recognised that living arrangements for adults with ID affects the risk of developing obesity and secondary health conditions, and that living in less structured environments are associated with increased risk (56, 121). Less attention however has been on evaluation of dietary intakes in relation to autonomy. Increased food related autonomy was not associated with differences in intakes of fruits, vegetables and fish. In our study however increased consumption of precooked meals and a tendency of increased intakes of soft drinks were observed. The frequent use of precooked meals implies that persons with ID and their caretakers need to be given guidance in how to find and select healthy precooked meals. This

as high energy and sodium intakes combined with low intakes of essential nutrients may be consumed with if unhealthy meals are selected. Furthermore, it is important to ensure that the uses of these meals are voluntary and not forced due to lack of support, as such practice would be a violation of the right to self-determination. High intakes of soft drinks have been recognized in previous descriptions, and high intakes were associated with increased risk of obesity (57, 93). We did not detect an association between frequency of soft drink consumption and BMI. However in our study we did not differentiate between sugar-sweetened soft drinks and artificially-sweetened soft drinks. We believe, in light of current policy, that there is an urgent need of further evaluation on the conflict between self-determination and diet quality. This could promote a constructive discussion about how to provide good health promoting support for persons with ID.

5.2.2 Relationship between genotype and risks of atherosclerotic cardiovascular disease

Specific genetic syndromes associated with ID most often present distinct patterns of medical complications and comorbidities as has been described for all three genetic conditions included in this study (27-29). Comorbidities present at birth or developing early in life is currently best described. The risk of developing secondary health conditions, such as CVD, in adulthood, and related to aging, is less well described in different genetic syndromes, especially in rare genetic conditions (256).

The relationship between the presence of CVD risk factors and hard end points like CVD events or death has not been extensively studied in adults with ID, let alone in small subgroups. Yet, similar rates of CVD death were reported among persons 50 years old or older with ID (122), and CVD was recognized as an important cause of death also for persons with ID (24). Until further studied, it seems reasonable to assume that the presents of known risk factors are accompanied by increased risk of CVD, also for subgroups associated with ID.

In this study we detected a distinct difference in metabolic risk profile between the subgroups, with elevated risk for development of CVD in the PWS group and the WS group, and low risk of CVD noted for the majority of participants with DS. These results are supported by the high cardiovascular-related premature deaths reported in the PWS and WS groups (172, 213), and the reduced risk of atherosclerosis described in DS (123).

Some of these measured differences in CVD risk between the diagnoses are likely related to genetic alterations found in the respective condition. From a genetic point of view, hemizygosity due to a deletion in the WS- critical region are accompanied with high risk of congenital structural cardiovascular abnormalities (108, 209, 222). Moreover, increased risks for development of major CVD risk factors later in life, such as hypertension and type 2 diabetes are also recognized (226, 229, 233). Our study confirms the elevated risk of hypertension and type 2 diabetes. However we also demonstrated an association between hypertension and abdominal obesity which emphasize the importance of integrating proper medical treatment with lifestyle interventions to reduce body weight for individuals with obesity in this subgroup. In PWS the lack of parentally active genes in the q11-q13 region on chromosome 15 leads to alternation in neuronal development and are accompanied by a distinct behavioral phenotype (28). Central in this is the hyperphagia which, if not externally controlled, lead to development of morbid obesity early in life (191). The more recently described complex endocrinological situation associated with the syndrome (188, 193, 203), is also likely to influence the risk of developing secondary conditions such as CVD later in life (257). In DS the reduced risk of atherosclerosis and hypertension is recognized, but the biological mechanisms behind are currently not described, but are most likely connected to the genetic basis of the diagnosis. Lower levels of homocysteine due to higher dosage of the gene, cystathionine beta synthase, have been suggested to contribute to the reduced development of atherosclerosis (126), but a causal relationship between homocysteine and CVD has not been established. Reduced risk of CVD seems to be the prevailing situation among individuals with DS, although it must be emphasized that not all persons present a low CVD risk profile. In our study metabolic syndrome, unfavorable blood lipid levels, and high prevalence of abdominal obesity were detected also in this subgroup. These finding are supported by a Swedish cohort study, where atherosclerosis was reported to be the cause of death among 7 % with DS (18).

The most common risk factor presented was abdominal obesity and linked to increased risk of other important risk factors of CVD as well documented for the general population (40). The second most prevalent risk factors found was hypertension, with an almost five times increased risk observed in the WS group, and almost three times increased risk seen in the PWS group. From the general population hypertension is recognized as major risk factor of ischemic heart disease, heart failure, stroke and renal disease. Moreover, the relationship

between blood pressure and risk of CVD events is continuous, consistent, and independent of other risk factors (247). In persons with hypertension healthy diet, weight control, and regular exercise is recommended (258). In the general population randomized trials have shown blood pressure lowering effects of increased fruit and vegetable consumption combined with reduced intakes of sodium (259). Increased intakes of fruits and vegetables are highly relevant in light of the low frequency intakes observed, especially among a majority of participants with WS. In contrast to most other nutrients, sodium in foods is primarily added in preparation or preservation. The frequent use of precooked meals described in persons living in community residences, may therefore be accompanied by high intakes of sodium. This implies that an evaluation of the total dietary intake of sodium from diets of persons with ID living in communities may be important, especially if diagnosed with hypertension.

Elevated prevalence rates of type 2 diabetes were observed in the PWS group and a clear tendency of increased risk was also seen in the WS group. Diabetes mellitus is a powerful risk factor of CVD in the general population (260, 261), and most likely also in persons with ID. Moreover, type 2 diabetes in itself is serious medical condition that influences everyday life for persons affected, and with potentially severe complications related also to other organ systems. Diabetic complications like micro- and macro vascular, nephropathy, neuropathy and retinopathy are strongly influenced by glycemic control (262-264). To obtain glycemic control, the individual have to combine information from nutritional intakes, level of physical activity, and glucose-lowering medical treatment. This is a complex task, especially for persons with cognitive limitations. Poor glycemic control has been reported in 52 % from a cohort of persons with ID and diabetes. Furthermore, increased risk of emergency admission due to diabetes related health complications were described in this group of adults with ID (265). To reduce the risk of diabetes associated complications good support for optimal diabetes management is therefore essential for the persons affected. In additions, health promoting initiatives to reduce the risk for development of type 2 diabetes are important, especially in high risk groups like the PWS group and the WS group. Again, such health promoting initiatives points towards the importance of preventive strategies and programs for weight reduction, increased physical activity and healthy diets to achieve such goal.

6 Conclusions

In all three subgroups we observed reduced levels of physical activity when compared to the general Norwegian population, and low adherence to physical activity recommendations. Especially low levels of activity were noted among females. No association between total physical activity and BMI was noted, however BMI was strongly associated with reduced physical capacity. Thus, indicate that the high rates of obesity observed may increase the individuals support needs and affect the person's abilities to participate in society.

Low intake frequency of fruit and vegetables was observed in a relative large proportion of persons with WS and DS. Furthermore, we found low intake frequencies of fish among the majority of individuals with WS, and a reduced proportion using omega-3 supplementation when compared to the two other subgroups. The results based on reported intake frequencies were supported by the measured biomarkers. Altogether, WS was found to be a nutritionally vulnerable group with both abdominal obesity and underweight detected, combined with reduced dietary quality.

When compared to living with relatives living in communities was accompanied by increased food related autonomy, but no difference in proportions with high and low intake frequencies of fruits, vegetables and fish. However a larger proportion with frequent consumption of precooked meals and indication of increased proportion with high intake frequency of soft drinks could be demonstrated. To increase diet quality, the latter may represent important areas to address in health promotion for persons with ID.

Abdominal obesity was the most prevalent metabolic risk factor observed and common in all three subgroups. In additions, an association between several important risk factors of CVD and abdominal obesity was observed, as previously recognized from the general population. Apart from this, a clear diversity in risk of CVD was observed between the genetic subgroups. The PWS and WS groups were found to present elevated risk, as high prevalence of several important metabolic risk factors of CVD was observed in these groups. The DS was associated with low risk of CVD, although not totally risk free.

To reduce the health inequality there is a need of diagnosis and gender adjusted strategies to promote public health in the studied genetic subgroups. Such health promotion should emphasise preventive strategies to avoid unhealthy weight gain, programs for weight

reduction, and improvements in lifestyle. Furthermore, development of tailored diagnose-specific health checks is needed to ensure optimal health outcome among adults with these genetic syndromes.

7 Future perspectives

For persons with genetic conditions associated with ID still there is a need for more knowledge of the developmental courses of secondary health complications related to lifestyle in adult age and in relation to aging. Ideally, such studies should be prospective in order to describe causal relationship. Improved recognition of secondary conditions that have a basis in genetics and lifestyle, and subsequent application of appropriate interventions to modify health outcomes in these genetic syndromes have the potential to reduce the described health inequalities.

There is a need for further development of dietary assessment techniques for use in adults with ID. Persons with ID are nutritionally vulnerable and new tools will be valuable in monitoring diets and measure effects of health promotion interventions aiming to increase the diet quality. The current legal and political view emphasizes equality, self-determination, participation and integration for persons with ID. Indeed, this is a positive development for the persons affected. However, in order to develop good support models integrating the right to self-determination with health promotion, there is an urgent need for more knowledge on how self-determinations influence levels of physical activity and dietary intake patterns.

Females with ID have lower median life expectancy when compared to males and the most years of life lost compared to the general population (24). Females with ID seem to be less engaged in physical activities when compared to male peers (36, 69). Furthermore, increased risk of obesity is described in females with ID (55-57). Altogether this point towards an important gender perspective which should be addressed in future interventions aiming to improve public health in persons with ID.

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Papers I-III

I

Research in Developmental Disabilities 34 (2013) 4395–4403

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Accelerometer-determined physical activity and walking capacity in persons with Down syndrome, Williams syndrome and Prader–Willi syndrome

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ARTICLE INFO

Article history:
Received 2 August 2013
Accepted 10 September 2013
Available online 18 October 2013

Keywords:
Accelerometer
Physical activity
Six-minute walk test
Down syndrome
Williams syndrome
Prader–Willi syndrome

ABSTRACT

In this study we describe by use of accelerometers the total physical activity (PA), intensity pattern and walking capacity in 87 persons age 16–45 years with Down syndrome (DS), Williams syndrome (WS) and Prader–Willi syndrome (PWS). Participants were recruited from all over Norway, and lived either with their parents or in community residences with support.

On average the participants generated 294 counts per minute (cpm) or 6712 steps per day, with most of the day spent in sedentary activity, 522 min/day, followed by 212 min/day in light PA, 71 min/day in lifestyle activity and 27 min/day in moderate-to-vigorous physical activity (MVPA). Inactivity was prevalent, as only 12% meet the current Nordic recommendations for PA.

When compared, no differences for total physical activity or time in MVPA were observed between the three groups. However, participant with DS spent a mean of 73 min/day less and 43 min/day less in sedentary activities compared to participants with PWS and WS, respectively, ($p = 0.011$, 95% CI: −10.9; −80.1). In addition the DS-group spent a mean of 66 min/day more in light PA than the PWS-group and 41 min/day more than the WS-group, ($p < 0.001$, 95% CI: 29.3; 79.7). Participants with PWS spent on average 30 min/day less in lifestyle activities compared to both participants with DS and WS, ($p < 0.001$, 95% CI: −14.2; −45.4). No association between total PA and BMI were observed. Males were more active than females across all diagnoses. Males accumulated on average 85 counts per minutes more than females, ($p = 0.002$, 95% CI: 33.3; 136.7), 2137 more steps per day, ($p = 0.002$, 95% CI: 778; 3496). The mean walking capacity during six-minutes was 507 m (SD 112 m) for males and 466 m (SD 88 m) for females. Distance walked during testing decreased with 33.6 m when comparing normal or underweight participants to overweight participants, and 78.1 m when comparing overweight to obese participants ($p < 0.001$ 95% CI: −40.4; −85.8). When adjusted for BMI no differences in walking capacity between the three genetic conditions were observed.

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0891-4222
http://dx.doi.org/10.1016/j.ridd.2013.09.021

1. Introduction

Regular physical activity (PA) and physical fitness improves functional ability, enhances independence and reduces the risk of non-communicable disorders such as cardiovascular disease, diabetes and several cancers (Nordic Council, 2005; WHO, 2010). The effectiveness of PA in relation to health depends on frequency, duration and intensity of activity, and is inherently difficult to assess due to its complex nature (Westerterp, 2009). Objective assessment of activity using activity monitors overcome many of the challenges related to self-reported measures of PA, such as social desirability bias and recall bias. Thus, accelerometers provide valid and reliable estimates of the degree, nature, and pattern of physical activity (Westerterp, 2009).

Walking capacity is a measurement for everyday physical capacity and cardiovascular fitness and is related to both levels of independence (Cowley et al., 2010) and long term health outcomes (Rasekaba, Lee, Naughton, Williams, & Holland, 2009). Walking is the most common form of exercise and PA in groups with intellectual disability (Draheim, Williams, & McCubbin, 2002). The six-minute walk test (6MWT) is a feasible and objective submaximal exercise test that assesses the distance a person can walk in six minutes (ATS Statement, 2002). In a variety of patient groups a distance less than 350 m walked in 6MWT is associated with increased mortality (Rasekaba et al., 2009).

Down syndrome (DS), Williams syndrome (WS) and Prader–Willis syndrome (PWS) are genetic conditions associated with mild or moderate intellectual disability. DS is caused by the presence of an extra copy or major portion of chromosome 21 (Hattori et al., 2000), WS by a deletion of the elastin gene on chromosome 7q11.23 (Morris, 2010) and PWS by the absence of paternally expressed genes in the 15q11-q13 chromosome region due to deletion, maternal disomy 15 (UPD) or an imprinting defect (Cassidy, Schwartz, Miller, & Driscoll, 2012). Even though molecular diagnosis is available today for all three conditions, diagnosis is in some patients based on clinical manifestations alone, especially in the adult patient population. Clinical manifestations of DS include typical physical, cognitive and behavioral characteristics which in most cases are easily recognized (Hunter, 2010). WS are recognized by typical facial features, short stature and connective tissue abnormalities in addition to a unique social and cognitive profile (Morris, 2010). Characteristics of PWS includes hypotonia, hypogonadism, a unique behavioral profile and childhood onset of hyperphagia that in absence of energy restriction will lead to obesity (Cassidy et al., 2012). It has previously been reported that individuals with DS and PWS have increased risk of inactivity and reduced physical capacity (Butler, Theodoro, Bittel, & Donnelly, 2007; Phillips & Holland, 2011; Temple & Stanish, 2009a), whereas specific knowledge on PA and everyday physical capacity in relation to WS is sparse.

In Norway all institutions for persons with intellectual disabilities closed, and individuals are offered supported living in community settings when moving from their parental homes (Beadle-Brown, Mansell, & Kozma, 2007). Independent living of individuals with intellectual disability in community settings has previously been associated with inactivity, low physical fitness and obesity (Doody & Doody, 2012; Draheim et al., 2002; Emerson, 2005; Hove, 2004; Martinez-Leal et al., 2011; Robertson et al., 2000). However, this knowledge is based on studies from countries with mixed types of living arrangements, where several confounding factors associated with persons living in institutions and persons living independently in communities, respectively, may occur. The complete deinstitutionalization in Norway opens an unique opportunity for studies of PA and physical capacity in a setting with increased focus on autonomy for all individuals, and for description of similarities and differences between subgroups associated with intellectual disability.

The aim of this study was (1) to describe levels of accelerometer-determined overall PA and sedentary behavior among persons with DS, WS and PWS; and (2) to investigate PA and walking capacity in relation to body mass index (BMI).

2. Methods

2.1. Ethical approval and recruitment procedures

Ethical approval for the study was granted by the Regional Committees for Medical and Health Research Ethics, South-East region.

Participants were recruited through existing information channels in relevant national-wide patient organizations, such as websites, membership bulletins etc. In addition a study-specific website was developed where general information, formal letter-to-participate and consent to participate-scheme was posted and available to download. In order to be eligible for inclusion, the individuals had to be between 16 and 45 years of age, and diagnosed with either DS, WS or PWS verified by standardized clinical methods (Holm et al., 1993; Preus, 1984) or by laboratory genetic testing. We used a convenient sampling frame. All participants who returned written informed consent to participate-scheme, signed by both the participant and legal guardian/parent were invited to participate.

2.2. Participants

A total of 96 participants, 40 with DS, 28 with WS and 28 with PWS from all over Norway participated in the study. All participants with clinical diagnosis were offered voluntary genetic testing for verification of their condition. Nine participants were eliminated from final analysis due to negative result from laboratory genetic testing and not for filling clinical criteria. In total 27 participants with DS have genetically verified trisomy 21 and 13 have clinically diagnosis. Of Participants with WS 18 have a genetically verified diagnosis whereas 7 have a clinically diagnosis (Preus, 1984). In the

PWS-group 21 have a genetically verified diagnosis (15 with deletion, 5 with UPD and 1 with unknown subtype) and one have clinically verified diagnosis (Holm et al., 1993). A total of 83 participants were included in PA assessment analysis and 87 in analysis of walking capacity.

2.3. Anthropometrics

The participant's weight, only wearing underwear, was measured twice on an impedance scale (Tanita BC-418MA, Arligton Heights, IL, USA) and recorded to the nearest 0.1 kg. Height was measured twice in upright position with heels placed into the wall and with head fixed in Frankfurt plane by use of a wall mounted standiometer (Seca 222, Birmingham, UK) and recorded to the nearest 0.1 cm. BMI was categorized by use of standard definitions of underweight, normal weight, overweight and obese. IsoBMI was used to define cut-offs for participants from 16 to 18 years of age. Due to small sample size, underweight participants ($n = 3$) were combined with normal weight in to a common normal or underweight category.

2.4. PA assessment

PA was assessed using the ActiGraph GT3X+ activity monitor (ActiGraph, Pensacola, FL, USA). The GTX3+ is lightweight and small and contains a micro-electro-mechanical system accelerometer (MEMS) that sampled the acceleration in three planes, by a 12-bit analog to digital converter, at 30 Hertz (user determined). The participants were instructed to wear the device in an elastic belt secured to the right hip in their home environment during all waking hours, except during swimming or bathing, for seven consecutive days. All participants were given two reminder-posters and encouraged to hang them up in visible places in their own homes. The accelerometers were returned by mail together with a registration of activities during the data collection period involving swimming, bicycling, resistance training or skiing activities. A total of 83 participants provided valid accelerometer recordings and were included in analysis. Drop-out was due to refusal to participate by two participants, medical safety concerns for one participant and lack of valid registration of activity in one of the returned accelerometers.

The acceleration data were stored in a raw and unfiltered format in units of gravity (Gs). Post-processing of the data included extraction of vertical axis data in 60-s epochs and derivation of the following variables: counts per minutes (cpm), steps taken per day, and minutes of intensity specific PA (sedentary behavior, light PA, and moderate-to-vigorous PA). The cut-points for intensity-specific PA have previously been used in large population studies on adults and older people (Hagstromer, Troiano, Sjostrom, & Berrigan, 2010; Hansen, Kolle, Dyrstad, Holme, & Anderssen, 2012). In order for a participant to be included in the analysis, a minimum of 4 days of at least 10 h per day of valid accelerometer recordings had to be achieved. Accelerometer non-wear time, defined as any consecutive strings of minutes with zero counts of at least 60 min with allowance for one interruption, was excluded from the analysis.

2.5. Assessment of walking capacity

Prior to the six-minute walk test (6MWT) all participants were familiarized with the test situation in two steps. First, the test was explained in general by use of pictures by researcher and participants were instructed to wear appropriate clothing and shoes. Second, a test technician demonstrated how to perform the 6MWT prior to actual testing. The participants performed two 6MWTs during the same day with a break in-between. All 6MWTs were conducted in a hallway using 30 m (m) laps. The rounding points of the lap were marked with cones and in addition each 3 m of the lap was marked on the floor. Testing was performed in accordance with standardized guidelines (ATS Statement, 2002) with exception of more frequent use of the encouragement component. Pulse oximetry (Creative Medical PC-60, Shenzhen, China) was used prior and right after testing. Two participants only completed one of the two tests; one due to medical safety concerns and the other due to lack of motivation for a second test.

2.6. Electronic questionnaire

Demographic data, information on place and type of residence and level of support were self-reported by use of an electronic feedback management tool (QuestBack, Oslo, Norway). The questionnaire was completed by the participants together with a parent or assistant. Level of support was categorized into four categories; 0–30 h of support per week, 31–60 h of support per week, more than 60 h of support per week and level of support unknown.

2.7. Statistical analysis

Descriptive statistics were calculated for all variables and assessed for normality and homogeneity of variance, and presented as mean with standard deviation (SD) or percent of population (%). To identify potential confounders that could interfere in the comparison between groups, initial analyses were performed by use of independent *t*-tests and analysis of variance (ANOVA) with use of turkey post hoc test where appropriate. Linear regressions adjusted for age and BMI where appropriate, were used to evaluate the PA and results of 6MWT in the different groups. In all analysis comparing the different genetic conditions PWS were used as reference group, with exception of analysis of sedentary PA and Light PA where DS were

used as reference group. Standard residuals and multicollinearity were investigated in the regression models. In the analysis including 6MWT only the results of the second walk test were used. For participants with only one completed walk-test, the results of this test were included. A p-value of less than 0.05 was regarded as statistical significant. All statistical analyses were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Sample characteristics

Characteristics of the study population are presented in Table 1. More females ($n = 54$) than males ($n = 33$) participated; however we found no significant differences in age, BMI or type of residence between the genders. Participants living with parents were overall 10.2 years younger than the participants living in supported community settings, ($p < 0.001$, 95% CI −7.2; −13.2). Of the participants living in supported community residences; 67% lived in group-homes, 20% in their own apartments geographically close to other similar apartments, and 12% in independent housing facilities. In addition, 48% received 0–30 h per week of support, 18% from 31 to 60 h per week of support, 18% more than 60 h support per week, whereas the level of support were unknown in 15% of the participants. We found no differences in level of received support based on type of community residence. However, persons with PWS received more support than both DS ($p = 0.023$) and WS ($p = 0.01$).

A total of 78% of the study population was either overweight or obese. The DS-group had the highest average BMI followed by the PWS-group and WS-group. The difference in BMI by diagnosis adjusted for age was found to be 2.85 ($p = 0.004$, 95% CI 1.19; 4.51).

3.2. Total PA and time spent in different PA intensities

Participants achieved a mean 6.2 days of valid activity recordings and a mean daily accelerometer wear time of 13.9 h ± 1.4 h. PA by diagnosis and gender is presented in Table 2. Regardless of diagnosis most of the day was spent in sedentary activity 522 min/day (63%), followed by 212 min/day of light activity (25%), 71 min/day in lifestyle activity (9%) and 27 min/day of MVPA (3%). The total PA measured by cpm or steps per day did not differ significantly between the three groups. However a tendency that participants with PWS were less active than DS and WS was detected. For overall activity the PWS-group accumulated in mean 57 and 65 cpm less compared to participants with DS and WS, respectively, ($p = 0.055$, 95% CI: −119.2; 1.4). A large variation in PA was observed, especially in the WS-group and PWS-group, with an activity range of 103–788 cpm in the WS-group and range of 55–515 cpm in the PWS-group. In the DS-group the range was found to be 178–546 cpm. Time in different PA intensities is also presented in Table 2. Participant with DS spent a mean of 73 min/day less and 43 min/day less in sedentary activities compared to participants with PWS and WS, respectively, ($p = 0.011$, 95% CI: −10.9; −80.1). In addition the DS-group spent a mean of 66 min/day more than the PWS-group and 41 min/day more than the WS-group in light activities ($p < 0.001$, 95% CI: 29.3; 79.7). For lifestyle activities the PWS-group spent a mean of 30 min/day less compared to both DS and WS, ($p < 0.001$, 95% CI: −14.2; −45.4). No differences were found for time spent in MVPA. In all groups less than half of the time in MVPA was spent in bouts of 10 min or more.

Males were more active than females across all diagnoses. Males accumulated on average 85 cpm more than females ($p = 0.002$, 95% CI: 33.3; 136.7), 2137 more steps per day ($p = 0.002$, 95% CI: 778; 3496). Males also spent 23.6 more minutes a day in lifestyle activities ($p = 0.001$, 95% CI: 9.4; 37.9) and 13.8 more minutes a day in MVPA ($p = 0.003$, 95% CI: 4.7; 22.9). The largest gender difference was found among participants with WS with a mean of 147 cpm higher for males, whereas the mean gender differences were 63 cpm in DS-group and 56 cpm in PWS-group. No association with BMI-categories and total PA were observed. However some differences in time accumulated in sedentary activities and bouts of MVPA were found. Results for the BMI-categories are presented in Table 3. Under or normal weight participants spent a mean of 75 min/day and 62 min/day more in sedentary activities compared to overweight and obese, respectively ($p = 0.003$, 95% CI: 23.1; 105.2). On average obese subjects spent about 5 min/day less in both MVPA and bouts of MVPA compared to both normal weight and overweight subjects.

When participants living in supported community settings were compared to participants living with parents, no difference in overall PA or activity intensities was detected. Level of received support was not associated with the participants PA.

Table 1
Characteristics of study population by diagnosis.

	All ($n = 87$)	Down Syndrome ($n = 40$)	Williams syndrome ($n = 25$)	Prader–Willi syndrome ($n = 22$)
Females (%)	62.1	62.5	64.0	59.1
Community residence (%)	74.7*	60.0	84.0	90.9
Age (years)	28.5 (7.5)*	26.8 (7.5)	31.5 (6.2)	28.1 (7.5)
BMI (kg/m^2)	30.0 (6.7)*	31.8 (6.5)	26.6 (6.5)	30.7 (6.2)

Data presented as present of population or mean with (standard deviation).
* $p < 0.05$, when diagnosis were compared.

Table 2
Physical activity (PA) by diagnosis and gender.

	All ($n = 83$)	Downs syndrome ($n = 38$)	Williams syndrome ($n = 24$)	Prader–Willi syndrome ($n = 21$)
Total PA (counts/min)				
Male	347 (147.7)*	345 (93.4)	406 (204.7)	284 (142.7)
Female	262 (89.5)	282 (83.5)	259 (92.7)	228 (92.6)
All	294 (121.1)	306 (91.4)	314 (158.4)	249 (114.1)
Steps (steps/day)				
Male	8051 (3808)*	7584 (2440)	9954 (4985)	6725 (3948)
Female	5914 (2421)	6578 (2783)	5469 (1577)	5199 (2341)
All	6712 (3167)	6949 (2673)	7151 (3883)	5781 (3053)
Sedentary (min/day)				
Male	511 (86.9)	474 (91.0)†	524 (70.5)	559 (75.6)
Female	528 (76.3)	500 (63.0)	566 (91.2)	540 (63.9)
All	522 (80.3)	491 (74.4)†	534 (60.3)	564 (66.9)
Light PA (min/day)				
Male	227 (66.8)	255 (71.5)†	228 (50.4)	177 (48.0)
Female	203 (56.5)	232 (52.6)†	182 (48.5)	173 (49.2)
All	212 (61.4)	240 (60.3)†	199 (53.4)	174 (47.5)
Lifestyle PA (min/day)				
Male	86.0 (39.6)*	92.4 (29.6)	100.4 (53.5)	58.5 (24.6)††
Female	62.3 (25.6)	70.4 (14.8)	66.3 (35.5)	43.0 (18.2)††
All	71.2 (33.4)	78.5 (23.7)	79.1 (45.2)	48.9 (21.7)††
MVPA (min/day)[a]				
Male	35.8 (26.2)*	30.7 (17.7)	47.2 (34.4)	31.8 (27.7)
Female	22.0 (15.5)	22.5 (17.3)	20.5 (13.1)	22.7 (15.5)
All	27.1 (21.1)	25.5 (17.7)	30.5 (26.3)	26.2 (20.8)
Bouts MVPA (min/day)[b]				
Male	13.8 (15.8)	8.9 (10.5)	18.1 (17.3)	17.7 (20.9)
Female	9.5 (12.2)	9.6 (12.4)	6.9 (11.7)	12.1 (12.4)
All	11.1 (13.7)	9.4 (11.6)	11.1 (15.1)	14.2 (15.1)

All data are presented as mean with (standard deviation).
[a] Moderate-to-vigorous physical activity.
[b] All MVPA that occurred in bouts of 10 min or more with allowance for interruptions of 1–2 min.
* $p < 0.05$, when all males were compared to all females.
† $p < 0.05$, when diagnosis were compared by use of DS as reference group, adjusted for age and BMI.
†† $p < 0.05$, when diagnosis were compared by use of PWS as reference group, adjusted for age and BMI.

3.3. Adherence to physical activity recommendations

In the study population 12% meet the Nordic recommendations of physical activity (Nordic Council, 2005). More males than females met the recommendations, 14% and 10%, respectively. Diagnosis and gender specific prevalence are listed in Table 4. The highest proportions of participants meeting the PA recommendation were among participants with PWS (19%) followed by the participants with WS (13%) and participants with DS (8%).

Table 3
Physical activity (PA) by BMI category.

	Normal or underweight ($n = 18$)	Overweight ($n = 25$)	Obesity ($n = 38$)
Total PA (counts/min)	269.5 (111.9)	334 (136.4)	278 (110.3)
Steps (steps/day)	6907 (3104)	7629 (3683)	6010 (2704)
Sedentary (min/day)	575 (54.3)*	500 (83.2)	512 (79.3)
Light PA (min/day)	182 (36.9)	228 (67.9)	215 (62.3)
Lifestyle PA (min/day)	55.8 (22.2)	80.8 (40.3)	71.8 (30.6)
MVPA (min/day)[a]	29.2 (19.6)	33.2 (24.6)	22.1 (18.4)*
Bouts MVPA (min/day)[b]	13.4 (14.1)	13.7 (14.9)	8.3 (12.5)*

All data are presented as mean with (standard deviation).
* $p < 0.05$, when BMI categories were compared.
[a] Moderate-to-vigorous physical activity.
[b] All MVPA that occurred in bouts of 10 min or more with allowance for interruptions of 1–2 min.

Table 4
Prevalence of the population meeting current Nordic physical activity recommendation[a].

	≥30 min of daily MVPA[a]
All (%)	12.0
Down syndrome	
Male (%)	7.1
Female (%)	8.3
Williams syndrome	
Male (%)	22.2
Female (%)	6.7
Prader–Willi syndrome	
Male (%)	25.0
Female (%)	15.4

[a] Thirty minutes or more of daily moderate-to-vigorous physical activity in bouts of 8–10 min.

3.4. Walking capacity

We found no significant difference in walking capacity between participants living with parents compared to participants living in supported community residence. However, as shown in Table 5, we found an association in walking capacity with gender and BMI. Males walked on average 41.0 m longer ($p = 0.014$, 95% CI: 9.9; 86.3) compared with females. The mean distance walked during testing decreased with 33.6 m when comparing under or normal weight to overweight, and 78.1 m when comparing overweight to obese, ($p < 0.001$ 95% CI: −40.4; −85.8). Participants with DS walked a mean of 54.7 m shorter than participants with WS and a mean of 49.6 m shorter than participants with PWS. However when this was adjusted for differences in BMI, this association was no longer significant.

4. Discussion

This study provides objectively measured PA and walking capacity measures in three genetic conditions associated with intellectual disability recruited from all over Norway. The use of objective methods and standard protocols facilitate the opportunity for comparison with previous research in the general adult population in Norway. This study is to the best of our knowledge, the first to report on PA and physical capacity for persons with WS.

Total PA and time in different PA intensities was in general for males in our study population in accordance to findings from the general Norwegian adult population 20–64 years of age (Hansen et al., 2012). However, male participants with DS used less time in sedentary PA and more time in lifestyle activities compared to both other groups in our study and the adult Norwegian population. In addition we observed a tendency of male participants with WS to be more active and males with

Table 5
Results of six-minute walk test by gender, diagnosis, place of residence and body mass index category.

	6-Minute walk test
M (SD)	
All ($n = 87$)	481.1 (99.1)
Male ($n = 33$)	506.6 (112.3)
Female ($n = 54$)	465.6 (87.5)
Diagnosis	
Down syndrome ($n = 40$)	452.9 (91.6)
Williams syndrome ($n = 25$)	507.6 (81.9)
Prader–Willi syndrome ($n = 22$)	502.5 (118.9)
Place of residence	
With parents ($n = 22$)	498.9 (107.1)
Supported living in communities ($n = 65$)	475.1 (96.3)
Body mass index category	
Under or normal weight ($n = 19$)	545.0 (89.1)*
Overweight ($n = 26$)	511.4 (107.6)
Obesity ($n = 40$)	433.5 (72.5)

All data are presented as mean meter walked during test with (standard deviation).
* $p < 0.05$, when BMI categories were compared.

PWS, with exception for time in MVPA, to be less active. In contrast females, in our study generate 262 cpm compared to 345 cpm among females in the adult Norwegian population (Hansen et al., 2012). Again the participants with PWS were found to be least active and to spend more time in sedentary activities and less in light PA and lifestyle PA, whereas no difference for time in MVPA was observed.

The clear gender difference with respect to total PA was in accordance with some previous research of PA in individuals with intellectual disability (Bodde, Seo, Frey, Van Puymbroeck, & Lohrmann, 2013; Emerson, 2005; Phillips & Holland, 2011) but in contrast to others (Robertson et al., 2000; Stanish, Temple, & Frey, 2006; Temple & Stanish, 2009a) with no difference between genders. This was also in contrast to what is found in the general adult Norwegian population, with no difference in overall PA between genders (Hansen et al., 2012).

Compared to other more similar study populations, total PA and activity in MVPA was lower for all participants as well as participants with DS, than in a mixed population of individuals with intellectual disability (Phillips & Holland, 2011). Some of the difference seen in overall PA may be explained by the fact that we used a less strict definition of non-wear time. Time in MVPA, accumulated in bouts of 10 min was in accordance with other reports (Bodde et al., 2013). Our study groups spent more time in MVPA, 11.1 min/day versus 7.7 min/day, but this may be due to a lower mean BMI in our study population. Overall activity level in PWS-group was higher than what was reported by Butler et al. (2013), and can mainly be explained by more time in MVPA, which indicate more frequent participation in exercise activities by our participants with PWS. Likewise, for the DS-group, we report higher total PA than Temple (2009b). However caution should be used when comparing results from different countries due to differences in political, cultural or environmental factors.

Physical activity has several positive effects in these groups (Bartlo & Klein, 2011) and needs to be emphasized and facilitated, as only 12% meets the current recommendations. This was lower than reports by use of objective methods from the general adult Norwegian population where 22% females and 20% males met the Nordic recommendation (Hansen et al., 2012), and also lower than reports from adult populations of mild intellectual disability of mixed age and etiology, ranging from 14–33% (Hilgenkamp, Reis, van Wijck, & Evenhuis, 2012; Peterson, Janz, & Lowe, 2008; Temple, Frey, & Stanish, 2006). However this was higher than what was reported for mixed groups of persons with intellectual disability from UK (Phillips & Holland, 2011).

The mean walking capacity in our study population, 507 m for males and 466 m for females, was lower than the reference values in normal weight healthy adult's age 20–40 years; 800 m for males and 699 m for females (Gibbons, Fruchter, Sloan, & Levy, 2001). In total 7% of the participants walked shorter than 350 m, a result associated with increased risk for health complications (Rasekaba et al., 2009). However, the mean waking capacity was higher than what was reported from a population of DS with and without severe cardiac disease (Vis et al., 2009), in agreement with results from Casey et al. evaluating the use of the 6MWT in a group of persons with DS (Casey, Wang, & Osterling, 2012), and lower than reports from a younger group of persons with intellectual disability (Elmahgoub, Van de Velde, Peersman, Cambier, & Calders, 2012) and in participants attending a special Olympic program (Nasuti, Stuart-Hill, & Temple, 2013). No clear differences in walking capacity were detected for the different genetic conditions. This may indicate that the small differences seen in PA assessment regarding total PA and time in different PA intensities were not a result of different physical capacity related to differences in syndrome specific somatic abnormalities. Based on this, we suggest that differences observed are possibly related to personality and behavioral characteristics related to the genetic conditions. In addition we suggest that the large differences in PA seen within the groups, at least partly, to be explained by differences in structure, focus and opportunities for PA in the support systems (Temple, 2009b). Further studies regarding these issues are warranted to define more accurately determinants for both inactivity and activity in these populations in Norway.

A negative association between BMI and walking capacity was found, whereas no association was found between BMI and total PA. The lack of association with PA was in contrast to findings from populations studies were increased BMI was associated with a reduction in PA (Hansen, Holme, Anderssen, & Kolle, 2013), and further reduction in PA over time (Lakerveld et al., 2011). The association between walking capacity and BMI was in agreement with the suggestion by Doody and Doody (2012), that obesity leads to reduced everyday capacity and possible increased need for assistance. The lack of association with PA and BMI may be due to the fact that most participants were overweight or obese. However, this may also indicate other limiting variables for PA in these groups than in the general population. Others have suggested that unique barriers may be present in these groups and includes; lack of ability to perform physical activity due to reduced environmental availability of physical activity resources (Howie et al., 2012), lack of transportation, lack of guidance and social support (Frey, Buchanan, & Rosser Sandt, 2005; Stanish et al., 2006; Temple, 2009b). In addition to this physical restrictions or limitations related to somatic abnormalities associated with each genetic disorder.

The study has limitations. The convenient sampling frame challenges the generalization in the studied groups. However about one third of the known Norwegian population of both PWS and WS in relevant age category participated in the study.

Accelerometers have been found to be valid and reliable for measuring PA in adults (Westerterp, 2009). However, current algorithms for categorizing activity in intensity levels may underestimate energy expenditure and intensity in the study population due to reduced mean height, reduced coordination of movements, lower maximum oxygen consumption and increased mean weight (Agiovlasitis, Beets, Motl, & Fernhall, 2012; Hinckson & Curtis, 2013). In addition, the measurement precision varies with different type of activities. While good precision is achieved when assessing walking and running, underestimation of activity is prevalent in water activities and activities not involving movement of the hip. The activity diary indicated that there might be a small underestimation in the PA assessment for 16% of the participants due to either swimming activities (6%), bicycling (2%) or resistance training (8%).

The standard reference method to measure cardiovascular fitness is the maximal oxygen consumption test (VO2 max). However, 6MWT provides a global assessment of exercise capacity and may better reflect everyday activity capacity than laboratory tests (ATS Statement, 2002). It is both feasible and reliable for individuals with an intellectual disability (Elmahgoub et al., 2012; Vis et al., 2009) but level of intellectual disability have effects on distance walked (Casey et al., 2012; Vis et al., 2009). In our groups the use of the results as an exact estimate of walking capacity may possibly also be affected by diagnosis related to restrictions such as mental rigidity and fluctuations in motivation.

5. Conclusions

Inactivity was prevalent among individuals in all diagnosis and females were more inactive than males. When diagnoses were compared similar results were obtained for total PA and time in MVPA. However, the participants with DS were found to spend less time in sedentary activities and to spend more time in light PA, whereas participants with PWS spent less time in lifestyle PA. Walking capacity was lower in all groups tested compared to normal population but overall in accordance with investigations in similar groups. A negative association between BMI and physical capacity was detected, whereas no association between BMI and total PA was observed.

An increased focus on promoting PA, especially MVPA and lifestyle PA in these groups is warranted, also in Norway. In addition, Norway is a country with emphasis on autonomy for adults with intellectual disability, and more research investigating how best to facilitate and motivate for PA in individuals with intellectual disabilities are needed.

Acknowledgments

The study was funded by Extra Stiftelsen and Frambu Resource Center for Rare disorders. The authors thank all participants, their caretakers and the organizations; The Norwegian Association for persons with Developmental Disabilities, The National Association for Prader–Willi syndrome, The Norwegian Association for Williams syndrome and The Norwegian Network for Down syndrome for their collaboration and support. In addition we thank personnel at Frambu for taking part in the data collection, especially Kaja Giltvedt, Sissel Widerøe Bredesen, Eva Elisabeth Næss and Kari Hagen.

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II

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COACTION PUBLISHING

ORIGINAL ARTICLE

Dietary aspects related to health and obesity in Williams syndrome, Down syndrome, and Prader–Willi syndrome

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Abstract

Background: Dietary aspects that might contribute to development of obesity and secondary conditions are not well documented in genetic subgroups associated with intellectual disability.
Objective: To describe the intake frequencies of selected foods in participants with Prader–Willi syndrome (PWS), Down syndrome (DS), and Williams syndrome (WS), and investigate the association with body mass index (BMI). To explore food-related autonomy and intake frequencies among persons with DS in different living arrangements.
Methods: Self-reported intake frequencies and measurement of plasma carotenoids and erythrocyte content of omega-3 fatty acids (FAs) were investigated in persons aged 16–42 years, with WS ($n=21$), DS ($n=40$), and PWS ($n=20$).
Results: A larger proportion of participants with PWS showed high-frequency intake of fruits ($p=0.012$) and vegetables ($p=0.004$), and had higher plasma carotenoids ($p<0.001$) compared to participants with DS and WS. Furthermore, a larger proportion of participants with WS were low-frequency consumers of fish ($p=0.005$), less likely to use omega-3 FA supplements ($p=0.023$), and had reduced erythrocyte concentrations of long-chain omega-3 FAs ($p<0.001$), compared to participants with PWS and DS. In DS, BMI was negatively associated with plasma carotenoids. Increased proportions of participants living in communities showed high-frequency intake of precooked meals ($p=0.030$), and a tendency toward high-frequency consumption of soft drinks ($p=0.079$), when compared to peers living with relatives. Participants in community residences were also more likely to participate frequently in food-related decisions and preparations.
Conclusions: Persons with WS had a less-favorable dietary pattern when compared to persons with PWS. A larger proportion of persons living in communities frequently consumed precooked meals and showed a tendency of high-frequency soft drink consumption. Otherwise, their intake frequencies of the investigated foods were similar to those living with relatives, but they participated more frequently in decisions and preparations of foods.

Keywords: *diet*; *carotenoids*; *omega-3 fatty acids*; *obesity*; *intellectual disability*; *autonomy*; *developmental disability*; *living arrangements*

Responsible Editor: Anna Ólafsdóttir, University of Iceland, Iceland.

Received: 18 July 2014; Revised: 5 November 2014; Accepted: 22 December 2014; Published: 3 February 2015

Currently, individuals with intellectual disability (ID) enjoy an increased life expectancy (1, 2) and experience increased integration in communities combined with focus on normalization and autonomy (3). Even so, persons with ID living in community residences have a high risk of developing obesity and secondary conditions related to poor lifestyle (4–7). In Norway all persons with ID are offered community residence with support when moving from their parental home. Support is financed by the local municipality, and is provided based on assessment of individual needs. This is a general national policy and provides an opportunity for descriptive studies of lifestyle-related factors in adult persons with ID living in community residences and also for comparisons between different genetic subgroups, and to those living with relatives.

A diet rich in fruit and vegetables and regular consumption of fish and omega-3 fatty acids (FAs) of marine origin are associated with several favorable health outcomes (8–11). In Norway, dietary guidelines to promote public

Citation: Food & Nutrition Research 2015, **59**: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487
(page number not for citation purpose)

health and prevent chronic diseases recommend a mainly plant-based diet rich in fruits and vegetables. Furthermore, use of long-chain omega-3 FAs supplementation is recommended to those with intake frequency of fish below two to three times a week (12). Suboptimal intakes of fruit and vegetables has been documented in the general adult Norwegian population, where about 35–40% meet the fruit intake recommendation and about 15% meet the recommendation of vegetable intake (13). Use of omega-3 FAs supplementation is common with daily use described in about 45% of the population (14). Previous studies of dietary intakes in adult persons with ID, have found low intakes of fruit and vegetables (6, 15–18), low intake frequency of fish (17), and low intakes of polyunsaturated FAs (19).

Sugar-sweetened soft drinks are important contributors to refined sugar intake (13), and the intake of soft drinks has been associated with increased energy intake and increased body weight (20, 21). Precooked meals consist of meals ready to eat or meals that only require heating. These meals come in a variety of subtypes and with variation in package size; both single portions and multi portions size are sold in grocery stores in Norway. They are often energy dense, with high fat and salt content, and often low in vegetables and fiber. Regular consumption of convenience food has been reported in adults with ID living in community residences (22). The consumption of precooked meals together with soft drinks is an important topic to investigate in groups of persons with ID, because of their possible influence on the risk of developing obesity, and the quality of diet (23).

Previous studies addressing dietary intakes in groups of adults with ID have mainly used food frequency questionnaires, food diaries maintained by proxy reporters, or combinations of proxy- and self-reported methods (6, 15, 16, 19). However, none of these dietary assessment methods have been validated for use in groups of adults with ID (24). Furthermore, the use of proxy reporters is inappropriate in persons with ID living mostly independently and receiving little support. Additional use of biomarkers therefore has the potential to objectively supplement the information generated from other dietary assessment techniques (25, 26).

Carotenoids are natural pigments found in fruits and vegetables that humans are unable to synthesize. Plant foods are therefore the primary source of carotenoids for humans. Six carotenoids, lycopene, lutein, zeaxanthin, β-cryptoxanthin, α-carotene, and β-carotene, can be found within a significant concentration range in plasma and can be used as biomarkers for fruit and vegetable consumption (27–29). FAs from the diet are incorporated into erythrocyte membranes (30). Erythrocytes have a lifespan of 120 days and lack the enzymes needed for FA metabolism; therefore, they are regarded as a reliable biomarker reflecting an individual's FA intake over the last several weeks. However, FAs not synthesized in humans, such as long-chain omega-3 FAs of marine origin, have the highest correlation with intake (31–33).

Williams syndrome (WS), Down syndrome (DS), and Prader–Willi syndrome (PWS) are genetic conditions mainly associated with mild-to-moderate ID, although a wider range in cognitive abilities can be observed. WS is caused by a deletion of the 7q11.23 chromosomal region (34). DS is due to the presence of an extra copy of a major portion of chromosome 21 (35), whereas PWS is caused by a lack of expression of paternally inherited genes in the 15q11-q13 chromosomal region due to deletion, maternal disomy 15, or an imprinting defect (36). Molecular diagnoses are available for all three conditions; however, diagnosis in some patients is based on clinical manifestations alone. PWS and DS are described to be associated with increased risk of obesity (6, 19, 36, 37), but this has not been described in any detail in relation to WS. In PWS the high risk of morbid obesity is linked to hyperphagia (38), reduced energy expenditure (39), and the obsessive behavioral profile of the syndrome (40). A low-energy diet combined with rigorous food supervision and restricted access to food is recommended management for the prevention of life-threatening obesity in this group (41–43). In DS reduced physical activity (44, 45), reduced basal metabolic rate (46), and increased risk of subclinical hypothyroidism are described as underlying features of the high obesity risk (47).

Persons with ID are a heterogeneous group, and to date few previous studies have included a description of dietary aspects among community-dwelling individuals in relation to diagnosis-specific subgroups. Furthermore, although high risk of obesity is described for persons with mild-to-moderate ID living in community residences (4, 5), dietary intakes and food-related autonomy in relation to weight status and changes in these aspects when moving from parental homes to community residences with support have previously not been investigated to any great extent. Therefore, in the present study, we aim to describe and compare the proportions with low and high intake frequencies of fruits, fruit juice, and vegetables; fish and omega-3 supplements; soft drinks and precooked meals; and biomarkers, and explore this in relation to weight status in individuals with DS, WS, and PWS. Moreover, the second aim was to explore possible differences in degree of food-related autonomy and proportion with low and high intake frequencies of the selected foods, between individuals in community residence with support and individuals living with relatives. In this second part of the study, we focused on persons with DS only.

Methods

Study sample

Participants were recruited from all over Norway using information circulated in collaboration with the following

Citation: Food & Nutrition Research 2015, **59**: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487

nationwide patient organizations: The Norwegian Association for Persons with Developmental Disabilities, The National Association for Prader–Willi syndrome, The Norwegian Association for Williams' Syndrome, and The Norwegian Network for Down Syndrome. In addition, information on the study and consent forms were posted on a study-specific website. The inclusion criteria were diagnosis with DS, WS, or PWS verified by standardized clinical methods (48, 49) or by laboratory genetic testing; age 16–45 years; and returned consent forms signed by the participant and legal guardian or parent. In total, 104 returned a signed consent forms. Four participants with PWS, three participants with DS, and one participant with WS dropped out of the study, so a total of 96 participants took part in the data collection. In the data analyses, a total of 81 participants were included, after elimination of nine participants due to negative results from laboratory genetic testing and for not fulfilling the clinical diagnostic criteria. Furthermore, two persons with PWS and four persons with WS living with relatives were excluded, as they were too few to be included in a comparison with diagnose specific peers living in communities. For this reason, only participants with DS were included in the analysis in which different living arrangements were compared. Ethical approval for the study was granted by the Regional Committee for Medical and Health Research Ethics, Southeast Region.

Collection of data

Data were collected during courses held at a national reference center for rare disorders in Norway. Participants attended the courses together with a parent or employed caregiver. All data collection was adapted to and performed in a manner to promote the participants themselves to be active and the main informants. An electronic questionnaire was used to collect demographic data (with the exception of weight and height): information about celiac disease diagnosis, hypothyroidism, and thyroid hormones substitution therapy; information on the intake frequency of fruits, vegetables, fruit juice, fish (including fish eaten both in hot and cold meals), soft drinks, and precooked meals; use of omega-3 supplementation; and degree of participation in decision-making about food and active preparation of food (Questback, Oslo, Norway). The participants, together with a parent/caregiver, used a computer to fill out the questionnaire during the courses. The instructed role of the parent/caregiver was to record the participant's response, and not themselves to be the main respondent. The food frequencies used were as follows: less than once a week, one to three times a week, four to six times a week, each day, and several times a day. These categories were later collapsed into two categories: three times a week or less, and four times a week or more, representing low- and high-frequency intake, respectively. Furthermore, we examined the proportion of daily fruit, vegetables, fish, and soft drink consumption, and the proportion of fish intake less than once a week. Information on daily use of omega-3 supplementation was collected based on 'yes' or 'no' responses with an additional open category in which participants could manually report the subtype of supplementation. Autonomy-related variables were collected in the following categories: never, rarely, occasionally, often, or always. These categories were later collapsed into two categories: 'never, rarely, or occasionally' and 'often or always', representing a low and high degree of autonomy, respectively. Weight was measured twice in light clothing on an impedance scale (Tanita BC-418 MA, Arlington Heights, IL, USA) and recorded to the nearest 0.1 kg. Height was measured twice in an upright position with heels placed against the wall and with head fixed in Frankfurt plane using a wall-mounted stadiometer (Seca 222, Birmingham, UK) and recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated using the standard formula. Blood samples were collected in the morning in 4-ml lithium-heparin-gel plasma tubes (Vacuette, Greiner Bio-one GmbH, Germany) after overnight fasting. The tubes were centrifuged at room temperature in a swing-out centrifuge at 1,500 g for 12 min and kept on ice until placement in a -80°C freezer. The samples were thawed in a refrigerator overnight before analyses of carotenoids and FAs were performed, at a laboratory with standardized procedures to perform such analyses.

Assessment of carotenoids

Plasma (100 μL) was pipetted into vials, proteins were precipitated, and carotenoids were extracted with isopropanol containing an internal standard (β-Apo-8 carotenal). After thorough mixing and subsequent centrifugation, an aliquot of the isopropanol phase was injected into the HPLC-UV. Separations were performed on a 3-μm YMC C30 column (150×4.6 mm internal diameter; YMC, Kyoto, Japan). Analyses were performed on a 100-series HPLC with a 1,260 diode array detector (453 nm) (Agilent Technologies, Palo Alto, CA, USA).

FA assessment

Erythrocytes were vortexed and pipetted into vials, and samples were methylated with 3N MeOH HCl. Methylated FAs were extracted with hexane, and the samples were neutralized with 3N KOH in water. The samples were then mixed and centrifuged, and the hexane phase was injected into a gas chromatograph with flame ionization detector. Analyses were performed on a 7890A GC with a split injector with a 7683B automatic liquid sampler using flame ionization detection (Agilent Technologies, Palo Alto, CA, USA). Separations were performed on an SP-2380 column (30 m $\times$ 0.25 mm internal diameter $\times$ 0.25 μm film thickness) from Supelco (Sigma-Aldrich, St. Louis, MO, USA).

Statistics

Standard descriptive statistics were calculated for all variables. Initially chi-square, one-way analysis of variance (ANOVA), and independent *t*-test were used to identify differences between the subgroups with respect to background variables. Level of support was regarded as collider in the investigations comparing the different genetic subgroups, and was for this reason considered not relevant to adjust for in the statistical analysis. Normality was assessed, and when violated, log-transformed variables were used. Ordinal categorical variables were dichotomized to avoid zero-cell problems and loss of statistical power. Chi-square tests were used to investigate proportions with low and high intake frequencies of fish by diagnosis, due to a zero-cell. Otherwise logistic regression models adjusted for BMI were used to investigate the association between proportions with low- and high-frequency consumers in the different food categories and use of omega-3 supplementation by diagnosis. Linear regression adjusted for BMI was used to investigate plasma carotenoids and erythrocyte FAs to detect differences between diagnoses. Based on initial analysis by use of ANOVA with Tukey post hoc test, the PWS-group was used as reference and compared to a combined group of persons with DS and WS in comparison of plasma carotenoids. Similarly, in the investigation of erythrocyte FAs, WS was used as reference and compared to a combined group of persons with PWS and DS. Assumption of linearity, interaction, and standard residuals were investigated when relevant in the models. Chi-square tests were used to investigate differences in proportions with low and high food intake frequencies and degree of participation in food-related tasks based on BMI-category in the diagnoses. In these analyses, to ensure test validity, normal weight and overweight participants were collapsed into one group and compared to obese participants. Pearson's correlation test was used to assess the association between BMI and plasma carotenoids and erythrocyte FAs by diagnosis. Chi-square tests were used to investigate proportions with high- and low-frequency intake of foods, high and low degree of autonomy, when living in communities was compared with living with relatives for persons with DS. Similarly, Mann–Whitney tests were used to investigate differences in plasma carotenoids and erythrocyte omega-3 FAs when the living arrangements were compared. All statistical analyses were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA), and *p*-values of less than 0.05 were regarded as statistically significant.

Results

The characteristics of the study population are presented by diagnosis in Table 1. More females than males

Table 1. Characteristics of the study population by living arrangement and diagnosis

	Living in community residence			Living with relatives		
	Prader–Willi syndrome ($n=20$)	Williams syndrome ($n=21$)	Down syndrome ($n=24$)	Down syndrome ($n=16$)	p^a Diagnosis	p^b Living arrangements
Age (years)	29.3 (5.3)	33.6 (6.4)	30.4 (6.4)	21.5 (5.8)	0.067	<0.001**
Females (%)	55.0	66.7	62.5	62.5	0.739	1.000
BMI (kg/m^2)	30.9 (6.1)	28.2 (5.8)	32.8 (6.6)	30.6 (6.3)	0.050	0.250
Smokers (%)	10.0	4.8	0	0	0.289	
Occupation					0.463	0.113
Student (%)	0	4.8	4.2	31.3		
Employed (%)	85.0	81.0	66.7	50.0		
Daycare attendant (%)	10.0	4.8	25.0	12.5		
Unemployed (%)	5.0	9.5	4.2	6.3		
Years lived in community residence (years)	8.5 (5.5)	9.4 (5.8)	7.3 (4.9)		0.443	
Level of support in community residence**					0.020*	
0–30 h/week (%)	40.0	47.6	54.2			
31–60 h/week (%)	10.0	23.8	20.8			
More than 60 h/week (%)	45.0	4.8	8.3			
Level of support unknown (%)	5.0	23.8	16.7			

The data are presented as percentage of the population or as the mean (standard deviation).

[a]*p*-Values are derived by comparison of persons in community residence with different diagnosis using chi-square tests and one-way analysis of variance (ANOVA); [b]*p*-values are derived by comparison of persons with DS living in community residence to persons with DS living with relatives using chi-square tests and independent *t*-test.

*$p<0.05$.

**$p<0.001$.

Citation: Food & Nutrition Research 2015, **59**: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487

participated in the study; however, there was no significant difference in age or BMI between the sexes. Likewise, the sex distribution was similar in the genetic subgroups. Overweight and obesity were prevalent, and 78% of the total study population had a BMI >25 kg/m^2. When the diagnosis-groups were compared, there was a small difference in BMI. Participants with DS and WS had the highest and lowest BMI's, respectively. Participants with DS living with their parents were on average 8.9 years younger than diagnosis-specific peers living in community settings. All persons with PWS followed a diet and had assistance to follow dietary regimens. None of the participants with PWS decided independently the amount of food to eat due to their well-known hyperphagia and high risk of developing obesity. However, variable degree of participation in food decisions was recorded. Some individuals did not take any part in decisions and preparation of food eaten, whereas most individuals took some part in food decisions for example, what type of fruit and vegetables to consume, what type of spreads to have on their bread, etc. Three persons with DS had celiac disease. Hypothyroidism was common and found in 17 persons with DS (43.6%), three persons with WS (12.0%), and three persons with PWS (13.6%).

In the PWS-group, a total of 70, 25, and 85% of participants consumed daily fruit, fruit juice, and vegetables, respectively. In the DS-group daily consumption of fruit was recorded in 33%, fruit juice in 37%, and vegetables in 29%. For participants with WS, daily consumption of fruit, fruit juice, and vegetables was recorded as 15, 9, and 20%, respectively. The proportions with intake frequency of three times or less and four times or more a week (low- and high-frequency intake) by diagnosis are shown in Fig. 1. A larger proportion of participants with PWS were

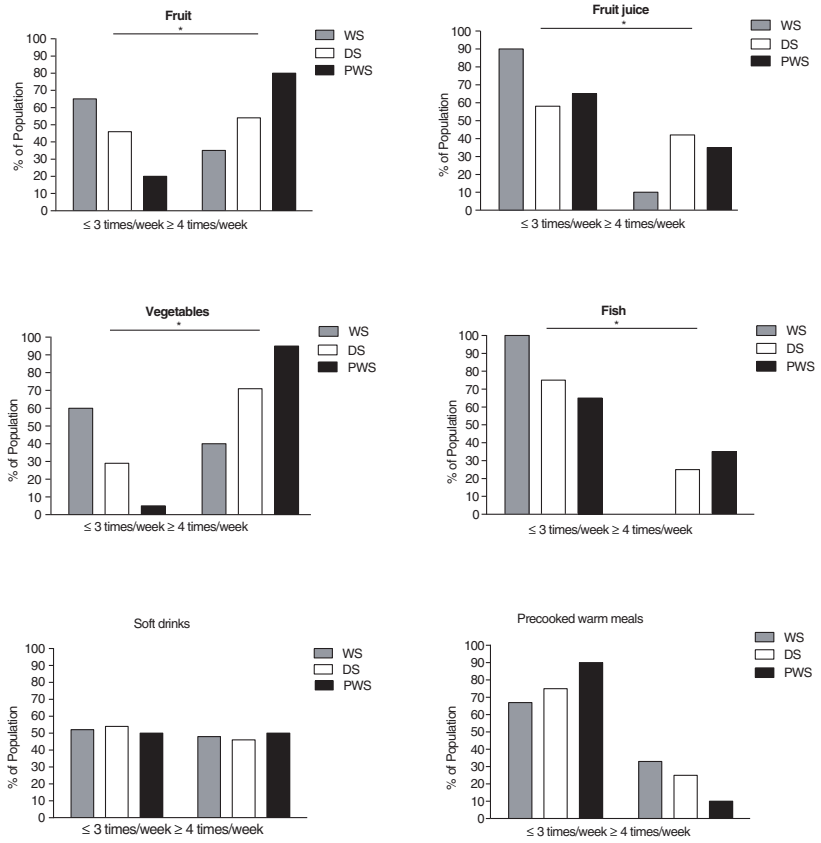

Fig. 1. Proportion low- and high-frequency consumers by diagnosis. Intake frequencies are presented as a percentage of the population diagnosed with WS ($n=21$), DS ($n=24$) or PWS ($n=20$).
*$p<0.05$ when participants with PWS were compared to participants with WS and DS using logistic regression models adjusted for BMI.

high-frequency consumers of fruit ($p = 0.012$) and vegetables (potatoes excluded, $p = 0.004$) compared to participants with WS and DS. Using participants with PWS as a reference in a logistic regression model adjusted for BMI, the odds ratio (OR) of being a high-frequency consumer of fruit was 0.10 (95% CI 0.02; 0.45) in the WS-group, and 0.32 (95% CI 0.08; 1.30) in the DS-group. Odds for being high-frequency consumers of vegetables were OR 0.03, (95% CI 0.003; 0.29) in the WS-group, and OR 0.14, (95% CI 0.02: 1.25) in the DS-group. The largest proportion of participants with high-frequency intake of fruit juice was in the DS-group. When compared to the PWS-group, we observed an OR of 1.35 (95% CI 0.39; 4.68) in the DS-group, and an OR of 0.19 (95% CI 0.03; 1.08) in the WS-group. Daily consumption of fish was reported in 25% of participants with PWS, 4% of participants with DS, and by none in the WS-group. A larger proportion of participants with WS were also found to be low-frequency consumers of fish ($p = 0.005$) compared to participants with PWS and DS. Overall, 20% of participants with WS reported consuming fish less than once a week, whereas the numbers of participants with DS and PWS were 2 and 4%, respectively. In addition, the participants with WS were less likely to use omega-3 supplementation; 24% in the WS-group compared to 50% in the two other groups, respectively, OR 0.24 (95% CI 0.07; 0.82), $p = 0.023$.

No significant differences were found among the groups with respect to low- and high-frequency intakes of soft drinks and precooked meals. The proportion of individuals consuming soft drinks daily or several times a day ranged from 21% in participants with DS to 31% in the PWS-group and 32% in the WS-group.

The plasma carotenoid concentrations and weight percent (w %) of omega-3 FAs in erythrocytes by diagnosis are shown in Table 2. In accordance with the results based on reported intake frequencies, participants with PWS were found to have higher plasma concentrations of total carotenoids compared with the other two groups, $p < 0.001$. Compared to participants with DS and WS, participants with PWS also had higher plasma concentrations of the single carotenoids: lutein ($p < 0.001$), zeaxanthin ($p = 0.006$), β-cryptoxanthin ($p < 0.001$), α-carotene ($p < 0.001$), and β-carotene ($p < 0.001$). No significant differences in these carotenoids were observed between participants with DS and WS.

When evaluating the omega-3 FAs in erythrocytes, lower levels of total omega-3 FAs were observed in the WS-group compared to the other two groups, $p < 0.001$. The differences between the groups using WS as reference were also significant for the individual FAs: eicosapentaenoic acid (EPA) ($p = 0.002$), docosapentaenoic acid (DPA) ($p = 0.001$), and docosahexaenoic acid (DHA) ($p < 0.001$). No association between erythrocyte omega-3 FAs and BMI was detected.

Intake frequencies and participation in selection and preparation of foods was investigated in relation to diagnosis and BMI-category. In DS, normal weight and overweight

Table 2. Carotenoids in plasma and omega-3 fatty acids in erythrocytes by diagnosis

	Living in community residence									Living with relatives		
	Prader–Willi syndrome ($n = 20$)			Williams syndrome ($n = 21$)			Down syndrome ($n = 24$)			Down syndrome ($n = 16$)		
Carotenoids (μmol/l)	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Lycopene	0.806	0.564	0.918	0.579	0.490	0.875	0.810	0.554	1.113	0.822	0.686	0.896
Lutein	0.259*	0.220	0.328	0.149	0.119	0.267	0.186	0.145	0.206	0.178	0.143	0.211
Zeaxanthin	0.084*	0.051	0.104	0.051	0.029	0.091	0.054	0.048	0.076	0.060	0.042	0.068
β-Cryptoxanthin	0.258*	0.176	0.326	0.138	0.069	0.248	0.128	0.103	0.227	0.121	0.074	0.177
α-Carotene	0.227*	0.178	0.377	0.084	0.041	0.126	0.103	0.066	0.146	0.076	0.048	0.116
β-carotene	0.984*	0.519	1.335	0.456	0.327	0.538	0.351	0.239	0.482	0.365	0.262	0.465
Total carotenoids	2.76*	2.14	3.14	1.63	1.17	2.22	1.76	1.34	1.99	1.65	1.43	1.81
Omega-3 fatty acids (w %)												
ALA[a]	0.193	0.180	0.209	0.189	0.172	0.203	0.201	0.174	0.220	0.207	0.162	0.228
EPA[b]	2.00	1.30	2.83	1.00**	0.75	1.40	1.10	0.90	1.70	1.20	1.10	1.45
DPA[c]	2.60	2.40	3.05	2.50**	2.35	2.90	2.75	2.63	3.10	2.70	2.60	2.88
DHA[d]	6.90	6.00	8.03	5.40**	4.65	6.30	6.15	5.80	7.50	6.75	5.25	7.30
Total omega-3 FAs	12.12	9.80	13.50	9.30**	8.55	10.51	10.19	9.44	12.75	10.67	9.56	11.72

Median plasma concentrations of carotenoids and median erythrocyte fatty acids presented with 25th and 75th percentiles (Q1 and Q3).
[a]α-Linolenic acid, C18:3; [b]eicosapentaenoic acid, C20:5; [c]docosapentaenoic acid, C22:5; [d]docosahexaenoic acid, C22:6.
*$p < 0.05$ when participants with PWS were compared to participants with WS and DS using linear regression models, adjusted for BMI.
**$p < 0.05$ when participants with WS were compared to participants with PWS and DS using linear regression models, adjusted for BMI.

Citation: Food & Nutrition Research 2015, 59: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487

participants were found to be more likely to consume fruits four times or more per week compared to obese participants, $p = 0.032$. A similar tendency was observed for intakes of vegetables, $p = 0.081$, whereas no other difference was observed in proportions with low and high intake frequencies of foods, or in participation in food selection and preparation by the groups based on BMI in DS. In PWS, normal weight and overweight participants reported more often intakes of fruit four times or more per week compared to obese participants, $p = 0.013$. No other significant differences in the proportions with low and high intake frequencies of foods or degree of participation in food-related tasks were observed in the PWS-group when this was evaluated in BMI-based groups. This was also the case in the WS-group. In Fig. 2, the association between BMI and measured plasma carotenoids is shown in the different diagnose groups. Increased BMI was associated with a reduction in total plasma carotenoids for persons with PWS and DS. This correlation, however, was only significant in DS, r -0.33, $p = 0.039$. In contrast, the lowest plasma carotenoid concentrations were found in those categorized as underweight and lower end of normal weight range among participants with WS.

When participants with DS living with parents ($n = 16$) were compared to those living in communities ($n = 24$), we found no differences in the proportions of low- and high-frequency consumers of fruit, fruit juice, vegetables, and fish. Moreover, no significant differences were observed in any of the biomarkers measured in blood from the two subgroups, as can be seen in Table 2. However, as shown in Fig. 3, a larger proportion of high-frequency consumers of precooked meals were observed in persons living in community residences ($p = 0.030$). We also observed a trend toward a larger proportion of high-frequency consumers of soft drinks in community-dwelling participants ($p = 0.079$). As displayed in Fig. 4, when compared to participants living with relatives, participants living in communities had a higher degree of participation in decisions regarding which foods to eat ($p = 0.037$) and which groceries to buy ($p < 0.001$), and participated more in the preparation of warm meals ($p = 0.005$), whereas only small changes were observed between the living arrangements with respect to participation in cold meal preparation.

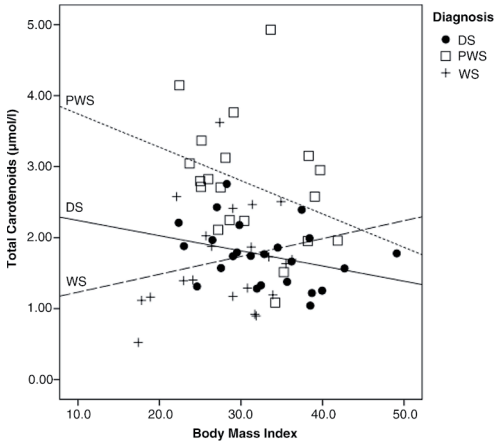

Fig. 2. The association between BMI and total carotenoids by diagnosis. Scatter plot include participants with DS ($n = 40$), participants with PWS ($n = 20$), and participants with WS ($n = 21$). The correlation was tested by use of person's correlation and significant for persons with DS, r -0.33, $p = 0.039$.

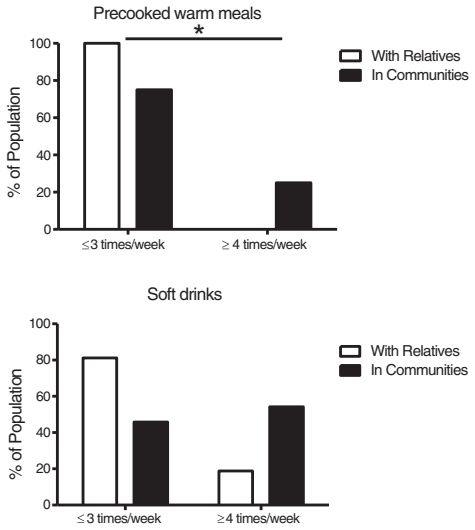

Fig. 3. Proportion low- and high-frequency consumers based on living arrangement. Intake frequencies are presented as a percentage of the population with DS living with relatives ($n = 16$) or in communities ($n = 24$).
*$p < 0.05$ when participants with DS living in community residences were compared to diagnose specific peers living with relatives using chi-square tests.

Discussion

In this study, we describe the proportion with low- and high-frequency consumption of selected food groups that are of particular interest to health and obesity in community-dwelling participants with three different genetic conditions associated with ID and compare the results to individuals living with relatives. Norway has a general national policy and transition practice for persons with ID, and this provides a national cohort with reduced probability of systematic differences in level of functioning or comorbidities between the subgroups based on living arrangements. A difference in age between the persons living in community residence versus living with relatives was however seen, as people with

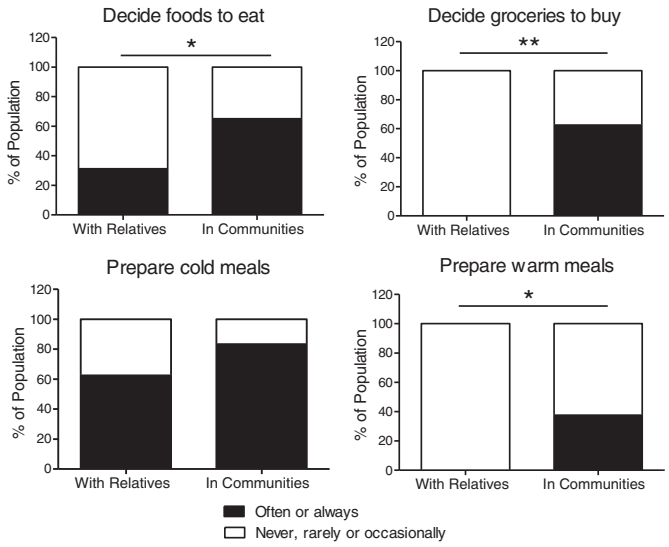

Fig. 4. Food-related autonomy for persons with Down syndrome in different living arrangements. Degrees of participation are presented as a proportion (%) of the population living with relatives ($n = 16$) or in communities ($n = 24$).
*$p < 0.05$ when participants living in community residences were compared to participants living with relatives using chi-square tests.
**$p < 0.001$ when participants living in community residences were compared to participants living with relatives using chi-square tests.

ID living with relatives often moves to community residence before 25 years of age.

We included adolescents and adults in the study, and the participants themselves were used as informants. For this reason, the dietary assessment methods used were a very simplified electronic method to evaluate intake frequencies in selected food groups. The intake frequencies were recorded in quite wide categories and without estimation of portion sizes, or description of food group subtype consumed. This decision was based on limitations in cognitive abilities of the study populations, in combination with knowledge that intake frequency alone explains the major variation in intake (50). To supplement these self-reported intake data, biomarkers of dietary intakes were measured in blood. To the best of our knowledge, this is the first report to use objective biochemical markers to support the information about dietary intakes obtained from questionnaires in groups of adults associated with ID. Biomarkers have been shown to have relative good correlation with intake measured by other assessment techniques (27, 29, 31, 33). This is a strength in our study, given the methodological challenges in recording habitual diets in general, and the challenges in addressing diets in persons with ID living in community residences, where a significant proportion of the individuals live unsupervised for many hours a day. The latter is a methodological challenge, making the use of proxy reporters difficult.

Overweight and obesity was prevalent in the study population, and the mean BMI of 30.0 kg/m^2 was elevated compared to the mean BMI of 27 kg/m^2 reported from the general adult Norwegian population (51). Increased risk of overweight and obesity in adult populations with ID is well known and emphasizes the rationale for investigations of determinants, such as diets, that may contribute to the high risk of obesity in these populations.

In the general adult Norwegian population, daily consumption of fruit, fruit juice, and vegetables are reported in about 55, 40, and 60%, respectively (52). Thus, our data suggests larger proportion with daily consumption of fruit and vegetables in the PWS-group, and reduced proportion with daily consumption of fruit and vegetables in both the WS-group and the DS-group. Our data cannot be evaluated with respect to adherence to food based dietary guidelines for intakes of fruit and vegetables due to the types of methods used. However, intake frequencies of three times or less per week suggest intakes below the recommended level. In participants with WS, such low consumption frequency of fruit and vegetables was observed in 71 and 58%, respectively. In DS, 40% were low-frequency consumers of fruit and 25% were low-frequency consumers of vegetables, whereas the corresponding numbers for participants with PWS were 23 and 5%, respectively. These findings, with the exception of those in the PWS-group, were in accordance with the previously described low intakes of fruit and vegetables

Citation: Food & Nutrition Research 2015, **59**: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487

in several studies of community-dwelling persons with ID (15, 16, 18) and with DS (6). However, low intake frequency of fruit and vegetables has previously not been described for an adult population with WS. These findings are interesting in light of the high risk of developing hypertension associated with WS (53), and the fact that diets rich in fruits and vegetables may contribute to reduce the risk of hypertension (54). Even so, this association needs to be further evaluated in relation to WS.

The biomarkers studied overall support the data obtained from the food intake frequency questionnaire. A reduction in plasma carotenoids of about 40% in WS, and about 35% in DS, was observed when compared to measured levels in PWS. There are a few genetic alterations know to affect the level of carotenoids in plasma (55). However, none of these are located on the chromosomes known to be involved in the included subgroups, and provides support that the measured difference is due to consumption inequality. Unfortunately, the measured carotenoids cannot be used to calculate actual intake of fruit and vegetables in the groups. However, the underlying concept is that the use of such objective markers in blood is related to intake and takes in to account effect of absorption and metabolism such as oxidative stress and excretion, and by this provides supportive data that should be of high value in investigations on fruit and vegetable intakes and health outcomes (25).

Increased BMI was associated with a reduction in plasma carotenoid concentrations in the PWS and DS groups, although this correlation was only significant for individuals with DS. This might suggest that persons with increased BMI in some subgroups consume less fruit and vegetables. This tendency was supported by the results based on reported intake frequencies in relation to BMI-categories. This finding is furthermore in accordance with descriptions from other investigations in overweight and obese individuals with ID (16) and from adults in the general populations where BMI has been found to be negatively associated with plasma carotenoid levels (28). Even so, it has also been suggested that the observed difference in plasma carotenoids related to weight status also might be influenced by difference in metabolism of carotenoids in persons with excessive body weight compared to persons with normal weight, although, the possible impact of this currently is not well described (25). In WS, persons classified as having a BMI at the lower end of normal range or as being underweight, showed a tendency toward lower intake frequency of fruits and vegetables and lower plasma concentrations of carotenoids. No severely underweight individuals participated in the study, but these findings may indicate that feeding problems typically occurring in early childhood in this group (34), for some individuals may persist into adulthood and continue as selective eating or other eating disorders (56). Obesity is described to be the most frequent weight related problem in adults with ID (4, 5). Nevertheless, the diversity observed between the groups in this study elucidates the heterogeneity found in adults with ID who were also underweight, and that feeding problems are more frequently observed in these groups compared to the general population (4). Further studies investigating the association between diets and BMI should describe and take into account individuals with feeding problems and selective eating pattern, as these individuals might also be found among persons in the normal BMI-range.

About 10% of the general Norwegian population consumes seafood daily (52) and about 15% consume fish meals less than once a week (13). When the diagnosis-groups were compared, intake frequencies of fish and omega-3 supplementations were lowest in the WS population, and 20% of individuals in this group reported an intake frequency of less than once a week, which is below the recommended frequency of two to three times a week for prevention of secondary conditions (12). In WS, the combination of low-frequency consumption of fish, less use of omega-3 supplementation, and reduced level of long chained omega-3 FAs in erythrocyte membranes indicate increased risk of insufficient intakes of essential omega-3 FAs, and potentially also insufficient intake of vitamin D. In Norway, fish and omega-3 supplements containing vitamin D are the most important sources of vitamin D. The reduced intakes of fish and omega-3 supplements found in the WS-group may be due to their vitamin D content, where dietary restrictions in childhood, implemented to resolve sporadic hypercalcemia, may have contributed to a habit of low intakes that continue through adolescence and into adulthood.

Data from the present study indicate that participants with PWS comply better with dietary recommendations for fruit, vegetables, fish, and omega-3 intake than participants in the WS-group and, in some aspects, participants in the DS-group. We suspect that this difference may be explained by frequent use of restrictive low-energy diets, in combination with the descriptions of dietary vulnerabilities (41, 42), and increased level of support associated with PWS in our study population.

About one-third of the study population consumed soft drinks daily or several times a day, a result that is similar to what is described from the general population (52). Furthermore, there was a tendency toward higher intake of soft drinks in community-dwelling participants with DS compared to peers living with relatives. Frequent consumption of soft drinks among persons living in communities has also previously been reported (16, 18, 21). Sugar-sweetened soft drinks are important contributors to refined sugar intake (13) and are compared to artificially-sweetened beverages associated with less-favorable health outcome (57). Frequent use of sugar-sweetened soft drinks may be one of the underlying factors contributing to the

increased risk of obesity in community-dwelling persons with ID (21). Unfortunately, in this study we do not have data to differentiate between the use of sugar-sweetened and artificially-sweetened soft drinks, and no association was observed between obesity and high intake frequency of soft drinks in this study. Nevertheless, daily use of soft drinks with and without sugar is in general associated with reduced dental health (58).

Intake of precooked meals was higher in community-dwelling participants with DS. The use of precooked meals in adults with ID can be a double-edged sword. On one hand, these meals can provide nutritional independence, but on the other hand, they are often energy dense, with high fat and salt content, and with low content of vegetables and fiber. Furthermore, they are often not adjusted to the reduced energy needs associated with DS and PWS, and if family-size package meals are selected, persons with ID eating alone might have difficulties dividing the meal into adequate portion size. For these reasons the total energy intake from and nutrient content of these meals needs to be evaluated, as our data indicate that they are an important part of the diet for a significant proportion of persons living in community residences. To comply with the law regulating the right to self-determination, the use of these meals also needs to be voluntary and not forced due to lack of proper training in cooking skills or assistance.

Living in communities was accompanied by increased influence on food choices and responsibility for foods. In this study, no difference in proportions with low and high intake frequencies of fruit, fruit juice, vegetables, fish, and omega-3 supplementation was detected when persons living in communities were compared to those living with relatives. This is an important finding as it is a common perception that increased autonomy in persons with ID in general leads to overall poor diets. Nevertheless, if individuals with ID are given freedom to make dietary decisions, this needs to be accompanied by proper training regarding healthy food choices and food preparation skills. Studies have shown that individuals with ID make healthier food choices after intervention targeting nutritional knowledge (59). Proper support in these aspects may also be of importance in the transition period when persons establish new routines in community settings. There might also be a need to increase knowledge and skills in food-related tasks among caregivers assisting these groups (60).

This study has several limitations. The method of recruitment and low participant numbers limit the statistical power and the generalizations, although approximately one-third of the known population of PWS and WS in Norway in the relevant age category participated, and we recruited participants from all over the country. No formal testing of intellectual functioning was conducted, and this is an important limitation, as there may be differences in these aspects related to the included genetic conditions, even though all three conditions are associated with similar level of ID. The fact that all participants cooperated well and were able to complete all aspects of the data collection, indicates that the average level of functioning in the study population might have been above the average in the respective diagnosis. The simplified dietary assessment technique used in this study does not include all aspects of dietary intake, and can only be used to describe some overall food intake frequency patterns. Additional use of digital photography of meals consumed would probably have improved the dietary intake estimates (61, 62). Furthermore, a validation of the individuals' abilities to report diets at this consumption level would have been valuable. Nevertheless, an agreement in results between the reported intake frequencies and measured biomarkers was observed, providing credibility and support to the results obtained. For these reasons, the results of the present study must be regarded as explorative rather than conclusive.

Persons with WS had a less-favorable dietary pattern, as indicated by the larger proportion of low-frequency consumers of fruits and vegetables as well as lower plasma carotenoid concentrations when compared to persons with PWS. In addition, a larger proportion of persons with WS were low-frequency consumers of fish, fewer used omega-3 supplementation, and lower concentrations of erythrocyte omega-3 FAs were observed in persons with WS compared to persons with PWS and DS. A more comprehensive assessment of diets in adult persons with WS is warranted and should include assessment of medical and physical aspects that might influence food intakes. An increased proportion of persons with DS living in communities were high-frequency consumers of precooked meals, and there was a tendency toward a larger proportion of high-frequency consumers of soft drinks, when compared to peers living with relatives. Apart from this, their intake frequencies of the investigated foods were similar to those living with relatives, even though they had higher degree of food-related autonomy.

Acknowledgements

This study was funded by the Extra Stiftelsen and Frambu Resource Centre for Rare Disorders. The authors thank the collaborating patient organizations and are grateful to Kari Hagen for her contribution during data collection at Frambu.

Conflict of interest and funding

The authors declare no conflict of interests. The study was founded by Extrastiftelsen and Frambu Resource Centre for Rare Disorders.

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Citation: Food & Nutrition Research 2015, 59: 25487 - http://dx.doi.org/10.3402/fnr.v59.25487

III

Title

The prevalence of metabolic risk factors of atherosclerotic cardiovascular disease in Williams syndrome, Prader-Willi syndrome and Down syndrome

Running Title

Risk of atherosclerotic cardiovascular disease

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This study was funded by the ExtraStiftelsen and the Throne Holst Foundation. The founding sources had no involvement in study design, interpretation of data or writing of the manuscript. The authors declare no conflict of interests.

ACKNOWLEDGEMENTS

The authors thank HUNT Research Centre for their collaboration and contribution of data from the HUNT-3 study. In addition, we would like to express our gratitude to Rita S. Stige, Kari Stenslie, Gro Trae, Kari Hagen and Annicke Stranda for their contributions during data collection.

ABSTRACT

Background

Risk of atherosclerotic cardiovascular disease (CVD) and association with abdominal obesity have not been extensively studied in genetic syndromes associated with intellectual disability.

Methods

A cross-sectional study was conducted in individuals' age 20-43 years with Williams syndrome (WS) (n=21), Prader-Willi syndrome (PWS) (n=20) and Down syndrome (DS) (n=31). Established metabolic risk factors of CVD were assessed.

Results

High prevalence of hypertension and type 2 diabetes was seen in the PWS group, whereas low prevalence rates were found in DS. In WS, we found a high prevalence of hypertension and indication of increased risk of type 2 diabetes, combined with better blood lipid profile. Abdominal obesity was prevalent in all three subgroups and was associated with an increased risk of hypertension and metabolic syndrome.

Conclusion

PWS and WS had increased risk of CVD. In order to prevent CVD in these groups, regular assessments of the known risk factors are recommended.

KEYWORDS

Atherosclerosis, cardiovascular disease, abdominal obesity, hypertension, type 2 diabetes

INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is an important cause of death also in individuals with intellectual disability (ID) (Heslop, 2013). Different groups with ID share common health challenges, many of which are related to lifestyle such as high prevalence of inactivity (Nordstrom, Hansen, Paus, & Kolset, 2013; Phillips & Holland, 2011). Even so, from a genetic point of view they represent a heterogeneous group with distinct patterns of comorbidities, possibly also with variability in risk of CVD.

Williams syndrome (WS, Williams-Beuren syndrome), Prader-Willi syndrome (PWS), and Down syndrome (DS) are genetically determined conditions associated with mild to moderate ID. The estimated prevalence of the conditions varies from 1:7500 in WS (Stromme, Bjornstad, & Ramstad, 2002), to 1:25.000 in PWS (Smith et al., 2003), and 1:1200 in DS (Presson et al., 2013).

WS is caused by a microdeletion of genes on chromosome 7q11.23, typically affecting 26-28 genes including the elastin coding gene, ELN (Pober, 2010). The lack of functional elastin in WS (Nickerson, Greenberg, Keating, McCaskill, & Shaffer, 1995), is linked to development of congenital cardiovascular abnormalities, observed in about 80 % of the patients. The structural cardiovascular irregularity most often includes some form of arterial stenosis (Adams & Schmaier, 2012; Collins, 2013; Del Pasqua et al., 2009). Furthermore, elastin insufficiency may lead to vascular stiffness and development of hypertension (Kozel et al., 2014), which is reported to occur in 40-55 % of young adults (Broder et al., 1999; Eronen et al., 2002). In contrast, loss in functional copies of the NCF1 gene, which is one of the genes variably deleted in WS, may have a protective effect against hypertension (Del Campo et al., 2006; Kozel et al., 2014). Diabetes and impaired glucose tolerance is reported in 63-75 % of adult persons with WS (Masserini et al., 2013; Pober et al., 2010). The syntaxin-1A gene and MLXIPL gene, located in the 7q11.23-region, are suspected to be involved in the abnormal

glucose regulation reported in WS (Pober et al., 2010). Previously, a 25-100 times higher risk of sudden cardiac death has been described in WS (Wessel et al., 2004).

PWS is due to lack of paternal expression of genes in the 15q11-q13-region caused by deletion, maternal uniparental disomy 15, or an imprinting defect (M. G. Butler, 2011). Clinical hallmarks of the condition include neonatal hypotonia, later hyperphagia and several endocrine disturbances, such as growth hormone deficiency, hypogonadism and central adrenal insufficiency (Cassidy, Schwartz, Miller, & Driscoll, 2012). The prevalence of hypertension in persons with PWS is reported to range from 9-21 %, diabetes in 15-24 %, and metabolic syndrome and dyslipidemia in 35 %, respectively. All factors were shown to be associated with obesity (J. V. Butler et al., 2002; Grugni et al., 2012; Hoybye, Hilding, Jacobsson, & Thoren, 2002; Sinnema et al., 2011; Sode-Carlsen et al., 2010). High risk of obesity is recognized in PWS and a low-energy diet combined with rigorous food supervision in combination with regular physical activity is recommended for prevention and treatment of obesity (Goldstone et al., 2008). In PWS, a high premature mortality rate due to cardiorespiratory complications has been described (Grugni et al., 2008)

DS is caused by an extra copy or major portion of chromosome 21 (Hattori et al., 2000). Congenital heart defect is prevalent with atrioventricular and ventricular septal defects as the most common features (Weijerman et al., 2010). DS has been associated with several risk factors of CVD, including inactivity, high risk of obesity, and insulin resistance (Melville, Cooper, McGrother, Thorp, & Collacott, 2005; Nordstrom et al., 2013; Real de Asua, Parra, Costa, Moldenhauer, & Suarez, 2014). However, most persons with DS have low blood pressure (Draheim, McCubbin, & Williams, 2002), and reduced formation of atherosclerotic lesions in adult age (Draheim, Geijer, & Dengel, 2010). The biological mechanisms behind this remain unknown. It has been suggested that lower levels of homocysteine due to higher

dosage of the gene, cystathionine beta synthase, contribute to the reduced development of atherosclerosis (Vis et al., 2009).

Persons with mild to moderate ID have increased risk of developing obesity (Melville, Hamilton, Hankey, Miller, & Boyle, 2007). Waist circumference (WC) provides information about body shape and abdominal obesity, and WC has good predictive abilities for obesity-related health risks (Janssen, Katzmarzyk, & Ross, 2004). In addition, WC is an easy tool to use in clinical practices. Currently, few studies have investigated the association between excessive abdominal fat mass and risk factors of CVD in specific conditions associated with ID.

In this study we aimed 1) to explore the prevalence of metabolic risk factors of CVD in adults with three different genetic conditions, and compare the prevalence rates in the included groups to those in the general population, and 2) to investigate the associations between abdominal obesity and the CVD risk factors. Our hypothesis was that persons with WS and PWS have increased risk of CVD, whereas persons with DS display reduced CVD risk. Furthermore, we hypothesized that abdominal obesity was associated with increased risk of CVD in the investigated groups with ID.

METHODS

Participants

Information about the study was posted on a study-specific website and was spread in collaboration with relevant nationwide patient organizations. Recruitment was performed using a convenient sampling frame. Inclusion criteria were diagnosis with DS, WS or PWS, age between 16-45 years, and returned consent forms to participate, signed by both the participant and legal guardian/parent. All participants who returned a signed consent form

were invited to participate. A total of 96 participants from all over Norway took part in the study. Seventy-two participants were included in the final analyses, after excluding 15 participants younger than 20 years of age, to facilitate a comparison of results to prevalence data from a Norwegian cohort study. Furthermore, nine participants were excluded due to negative results from laboratory genetic testing and assessment of clinical criteria. In total, 80 % of the participants had their genetic condition verified by molecular testing, and the rest by use of standard clinical methods. No participants reported any previous atherosclerotic CVD. More information about characteristics of the study populations are presented in Table 1. The Regional Committee for Medical and Health Research Ethics, Southeast Region provided ethical approval for the study, with reference number 2012/140.

Data collection

We used an electronic questionnaire to collect demographic data, information on smoking habits, alcohol consumption, current use of medication, information about previous diagnosis of dyslipidemia, diabetes, hypertension and metabolic syndrome, medical history of coronary heart disease and cerebrovascular disease. The participants, together with an employed caregiver or parent, used a computer to fill out the questionnaire. Intakes of medication were later categorized in accordance with their primary cause of prescription. Their alcohol intake was collected in categories of: Never or less than once a month, 1-3 times a month, 1-2 times a week, 3 times a week or more, and units of alcohol consumed on each occasion was recorded.

Laboratory data

Blood samples were collected in the morning after overnight fasting and samples for plasma and serum were centrifuged within 2 h. Analysis of hemoglobin A1c (HbA1c), total cholesterol (cholesterol), high density lipoprotein (HDL) cholesterol, triglycerides (TG),

thyroid stimulating hormone (TSH), and free T4 was performed in fresh blood samples in accordance with standard protocols at the clinical laboratory of the regional university hospital. Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Determination of apolipoprotein A1 (apo A1), apolipoprotein B (apo B), lipoprotein (a) (Lp (a)) was performed on heparin plasma after two freeze and thaw cycles with the use of immunoturbidimetric assays. Lower sensitivity range for Lp (a) was 60 mg/l and values below this were recorded as 50 mg/l.

Blood pressure

Blood pressure was measured by trained testing personnel according to recommendations provided by the American Heart Association Council on high blood pressure research (Pickering et al., 2005). An upper arm automatic blood pressure device with oscillometric measurement technique was used (Microlife BP A100 Plus, Microlife, Widnau, Switzerland). Participants were familiarized with blood pressure measurements and screened for differences in blood pressure between the arms on day one of the data collection. The next day measurements were taken three times with one minute intervals in between, after at least 10 minutes of rest prior to measurement. A mean of these three measurements was then calculated and recorded. Measurements were taken in the arm with the highest pressure recorded in the screening or, if no difference was observed, in the dominant arm. The mean deviance in the measures was 4.9 mmHg in systolic and 4.8 mmHg in diastolic blood pressure.

Body composition

Body composition measurements were taken in light clothing with bare feet. WC was measured twice by stretch-resistant tape (Seca, Birmingham, UK), with tape emphasized to be horizontal, and the person placed in an upright position. Measurements were taken directly on the skin, at the midpoint between the lowest rib and iliac crest after exhalation, and were

recorded at the nearest 0.1 cm. If the measurements differed more than 1.0 cm, a third measurement was taken to determine which was the most reliable. An average of the two recorded measurements was calculated and used.

Prevalence of metabolic risk factors in the general population

To facilitate a comparison of the included groups to the general Norwegian population, prevalence data for the different metabolic risk factors was obtained from the HUNT 3 Study. This is a large Norwegian cohort study with data collected from about 14,000 participants in the age range of 20-43 years. The HUNT 3 survey is the latest data collection and was carried out from 2006 to 2008 (Krokstad et al., 2013).

Definition of metabolic risk factors

Hypercholesterolemia was defined as serum total cholesterol ≥ 5.0 mmol/l and serum LDL cholesterol ≥ 3.0 mmol/l or use of lipid-lowering medication (Perk et al., 2012). No information about LDL cholesterol was available from the HUNT 3 study. Increased total cholesterol was defined as total cholesterol ≥ 5.0 mmol/l, and used for comparison to the general population. Increased total cholesterol: HDL cholesterol ratio was defined as ≥ 5 (Norheim, 2009).

Metabolic syndrome was defined if participants had three or more of the following criteria: WC ≥94 cm for males and ≥ 80 cm for females; serum triglycerides > 1.7 mmol/l; serum HDL-cholesterol <1.0 mmol/l for males and <1.3 mmol/l for females; mean systolic blood pressure of ≥130 mmHg and/or mean diastolic blood pressure of ≥85 mmHg or use of antihypertensive medication; HbA1c > 6.0 % or use of glucose-lowering medication (Alberti et al., 2009; Nathan et al., 2008). In the general population; serum glucose > 7.8 mmol/l or use of glucose-lowering medication replaced the above described HbA1c dependent criteria.

Diabetes was defined as HbA1c ≥6.5 % or previously diagnosed with diabetes and use of glucose-lowering medication (The International Expert Committee, 2009). In the general population diabetes was defined as serum glucose >11.1 mmol/l or previously diagnosed with diabetes and use of glucose-lowering medication (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus., 1997).

Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication (angiotensin II- receptor antagonists, calcium antagonists or ACE-inhibitors) (James et al., 2014). Persons using monotherapy with β-blockers were defined as having hypertension only if they reported previous diagnoses of hypertension (n=1).

Abdominal fat mass was categorized by use of the recommended cut-point for Caucasians, where WC ≥ 94 cm for males and ≥ 80 cm for females were defined as increased WC. WC ≥ 102 cm for males and ≥ 88 cm for females were defined as abdominal obesity (World Health Organization, 2000).

Statistical analysis

Initially, one-way analysis of variance (ANOVA) and Person's chi-square test were used to identify differences between the subgroups. All measured biochemical and physical variables were checked for missing data, descriptive statistics calculated, and normality assessed. The values in the subgroups were compared by use of ANOVA, or if normality was violated by use of Kruskal-Wallis test. The proportions of persons fulfilling the criteria of the metabolic risk factors were explored in contingency tables in subgroups based on genetic diagnosis. We used Pearson's chi-square tests to investigate differences in prevalence of risk factors between genetic subgroups. For the comparison of increased total cholesterol: HDL cholesterol ratio, only the PWS and DS group was included. Similarly, in hypertension only the WS and PWS

groups were compared. Furthermore, in prevalence of type 2 diabetes, due to low numbers we used Fishers exact test to compare the WS group to the PWS group only. To compare the prevalence rates of the metabolic risk factors of the included subgroups to those of the general population, we calculated relative risk estimates for all three subgroups.

The associations between abdominal obesity and metabolic risk factors were investigated using Pearson's chi-square test. To ensure test validity a combined group of those with normal WC and increased WC was used in comparison to abdominal obesity. In comparing individuals with and without abdominal obesity, independent t-tests were used in measured systolic and diastolic blood pressure. Prior to analysis, proportions using antihypertensive medication in the groups were investigated. As the proportion using medication was equal in the WC category groups, analysis was not corrected for use of medication. All statistical analyses were performed using SPSS 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

As shown in Table 1, there was a difference in age between the subgroups. Individuals with WS were the oldest and those with DS the youngest. Among participants with DS, fewer lived in community residences with support, compared to the WS and PWS group. Alcohol consumption was low and all participants who reported drinking alcohol had an intake equal to 1-2 units when alcohol was consumed. Few in the study population smoked. Furthermore, analyses on biochemical and physical parameters were performed (Table 2). Thyroid-related disorders were frequently reported and thyroid substitution therapy was used by 17 participants in the study population (Table 1). No participants had low levels of free T4 at evaluation, but approximately 20 % in all three genetic subgroups were found to present mildly elevated TSH levels and subclinical hypothyroidism. Nine participants with PWS were on growth hormone therapy, but there were no significant differences in the measured

parameters (Table 2) when participants using growth hormone were compared to participants without growth hormone treatment.

The prevalence of metabolic risk factors of CVD in the genetic conditions is presented in Table 3A, and the prevalence rates from the general population in Table 3B. To investigate possible differences between the subgroups, established metabolic risk factors were compared both between the groups and with data from the general population. No differences in prevalence of hypercholesterolemia or increased total cholesterol were evident when the three subgroups were compared. In addition, no difference in prevalence of increased total cholesterol was detected when we compared the subgroups to the general population, relative risk (RR) 1.3, 95 % CI (0.93; 1.82), p=0.19 in the WS group, RR 1.2, 95 % CI (0.78; 1.7), p=0.50 in the PWS group, and RR 1.2, 95 % CI (0.84; 1.6), p=0.41 in the DS group. A better blood lipid profile, as indicated by higher HDL cholesterol and Apo A1 levels, and reduced Apo B levels, total cholesterol: HDL cholesterol ratio, and Apo B: Apo A1 ratio (Table 2), was evident when the WS group was compared to the PWS and DS groups. Furthermore, reduced prevalence of increased total cholesterol: HDL cholesterol ratio was noted, (RR) 0.2, 95 % CI (0.02; 1.3), but this difference was not significant, p=0.07, when the WS group was compared to the general population. In addition to this, we observed a high risk of hypertension in the WS group, RR 4.8, 95 % CI (3.2; 7.2), p<0.001, and in the PWS group, RR 2.7, 95 % CI (1.4; 5.3), p=0.007, when compared to prevalence in the general population. Low prevalence of hypertension was observed in the DS group and lower levels in systolic and diastolic blood pressure were measured when compared to the WS group and the PWS group (Table 2). When the prevalence of metabolic syndrome was compared, no differences between the diagnosis-groups were detected or when compared to the general population. However, increased risk of type 2 diabetes was evident in the PWS group when compared to the general population, RR 3.2, 95 % CI (1.0; 8.5), p=0.04. Furthermore, increased risk of

type 2 diabetes, although not significant, was also noted in the WS group, RR 3.0, 95 % CI (0.93; 10.7), p=0.05, when compared to the general population. Low prevalence of type 2 diabetes was observed in the DS group.

Excessive abdominal fat mass was common in all three groups and there were no significant differences in prevalence of increased WC and abdominal obesity when the subgroups were compared to each other (Table 3A). Even so, in the WS group mean measured WC was reduced compared to the other two groups (Table 2). Accordingly, in comparison with the general population, elevated risk of increased WC was seen in the PWS group, RR 1.5, 95 % CI (1.3; 1.7), p=0.007 and in the DS group, RR 1.3, 95 % CI (1.1; 1.6), p=0.02, but not in the WS group. Moreover, we observed an increased risk of abdominal obesity in all included subgroups when compared to the general population, with RR 1.8, 95 % CI (1.3; 2.5), p=0.008 in the WS group, RR 2.3, 95 % CI (1.9; 2.9), p<0.001 in the PWS group, and 1.9, 95 % CI (1.5; 2.4), p<0.001 in the DS group.

To investigate the association between abdominal obesity and the other risk factors presented, all individuals with abdominal obesity were compared to a combined group of participants with normal and increased WC. The mean age and gender distribution were similar in the subgroups based on WC. Using the chi-square test, we found abdominal obesity to be associated with hypertension, $x^2 = 4.2$, p=0.04, and metabolic syndrome, $x^2 = 4.9$, p=0.03. In addition, abdominal obesity was associated with a mean increase in systolic blood pressure of 13.0 mmHg, 95 % CI (5.4; 20.8), p=0.001, and mean increase in diastolic blood pressure of 7.6 mmHg, 95 % CI (2.1; 13.1), p=0.007. As shown in Figures 1A and 1B, WS was the subgroup with the largest difference in measured systolic and diastolic blood pressure when persons with abdominal obesity were compared to persons with normal and increased WC.

DISCUSSION

In this study we describe diversity in CVD risk profile between the included genetic syndromes, and we found an increased risk of CVD in the PWS group and WS groups. High prevalence of hypertension and type 2 diabetes was seen in the PWS group, whereas low prevalence rates were found in DS. High prevalence of hypertension and a clear indication of increased risk of type 2 diabetes were also seen in the WS group, combined with a better blood lipid profile. Abdominal obesity was prevalent in all three subgroups and associated with increased risk of CVD. The described elevated risk for development of CVD in the PWS and the WS groups, are supported by previous reports of high premature mortality rate due to cardiorespiratory complications and sudden cardiac deaths in these groups (Grugni et al., 2008; Wessel et al., 2004). Hence, these data highlights the importance of identifying risk factors of CVD, and persons within these groups at particular risk.

The prevalence of hypertension that we observed in the PWS group was higher than previously reported (Hoybye et al., 2002; Sinnema et al., 2011). However, the latter reports were based on younger individuals or relied on questionnaire-reported hypertension, which may explain the differences observed. Apart from this, the prevalence rates of CVD risk factors and the association with abdominal obesity in this study, were in accordance to previous reports (J. V. Butler et al., 2002; Grugni et al., 2012; Hoybye et al., 2002; Sinnema et al., 2011). One strength of this study is the use of biochemical and physical measures which contrast with several previous reports that use questionnaires or interviews (J. V. Butler et al., 2002; Sinnema et al., 2011). Furthermore, we assessed several established metabolic risk factors, and observed multiple elevated metabolic risk factors. This finding elucidates that individuals with PWS may benefit from regular assessment of their overall CVD risk.

Individuals with PWS have an extremely high risk of developing obesity due to the hyperphagic behavior (Holland et al., 1993). The fat mass in PWS is mainly located subcutaneously and is therefore accompanied by less adverse metabolic effects (Sode-Carlsen et al., 2010). Even so, in this study elevated risk of metabolic complications was noted in obese persons with PWS when compared to lean individuals. The large proportion with abdominal obesity that was observed supports the need for lifelong strategies to reduce morbid obesity in the PWS group. Controlled energy-restricted diets are essential and macronutrient balanced diets combined with rich intakes of fiber have shown better body weight outcomes compared to simple energy-restricted diets (Miller, Lynn, Shuster, & Driscoll, 2013).

Trials with growth hormone treatment have indicated positive effects on blood lipids, body composition measures and physical activity levels in PWS (M. G. Butler et al., 2013; Sode-Carlsen et al., 2012; van der Klaauw et al., 2006). Possible adverse effects on glucose regulation with an increased risk of insulin resistance have also been observed, and are probably related to a normalization of fat mass distribution during treatment (Jorgensen et al., 2014). In this study there were no significant differences in the levels of the measured parameters between persons using and not using growth hormones. However, the study was not designed for evaluation of potential effects of growth hormone treatment, and hence probably lacks statistical power to evaluate any positive or adverse treatment effects.

Blood lipids have previously not been described in any great extent in adults with WS. We found more favorable blood lipid profiles among persons in the WS group when compared to the two other included subgroups. Indications of a higher level of physical activity among males with WS compared to the two other groups have been reported and could be part of the explanation of the difference observed (Nordstrom et al., 2013). A clear tendency of elevated risk of type 2 diabetes was observed in WS and this was in line with the descriptions of a high

prevalence of type 2 diabetes and glucose intolerance in this group and linked to the genetic hemizygozity in the 7q11.23-region (Pober et al., 2010). In addition, a high prevalence of hypertension was observed. Previously, genetic alterations linked to the risk of hypertension have been described (Kozel et al., 2014). A new perspective in this study was the described association between abdominal obesity and an increase in blood pressure. The WS group was the subgroup with the largest measured effect on blood pressure by abdominal obesity. This indicates that abdominal obesity may be an important intervention target in prevention of CVD among individuals in this vulnerable group.

In DS, the reduced risk of hypertension and the development of atherosclerosis are well documented (Draheim et al., 2010; Draheim et al., 2002). Recently, abdominal obesity in DS was demonstrated as being associated with an increased risk of insulin resistance and with small non-significant adverse effects on blood lipids (Real de Asua et al., 2014). Our results supports an increased risk associated with abdominal obesity, as abdominal obesity was found to be accompanied with increased risk of metabolic syndrome.

Increased susceptibility to a variety of autoimmune disorders is described in DS. These include type 1 diabetes and thyroid autoimmunity most often manifested as hypothyroidism (Goldacre, Wotton, Seagroatt, & Yeates, 2004). No individuals with type 1 diabetes participated and no participants with untreated hypothyroidism were detected. Even so, subclinical hypothyroidism was noted in a relatively large subpopulation of all the included genetic syndromes. Hypothyroidism and subclinical hypothyroidism are often accompanied by serum lipid concentrations associated with increased risk of CVD, which can be improved through thyroid replacement therapy (Asvold, Vatten, Nilsen, & Bjoro, 2007; Cappola & Ladenson, 2003). Therefore, it may be important to monitor the thyroid function on a regular basis for optimal long-term prevention of CVD in these genetic conditions.

This study has limitations. The small study sample, low statistical power and recruiting procedure make the study explorative and hypothesis generating, rather than conclusive. However, a low number of participants is a general challenge for studies on rare conditions, and in this study about one third of the known Norwegian population of WS and PWS in the relevant age category participated. Nevertheless, the low number of participants limits the statistical procedures and increases the risk of type II errors. Unfortunately, statistical corrections of potential confounders, such as diversity in living arrangements and age, were difficult to perform when the diagnoses were compared. This may have influenced the results. Furthermore, in comparison to the general population, there were some differences in time of data collection, methodology, and available measured parameters. These differences include non-fasting blood samples and lack of information about HbA1c values in the general population, and also lack of information about blood glucose in the genetic subgroups. This resulted in some differences in definitions of the metabolic risk factors used between the study population and the general population. Although this comparison must be interpreted with caution, the data presented does provide important information on the CVD risk profile in the genetic conditions.

CONCLUSIONS

Heterogeneity in risk of CVD was observed between the included genetic conditions. PWS and WS were found to have an increased risk of CVD, whereas DS was associated with reduced risk. Abdominal obesity was prevalent and closely associated with important metabolic risk factors in all three groups, suggesting a link between abdominal obesity and increased CVD risk in the studied groups as is established in people without ID. In order to identify and treat individuals at high CVD risk, regular assessment of the overall risk of CVD is warranted in adult persons with PWS and WS.

CONFLICT OF INTEREST

None

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Table 1: Characteristics of the study population by diagnosis

	Williams syndrome (n=21)	**Prader-Willi syndrome** (n=20)	**Down Syndrome** (n=31)	**P-values**[1]
Age (years)	34.2 (5.4)	29.3 (5.3)	29.4 (6.6)	0.008*
Males (%)	33	45	39	0.745
Community residence (%)	84	91	60	0.012*
Occupation				0.304
Student (%)	0	0	3	
Employed (%)	71	85	81	
Daycare attendant (%)	5	10	23	
Unemployed (%)	14	5	3	
Alcohol consumption				0.586
Weekly	0	5	0	
1-3 times a month	19	20	16	
Less than once a month	81	75	84	
Smokers (%)	5	10	0	0.215
Medication				
Lipid lowering medication (%)	0	0	3	
Antihypertensive medication (%)	33	14	0	
Glucose lowering medication (%)	14	5	0	
Thyroid substitution therapy (%)	14	5	45	
Growth hormone therapy (%)	0	45	0	
Sex hormone therapy (%)	0	20	0	

The data are presented as mean with (SD) or percentage of the population.

[1]P-values were derived from comparing the different diagnosis groups using one-way analysis of variance (ANOVA) and Pearson's chi-square tests.

Table 2: Biochemical values and physical values by diagnosis

	Williams syndrome (n=25)		Prader-Willi syndrome (n=22)		Down syndrome (n=40)		p-values[1]
	Median	Min – Max	Median	Min - Max	Median	Min - Max	
Cholesterol (mmol/l)	5.2	4.0 – 6.7	5.2	3.5 – 6.7	5.0	3.4 – 7.5	0.68[a]
LDL cholesterol (mmol/l)	3.0	2.0 – 4.0	3.0	2.0 – 4.0	3.0	1.0 – 4.8	0.21[a]
HDL cholesterol (mmol/l)	1.5	0.9 – 2.3	1.2	0.7 – 1.8	1.2	0.8 – 2.1	0.007[b]*
Cholesterol/ HDL cholesterol-ratio	3.5	2.6 – 4.7	4.3	2.4 – 8.1	4.0	1.8 – 9.4	0.023[b]
Triglycerides (mmol/l)	0.9	0.6 – 1.7	1.2	0.5 – 3.0	1.2	0.6 – 4.7	0.13[b]
Apo A1 (g/l)	1.6	1.0 – 2.1	1.4	1.0 – 1.9	1.4	1.0 – 2.1	0.03[a]*
Apo B (g/l)	0.9	0.6 – 1.1	1.1	0.7 – 1.4	1.0	0.4 – 1.6	0.06[b]*
Apo B/ Apo A1 – ratio	0.6	0.4 – 0.8	0.8	0.4 – 1.3	0.6	0.2 – 1.3	0.01[b]*
Lp(a) (mg/l)	232	50 – 1128	334	50 - 1449	386	50 - 2519	0.16[b]
HbA1c (%)	5.4	3.8 – 8.9	5.6	5.0 – 9.0	5.3	4.7 – 6.1	0.13[b]
Systolic blood pressure (mmHg)	125	102 – 163	123	108 - 152	113	87 - 132	0.001[a]*
Diastolic blood pressure (mmHg)	77	50 – 100	78	62 - 105	68	56 - 89	<0.001[a]*
WC (cm)	93	62 – 120	103	81 - 146	100	72 - 128	0.002[a]*

Data is presented as population medians with minimum and maximum values.

P-values were derived by comparison of the subgroups with use of one-way analysis of variance (ANOVA)[a] or Kruskal-Wallis test[b].

* $P<0.05$.

Table 3A: Prevalence of metabolic risk factors by diagnosis

	Williams syndrome (n=21)	Prader-Willi syndrome (n=20)	Down syndrome (n=31)	x^2	p-value
	%	%	%		
Hypercholesterolemia	14.3	40.0	19.4	4.30	0.12[a]
Increased total cholesterol	61.9	55.0	54.8	0.30	0.86[a]
Increased total cholesterol: HDL-cholesterol ratio	0	40.0	32.3	0.32	0.77[b]
Hypertension	52.4	30.0	0	1.50	0.21[c]
Metabolic syndrome	14.3	25.0	19.4	0.75	0.69[a]
Type 2 Diabetes mellitus	14.3	15.0	0		1.00[d]
Increased waist circumference	71.4	90.0	80.6	2.26	0.32[a]
Abdominal obesity	61.9	80.0	64.5	1.86	0.40[a]

Data is presented as percent of populations.

[a]Comparing the subgroups with use of Pearson's chi-square test

[b]Comparing the PWS-group and the DS-group with use of Pearson's chi-square test

[c]Comparing the WS-group and the PWS-group with use of Pearson's chi-square test

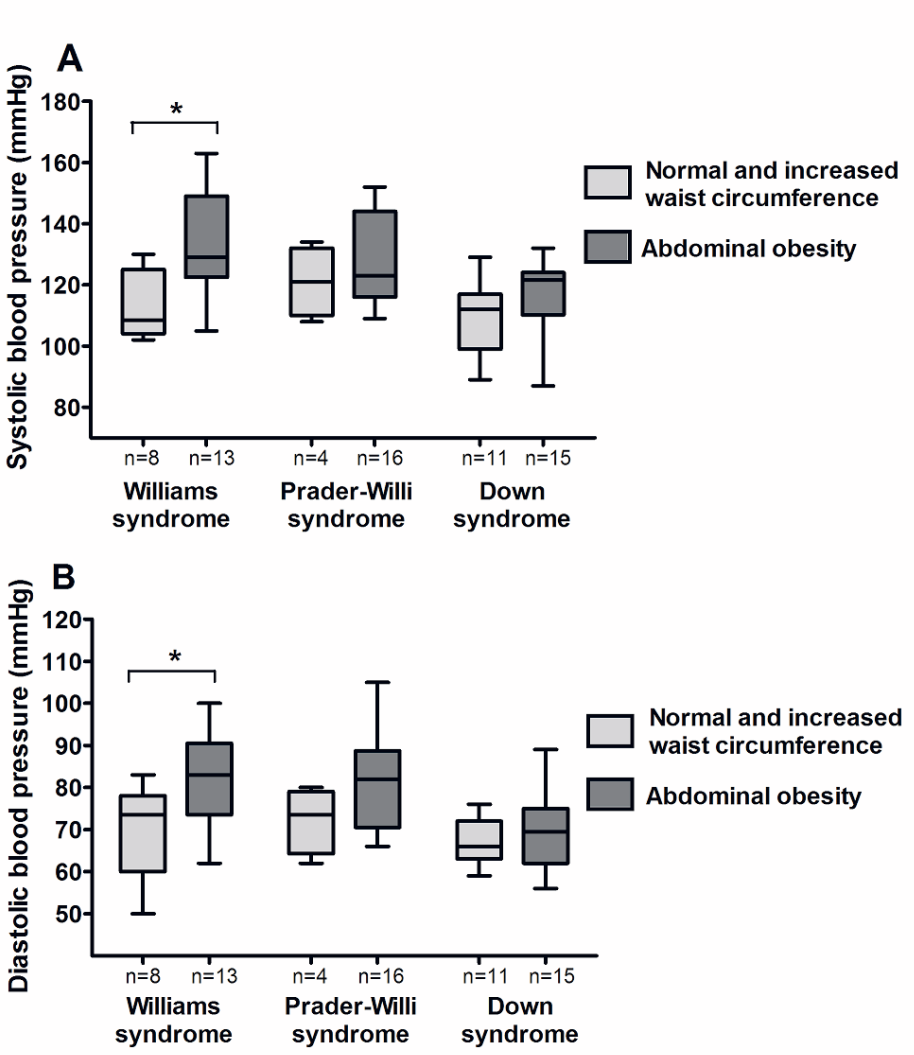
[d]Comparing the WS-group to the PWS-group by use of Fisher's exact test.

Table 3B: Prevalence of metabolic risk factors in the HUNT-3 study population

	General population	
	%	Total (n)
Increased total cholesterol	47.5	13642
Increased total cholesterol: HDL cholesterol ratio	20.6	13641
Hypertension	11.0	12396
Metabolic syndrome	23.2	13213
Type 2 Diabetes mellitus	0.5	14178
Increased waist circumference	60.6	13977
Abdominal obesity	34.3	13977

Data is presented as percent of populations and with the total number of participants assessed per variable.

Figure 1: Blood pressure comparing normal waist circumference and increased waist circumference to abdominal obesity by diagnosis



Box-plot with whiskers indicating min and max values. P-values were calculated by use of independent t-tests comparing persons with normal- and increased WC to persons with abdominal obesity by diagnosis.