Cardiovascular Disease Risk Factors in Older People with Intellectual Disabilities

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General introduction

There is an increasing group of older people with intellectual disability in The Netherlands. Intellectual disability is defined as significant limitations both in intellectual functioning (an IQ lower than 70) and problems in adaptive behavior, which cover a range of everyday social and practical skills, and occur before the age of eighteen [1]. In the Netherlands approximately 160,000 people with intellectual disability receive special education or any other form of support [2]. The population with intellectual disability is increasingly growing older, reaching almost the same life expectancy as the general population, which means that there are over 30,000 people with ID aged 50 years and over, making use of some form of specialized care services. Currently most people with intellectual disability live in the general community. This means that half of all people aged 50 years and over live in the community, for example in group homes or with ambulatory support, making use of standard general and secondary health services. The other half lives in a setting with more specialized care, receiving specialist medical care by ID physicians [3]. Moreover, it is estimated that there are over 1.1 million people with borderline intellectual disability (IQ 70–85) in The Netherlands [4], who do not all have access to specialized care or support services and grow older, too.

This increasing group of aging people more and more faces the same health problems as the general older population. Due to improved knowledge and care on the disability-specific health challenges (syndromes with specific morbidity, epilepsy, recurrent pneumonia due to reflux and aspiration) such issues no longer are a main cause of early mortality. The normal age-related diseases, such as cardiovascular disease, cancer and dementia are now the most encountered diseases in older people with intellectual disabilities. In the general population there is a lot of attention and research into the occurrence of these diseases, which is the basis for prevention, but also for early treatment. This attention lacks in the intellectually disabled population. Until the Healthy Aging and Intellectual Disability study was started, no large preventive studies had been published or preventive health campaigns undertaken. This might be due to the fact that large studies in this population are difficult to perform. But in general, cardiovascular disease risks have received too little attention. Moreover there was a lack of preventive attitude in the care for people with intellectual disabilities. This means that without interventions, the burden of cardiovascular disease and cardiovascular mortality can increase in older people with intellectual disability, in contrast to the decreasing trend in the general population. Cardiovascular disease, such as myocardial infarction or stroke, in addition to the existent intellectual and possibly physical disabilities, will worsen disabilities and make people

more dependent on others in daily activities and in care. This decreases quality of life and increases health care costs for this population.

First of all, the health care problem needs to be mapped. How big is the problem we are facing? Then, targeted interventions can be designed, to improve knowledge in daily practice and thus change health-related behavior (lifestyle). This includes education of personal care-givers and people with intellectual disabilities themselves. Scientific knowledge can be improved, to unravel which mechanisms of disease are of particular interest in this specific population. Then evidence based interventions can be designed, that should not only be started, but also continued in order to result in significant health improvement.

The Healthy Aging and Intellectual Disability study

To gain more knowledge on the health and aging aspects of the growing population of older people with ID, the Healthy Aging and Intellectual Disability (HA-ID) study was initiated [5]. This study was explicitly designed to focus on preventive health care. Three large care organizations and two university departments participated in this study. The care organizations offer low to high level specialized support and care to people with intellectual disability. This is a unique collaboration between these organizations and the university, with the aims to improve scientific knowledge, advance expertise of professional staff, and develop evidence-based interventions for daily practice. Research themes were chosen based on actual questions from clients and professional staff, but also based on current epidemiologic research trends in the general older population [6, 7]. Subthemes in the HA-ID study were: (1) Physical activity and fitness, (2) Nutrition and nutritional state, and (3) Mood and anxiety. By studying these themes and the interrelationships, a comprehensive concept of health and health-needs in aging people with intellectual disability would be created. Through physical examination, laboratory examination, and use of screening and diagnostic psychiatric interviews, data were collected on 1050 participants, which was a near-representative sample for the total older population using formal intellectual disability care [5].

Cardiovascular risk factors

Atherosclerotic cardiovascular diseases are a major cause of death in the older general population. In older people with intellectual disability, international research into cardiovascular morbidity was scarce. Only two Dutch studies indicated that cardiovascular

events occurred at least as frequently as in the general population, but underdiagnosis was suggested [8, 9]. Cardiovascular diseases are caused by cardiovascular risk factors, such as obesity, hypertension, diabetes, hypercholesterolemia (a combination of these factors is defined as the metabolic syndrome), smoking, physical inactivity and also a genetic predisposition.

Research into cardiovascular risk factors was practically limited to research into obesity. It had been shown that obesity was an increasing problem in adults with intellectual disability [10-16]. In population-based studies, the prevalence of obesity (by Body Mass Index (BMI)) was significantly higher than in the general population [17-19]. Obesity in older people with intellectual disability was less often studied and only in smaller or biased samples [20, 21]. Although it was well established that waist-to-hip ratio and, to a somewhat lesser extent, the waist circumference were much stronger indicators for risk on myocardial infarction than BMI[22], all larger studies only investigated BMI outcomes [15-18]. Body fat percentage would provide more information on nutritional state than weight data only, but this had not been studied on a large scale in adults with intellectual disability [10], and had never been studied in older people with intellectual disability. Other cardiovascular risk factors (diabetes, hypertension and hypercholesterolemia) had been insufficiently investigated in older people with intellectual disability. Until the start of the HA-ID study, earlier studies had only been performed in small or biased populations [20, 21, 23-25], or were based on questionnaires [26-28] and results had been inconclusive. Cardiovascular risk factors were reported to occur less frequently [26, 29], similar [21, 23, 24, 30] or more frequently [21, 25] than in the general population.

Since cardiovascular risk factors are, apart from the genetic predisposition, lifestyle-related, people with an unhealthy diet and a sedentary lifestyle are more at risk. Physical inactivity is a widespread problem among people with intellectual disability [31, 32]. Physical inactivity is a well-known risk for developing obesity. But also the larger muscles metabolize body glucose, and thereby contribute to the development of diabetes when muscles are inactive for long periods during the day [33]. There are indications that people with mild or borderline intellectual disability and those who live relatively independent are more at risk of obesity than people with more severe levels of intellectual disability [17-19, 34], which suggested that these people made more unhealthy choices regarding their lifestyle (diet) as they might not be able to oversee long-term consequences. Another important causal factor in cardiovascular risk factors is the widespread use of antipsychotic medication [35, 36]. These agents are often prescribed off-label, usually for behavioral

problems, such as aggression or self-injurious behavior [35], but effectivity on these indications has not been proven [37]. Especially atypical antipsychotic drugs have the well-known side-effect of weight gain and development of the metabolic syndrome [38-40].

Atherosclerosis

The presence of cardiovascular risk factors leads to the development of atherosclerosis. This may first appear in the smaller peripheral vessels. Peripheral arterial disease (atherosclerosis distal from the aortic bifurcation) is a vascular disease, which can lead to pain in the lower limbs while walking. But it is also an indicator of generalized atherosclerosis [41] and an increased risk of larger cardiovascular events (such as myocardial infarction and cerebrovascular accidents) and mortality [41-43]. There was no information on the prevalence of (peripheral) atherosclerosis in older people with intellectual disability.

Comorbid conditions

Cardiovascular risk factors are bidirectionally related to depression and anxiety [44-47]. Underlying mechanisms are that depression and anxiety cause hormonal effects, resulting in abdominal fat accumulation, impaired glucose tolerance and high blood pressure [44, 46, 47]. Moreover, people with anxiety and depression tend to have poor health behavior (e.g. unhealthy diet, smoking, sleep disturbance and low physical activity) [44, 47]. In the opposite direction, depression and anxiety may be caused by increased levels of inflammatory proteins, released from atherosclerotic plaques in the blood vessels, as well as impaired glucose homeostasis and cerebral vascular damage [44, 47]. Further, obesity, diabetes, cardiovascular disease and the subsequent necessary lifestyle changes may result in low self-esteem and fear [44, 46, 47].

As part of the cardiovascular risk management, kidney functioning should be monitored, as kidney functioning is decreased by hypertension, diabetes and atherosclerosis. In this way, kidney disease may advance cardiovascular morbidity and mortality. Only one limited study on kidney functioning in adolescents with intellectual disability was available [48], suggesting that chronic kidney disease was a significant health problem, but no studies were available in adults and older people with intellectual disability.

Study aims

This study was performed to give more insight into the prevalence and associations of cardiovascular risk factors, and the subsequent development of atherosclerosis, in older people with intellectual disability in a large unbiased population sample.

The first cardiovascular disease risk factor, obesity, will be described in chapter 2. Using multiple measures of anthropometry, an overview will be provided of the full scope of this health issue. In addition to BMI measurement information on body composition, based on skin fold measurement to calculate body fat percentage will also be provided. Moreover, a broad range of associated client characteristics, such as gender, age, independent living and use of atypical antipsychotics will be presented.

The other cardiovascular risk factors, hypertension, diabetes, hypercholesterolemia and the metabolic syndrome, will be described in chapter 3. Prevalence will be described, indicating not only a burden of disease due to these conditions, but also a risk on subsequent cardiovascular disease. Associated factors will be described, indicating which subgroups may be particularly at risk.

The consequences of the cardiovascular risk profiles as described in chapter 2 and 3, the development of atherosclerosis, will be reported in chapter 4. In this chapter, results on prevalence and associated factors of peripheral arterial disease, as measured by the ankle-brachial index will be presented. As this is also an indication for the occurrence of larger cardiovascular events this also contributes to the total cardiovascular risk profile.

Studying the interrelationships of subthemes (in this case nutritional state and mood disorders) was one of the main goals of the HA-ID study, providing a comprehensive view on mechanisms and comorbidity. The bidirectional relationship of the cardiovascular risk factors and atherosclerosis and depression and anxiety will be described in chapter 5.

As no cardiovascular risk management is complete without screening for possible kidney damage, in chapter 6 chronic kidney disease will be studied, as an associated factor of cardiovascular risk factors and atherosclerosis.

The general discussion (chapter 7) reflects on the findings in this thesis and provides recommendations for clinical practice and future research.

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Overweight and obesity in older people with intellectual disability

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ABSTRACT

Overweight and obesity are major health problems associated with increased cardiovascular disease risk, which is not sufficiently studied in people with intellectual disability yet. The present study was part of the Healthy Aging in Intellectual Disability (HA-ID) study. The aim of this study was to establish (1) the prevalence of overweight, obesity and body fat percentage in older people with intellectual disability (ID) through measurement of Body Mass Index (BMI), waist circumference, waist to hip ratio (WHR) and skin fold thickness, and compare this with prevalence of overweight and obesity in the general population, and (2) the association of overweight and obesity with participant and treatment characteristics (gender, age, level of ID, Down syndrome, autism, independent living, smoking, (instrumental) activities of daily living ((I)ADL), physical activity and use of atypical antipsychotic medication) using regression analyses. In this cross-sectional study 945 persons, aged 50 and over with borderline to profound ID, living in central settings, in community settings and independently were included. Overweight and obesity were highly prevalent, with more obesity (26%) than in the general Dutch older population (10%) as measured by BMI, and 46-48% obesity as measured by waist circumference and WHR respectively. Women, people with Down syndrome, higher age, less severe ID, autism, people who are able to eat independently, preparing meals and doing groceries independently, people with physical inactivity and use of atypical antipsychotics were significantly more at risk of being overweight or obese. This merits specific actions by policy makers and clinical practice to improve health outcomes.

2.1 INTRODUCTION

Overweight and obesity are major health problems worldwide. They are generally known to cause cardiovascular disease and are the third risk factor for causes of death in middle and high income countries [49]. It has been shown that obesity is an increasing problem in adults with intellectual disability (ID) [10-16]. In population based studies in this group, the prevalence of obesity (by Body Mass Index (BMI)) ranges from 21 to 35%, which is significantly higher than in the general population [17-19]. Within the ID population, people with Down syndrome [50-52], women, people with mild ID and people who live independently [17-19, 34] are more at risk of being overweight or obese.

With increasing longevity in people with ID, obesity can be expected to become a major problem in older people with ID as well. However data on this group are scarce, and only available from small or biased samples. In a retrospective chart study among 155 Australians aged 40-74 who visited a specialized clinic for ageing people with ID, 85 patients had their weight checked. 70% were overweight or obese [20]. In a cross-sectional study among 470 Dutch people with ID, aged 50-90, 24.7% of the respondents was centrally overweight and 45.7% had central obesity as measured by waist circumference, whereas 15% had obesity as measured by BMI. This sample was biased, because women and people with moderate and severe ID were overrepresented [21].

Although it is well established that waist-to-hip ratio (WHR) and, to a somewhat lesser extent, the waist circumference are much stronger indicators for risk on myocardial infarction than BMI [22], all large studies investigated BMI outcomes [15-18]. Body fat percentage would provide more information on nutritional state than weight data only (how is the body composed, and what are the consequences, for example, if there is loss of muscle mass due to obesity, which would give an increased body fat percentage), but this has not been studied on a large scale in adults with ID [10], and has never been studied in older people with ID. Knowledge on cardiovascular morbidity risk and nutritional state in this population is thus incomplete.

Studying related factors will provide insight into risk factors of obesity and information needed for the design of interventions. Apart from already identified determinants we studied the following potential determinants. Since level of ID and activities of daily living (ADL) and instrumental activities of daily living (IADL) are related [53], it can be expected that high ADL and IADL scores are also correlated with obesity. Furthermore, we expected that lower levels of physical activity would predict obesity [32]. Adolescents

with autism and ID have a higher prevalence of obesity than adolescents with other types of disabilities [54]. There may also be high levels of obesity in older people with ID and autism. Finally it is well known that people with ID tend to be overmedicated with antipsychotic drugs [35]. The metabolic consequences of the use of atypical antipsychotic medication are well established, including weight gain [55]. Thus we hypothesized that the use of atypical antipsychotics is one of the determinants of obesity in older people with ID.

The aim of the present study is to provide information on overweight and obesity in a large sample of older adults with ID, investigating:

1. the prevalence of overweight, obesity and body fat percentage through measurement of BMI, waist circumference, WHR and skinfold thickness, and compare this with prevalence of overweight and obesity in the general population.
2. the association of overweight and obesity with participant and treatment characteristics (gender, age, level of ID, Down syndrome, autism, independent living, smoking, ADL, IADL, physical activity and use of atypical antipsychotic medication).

2.2 METHODS

2.2.1 Design

This study is part of a large cross-sectional study, titled 'Healthy Ageing and Intellectual Disability' (HA-ID) [5]. Three care-providing organizations in the Netherlands participated in the study. These organizations offer low to high level specialized support and care to people with ID. Subthemes in this study are: (1) Physical activity and fitness, (2) Nutrition and nutritional state, and (3) Mood and anxiety [5]. Assessing overweight, obesity and body composition is part of the subtheme concerning nutrition and nutritional state. Ethical clearance has been provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care providing organizations. The study adheres to the Declaration of Helsinki for research involving human subjects [56].

2.2.2 Participants

A full description of details about design, recruitment and representativeness of the sample, as well as diagnostic methods, has been published elsewhere [5]. All 2150 clients of the three participating organizations, aged 50 years and over, were invited to participate. Informed consent was provided by 1069 clients or their legal representatives, of whom 1050 clients participated in the assessments. This study population was almost representative for the total Dutch older ID population receiving formal care or support. Only people living independently and people aged 80 years and over were slightly underrepresented [5].

2.2.3 Data collection

Gender and age were collected from the records of the care providers. Participant characteristics were obtained from medical files and files of the behavioural therapists. General practitioners and specialized ID physicians recorded etiology (Down syndrome yes/no) and use of atypical antipsychotic medication (olanzapine, risperidone and quetiapine). Psychologists or behavioural therapists recorded level of ID and diagnosis of autism.

Participants underwent physical examination to assess indicators of overweight and obesity and body composition by specially trained medical assistants. When people showed any kind of (unusual) resistance, measurements were immediately stopped and people were considered as non-participants. Body height was measured using a Seca stadiometer, type 214, with the participant standing, wearing no shoes. For non-ambulant people, knee height was measured using a non-stretchable flexible tape, and Chumlea's formula was used to calculate body height [57]. Weight was measured using a digital floor scale (Seca robusta type 813), with participants wearing light clothes and no shoes. BMI was calculated by weight divided by squared height [58]. BMI ≥25 kg/m² was classified as overweight and ≥30 kg/m² as obese. Using non-stretchable standard tapes, waist circumference was measured over the unclothed abdomen at the narrowest point between the costal margin and iliac crest, and hip circumference was measured over light clothing at the level of the widest diameter around the buttocks. For men waist circumference ≥94 cm was classified as overweight and ≥102 cm as obese. For women, waist circumference ≥80 cm was classified as overweight and ≥88 cm as obese. Waist-to-hip ratio (WHR) ≥0.90 was classified as overweight and ≥1.00 as obese for men, and WHR ≥0.80 was classified as overweight and ≥0.88 as obese for women [58]. Thickness of

skinfolds was measured with a skinfold caliper (Harpenden). The sum of four skinfolds: triceps, biceps, subscapular and suprailiacal, was used to calculate body density using the Visser equation [59]. The Visser equation has been validated in a Dutch group of older adults. Body fat percentage was calculated from body density using Siri's equation [60].

Physical activity was assessed by wearing pedometers for two weeks [32]. We classified a minimum of 7500 steps/day as sufficient physical activity [32]. Professional care-givers were asked about smoking (minimum 1/day), activities of daily living (ADL) by Barthel index [61] and Instrumental Activities of Daily Living by Lawton and Brody [53, 62].

Comparable data from the general Dutch population were only found for BMI. Statistics Netherlands interviewed 10,000 Dutch adults by telephone in 2009 and published age and gender specific results [63].

2.2.4 Statistical analysis

Data were analyzed using IBM SPSS Statistics 17.0. Descriptive statistics are provided. With chi-square analysis we explored if there are any differences between the participants of the abovementioned assessments and the total HA-ID study population in gender, age (age groups 50-59, 60-69, 70-79, 80+), level of ID (borderline, mild, moderate, severe, profound) and independent living (central setting, community based or independent with ambulatory support, with relatives).

To explore associations between weight data (BMI, waist circumference, WHR and body fat percentage) (dependent variables) and participant characteristics; gender (n=945), age(n=945), level of ID (n=924), diagnosis of Down syndrome (n=830), diagnosis of autism (n=888), smoking (n=899), independent living (n=945), ADL items and total score (n=905), IADL items and total score (n=905), physical activity (n=253), use of atypical antipsychotics (n=837) (independent variables), univariate logistic regression (BMI, waist circumference and WHR) and univariate linear regression (body composition) analyses were performed. If an independent variable showed a significant association ($p<0.05$) with the dependent variable, it was subsequently entered into a multivariate regression analysis. Items of ADL and IADL were all entered separately in the univariate analyses. From ADL and IADL the separate item or total score that correlated strongest was entered in the multivariate model (to prevent multicollinearity).

For BMI, multinomial regression analysis was used to compare groups with normal BMI, overweight and obesity. For waist circumference and WHR, binomial logistic regression

analyses were used for people with obesity versus people with normal weight and/or overweight, because of the small amount of people in the normal weight group.

Because no generally accepted reference values exist for the amount of body fat, body fat percentage was used as a linear measure. Therefore, multivariate linear regression was performed to study associations.

Independent variables were entered into the multivariate regression equation simultaneously. Independent variables were checked for multicollinearity, using Pearson's correlation coefficient. If a reasonably high correlation existed (>.400), we entered the variables separately in the models, to see if any change in associations with the dependent variable or explaining value of the model occurred. If this happened, we would provide both models in the results section. For linear regression two measures for multicollinearity are provided. A Variance Inflation Factor (VIF) of 10 or higher is reason for concern (Myers, 1990), and Tolerance values should be 0.2 or higher.

People with missing data on BMI, waist circumference, WHR or body fat percentage were excluded from analysis in that particular model.

2.3 RESULTS

2.3.1 Study population

Of the 1050 participants in the total cohort, 945 participated in the physical examination. Mean age was 61.5 years (range 50-93). Characteristics of the study population are shown in Table 2.1. Representativeness of the groups of participants are shown in Table 2.2. People with profound ID, living in central settings were underrepresented, whereas people with mild ID, living in community settings were slightly overrepresented. This reflects resistance to physical assessments. Moreover, the smallest age group, people aged 80 and over, were underrepresented in the assessment of BMI and waist circumference, and men were overrepresented in measurement of body fat percentage.

2.3.2 Prevalence of overweight and obesity

Prevalence of overweight and obesity by BMI, waist circumference and waist-to-hip ratio (WHR) are presented in Table 2.2. Mean body fat percentage (n=664) was 37.6% (95% confidence interval (CI) 37.0-38.1%, SD 7.1), 31.6% (95% CI 31.3-31.9%, SD

2.9) in men and 44.7% (95% CI 44.4-45.0%, SD 2.9) in women. Comparison with the prevalence of overweight and obesity by BMI in the general population is shown in Table 2.3.

Table 2.1 Characteristics of the study population (n=945)

	N	%
Gender		
Male	482	51.0
Female	463	49.0
Level of ID		
Borderline	30	3.2
Mild	204	21.6
Moderate	454	48.0
Severe	151	16.0
Profound	84	8.9
Unknown	7	0.7
Down syndrome	132	14.0
Autism	149	15.8

Table 2.2 Representativeness of the study population as compared to the Total HA-ID population

	BMI	Waist circumference	WHR	Body fat percentage
Gender	ns	ns	ns	+ (men)
Central setting	-	-	-	-
Community setting	+	+	+	+
Independent living	ns	ns	+	ns
Age 50-59	ns	ns	+	ns
Age 60-69	ns	ns	ns	ns
Age 70-79	ns	ns	-	ns
Age 80+	-	-	ns	ns
Borderline ID	ns	ns	+	ns
Mild ID	ns	ns	+	+
Moderate ID	ns	ns	ns	ns
Severe ID	ns	ns	ns	-
Profound ID	-	-	-	-

ns = non significant difference between study population and HA-ID population; - = underrepresented; + = overrepresented.

Table 2.3 Prevalence of overweight and obesity by BMI, waist circumference and waist-to-hip ratio in study population and comparison with BMI from general Dutch population (aged 45+) (Statistics Netherlands 2011)

	ID population			General population	
	Overweight% (95% CI)	Obese% (95% CI)		Overweight% (95% CI)	Obese% (95% CI)
BMI					
Male (n=454)	39.2 (34.7-43.7)	13.7 (10.5-16.8)	Male (n=1873)	47.7 (45.5-50.0)*	13.2 (11.6-14.7)
Female (n=439)	37.1 (32.6-41.7)	38.0 (33.5-42.6)	Female (n=1790)	35.3 (33.0-37.5)	14.8 (13.2-16.5)*
Total (n=893)	**38.2 (35.0-41.4)**	**25.6 (22.8-28.5)**	**Total (n=3663)**	**41.2 (39.6-42.8)**	**9.6 (8.7-10.6)***
Waist					
Male (n=461)	23.9 (20.0-27.8)	26.7 (22.6-30.7)			
Female (n=437)	19.0 (15.3-22.7)	66.4 (61.9-70.8)			
Total (n=898)	**21.5 (18.8-24.2)**	**46.0 (42.7-49.3)**			
Waist-hip ratio					
Male (n=418)	51.0 (46.2-55.8)	33.3 (28.7-37.8)			
Female (n=416)	22.4 (18.4-26.4)	63.0 (58.3-67.6)			
Total (n=834)	**36.7 (33.4-40.0)**	**48.0 (44.7-51.5)**			

* Confidence intervals do not overlap between ID population and general population.

2.3.3 Associations of overweight and obesity

2.3.3.1 Associations with BMI

Results of univariate analyses are shown in Table 2.4. Searching for multicollinearity resulted in significant correlations between level of ID, being able to eat independently (ADL) and being able to do groceries independently (IADL) with $p<0.001$ and Pearson's correlations between these variables were all 0.40-0.50. Thus the variables were first entered simultaneously in the analysis and subsequently the model was repeated with each time only one of these three variables. The whole model is shown in Table 2.4, with the results for these three measures entered separately. The proportion explained variance of the model did not increase and statistical significance and ORs of the other variables did not change significantly with this intervention.

Table 2.4 Regression analyses of BMI, waist circumference, WHR and body fat percentage

	BMI overweight			BMI obese			BMI obese compared to overweight			Waist circumference			WHR		Body fat percentage	
	Uni	Multi OR (95%CI)	OR (95%CI) from separate analyses	Uni	Multi OR (95%CI)	OR (95%CI) from separate analyses	Multi OR (95%CI)	OR (95%CI) from separate analyses	Uni	Multi	OR (95%CI) from separate analyses	Uni	Multi OR (95%CI)	Uni	Multi Beta
Women	***	2.0 (1.4-2.9)***		***	6.1 (3.9-9.6)***		3.2 (2.0-4.6)***		***	5.1 (2.7-9.7) ***		***	5.8 (4.2-8.1)***	***	0.9***
Older age	**	1.3 (1.1-1.7)*		-	1.2 (0.9-1.6)		0.9 (0.7-1.1)		**	0.8 (0.5-1.3)		**	1.4 (1.1-1.7)**	-	
(less severe) level of ID	***	1.1 (0.8-1.3)	1.4 (1.2-1.7) **† [1]	***	1.4 (1.1-1.9)*	2.0 (1.6-2.6) ***† [1]	1.4 (1.0-1.8)*	1.4 (1.1-1.8) **† [1]	***	1.4 (0.8-2.5)	1.6 (1.0-2.7) † [4]	-		***	0.01
Down syndrome	-			-					**	3.9 (1.1-13.0) *		***	1.8 (1.1-3.0)*	-	
Autism	**	1.1 (0.7-1.7)		***	2.4 (1.2-4.8)*		2.2 (1.1-4.3) *		***	2.1 (0.8-5.5)		-		***	0.02
Smoking	-			-					-			-		-	
Independent living	***			**					***	1.2 (0.7-2.2)	1.4 (0.8-2.5) † [5]	-		*	0.03

Total ADL score	*			-					-			-		-	
Independent eating (ADL)	***	1.7 (1.1-2.6)*	2.0 (1.4-2.9) ***†[2]	***	2.0 (1.2-3.4)*	3.3 (2.1-5.1) ***†[2]	1.2 (0.7-2.0)	1.6 (1.1-2.5) *†[2]	***	0.9 (0.3-2.8)	1.2 (0.4-3.6) †[6]	**	1.6 (1.2-2.3)**	*	0.04
Total IADL score	***			***					***			**		-	
Groceries independently (IADL)	***	1.4 (0.9-2.3)	1.9 (1.3-2.9) **†[3]	**	1.6 (0.9-2.8)	3.1 (1.9-4.9) ***†[3]	1.2 (0.7-1.9)	1.6 (1.0-2.4) *†[3]	**	1.9 (0.9-4.0)	2.2 (1.1-4.4) *†[7]	*		-	
Preparing meal independently (IADL)	**			**					*			**	1.6 (1.0-2.7)*	-	
Physical activity < 7500 steps/ day	-			-					***	3.7 (1.7-8.0) **		-		***	0.1***
Use of atypical antipsychotics	-	0.4 (0.2-1.0)		*	2.3 (1.0-5.3)		2.7 (1.2-6.4)*		-			-		-	

Note: BMI model: R^2=.21 , Waist circumference model: R^2=.33, WHR model: R^2=.25 (Nagelkerke), body fat percentage model: R^2=.87. *p<.05, **p<.01, ***p<0.001. - = not significant (p≥.05); † = ORs are results from separate analyses: [1] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and level of ID entered in the model; [2] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and independent eating (ADL) entered in the model; [3] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and doing groceries independently (IADL) entered in the model; [4] = Analysis with gender, age, Down syndrome, diagnosis of autism, less physical activity and level of ID entered in the model; [5] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and independent living entered in the model; [6] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and independent eating (ADL) entered in the model; [7] = Analysis with gender, age, diagnosis of autism, use of atypical antipsychotics and doing groceries independently (IADL) entered in the model.

Being female was a higher risk for both being overweight or obese vs normal weight, but also for being obese vs overweight. Increasing age was a higher risk for being overweight. Having a diagnosis of autism was associated with obesity. Use of atypical antipsychotics was associated with more obesity versus overweight. A less severe ID, being able to eat independently and being able to do groceries independently were all significantly correlated with overweight and obesity and also caused a higher risk for obesity compared to being overweight. The proportion explained variance (R^2) of the model was .21.

2.3.3.2 Associations with waist circumference

For waist circumference binomial (multivariate) logistic regression analysis was performed to find associations with the obesity group, compared to the normal/overweight group. Independent variables included in the model were gender, age, level of ID, Down syndrome, having a diagnosis of autism, (semi-) independent living, being able to eat independently (ADL), being able to do groceries independently (IADL) and physical activity<7500 steps/day. Possible multicollinearity existed between level of ID, independent living, being able to eat independently (ADL) and being able to do groceries independently (IADL). These variables were subsequently entered in separate models, together with gender, age, Down syndrome, having a diagnosis of autism and physical activity<7500 steps/day. The whole model is shown in Table 2.4 with the results for these four measures entered separately in the analysis. The proportion explained variance of the model (Table 2.4) did not increase and significance and ORs of the other variables did not change significantly with this intervention.

Women, people with Down syndrome, people who were physically inactive (<7500 steps/day) and people who were able to do groceries independently had significantly more obesity by waist circumference. The proportion explained variance (R^2) of the model was .33.

2.3.3.3 Associations of waist to hip ratio

For WHR, binomial (multivariate) logistic regression analysis was performed to investigate associations with the obesity group as compared to the normal/overweight group. Independent variables entered in the model were gender, age, Down syndrome, being able to eat independently (ADL), being able to prepare a meal independently (IADL). Multicollinearity was not a problem in this model. Women, people with higher age, people with Down syndrome, people who were able to eat and/or prepare a meal independently were significantly more at risk of being obese by WHR (Table 2.4). The proportion explained variance (R^2) of the model was .25.

2.3.3.4 Associations of body fat percentage

For body fat percentage, linear regression analysis was performed. Independent variables included in the model were gender, level of ID, Down syndrome, being able to eat independently (ADL), total score on IADL and physical activity<7500 steps/day. Based on Tolerance and VIF values, multicollinearity was not a problem in this model. Women and people who were physically inactive had a significantly higher body fat percentage (Table 2.4). The proportion explained variance (R^2) of the model was .78.

2.4 DISCUSSION

This is the first study applying multiple measures of overweight and obesity in a large sample of older adults with ID. Overweight and obesity are highly present within this group: 38% are overweight and 26% obese according to body mass index (BMI), whereas with waist circumference and waist-to-hip ratio (WHR), proportions of obesity are even higher, with 22-37% being overweight and 46-48% being obese, respectively. Compared to the general Dutch population aged 45+ [63] using BMI, prevalence of being overweight is similar, whereas obesity is more prevalent in people with ID (Table 2.2). Looking more closely, our results show that men with ID are less overweight, but similarly obese, whereas women with ID suffer more often from obesity, but no differences were observed for being overweight. For waist circumference, WHR and body fat percentage, no comparable data from the general Dutch population were available. Prevalence of obesity, as measured with waist circumference and WHR, were higher than prevalence of overweight. This was not found with BMI. As in the general population, women, people with higher age, and people with insufficient physical activity are more at risk for being overweight or obese [64]. ID-population specific risk groups are people with Down syndrome, people using atypical antipsychotics, people with autism, less severe ID and people who can eat independently and do groceries and prepare a meal independently.

With studying related factors of obesity in older people with ID explained variance was not very high for BMI (R^2=.21), waist circumference (R^2=.33) and WHR (R^2=.25). This means that obesity and overweight are also present in other subgroups than the above-mentioned risk groups, and that other factors (for example diet composition or genetic syndrome related factors), not yet identified in this study, may also account for obesity in this group. The explained variance of the body fat percentage model was very high (R^2=.78), which means that gender and physical inactivity account for a large part of the risk on a high body fat percentage.

A limitation of the present study was that we compared our data to published data of the general population and that these were not available for waist circumference, WHR and body fat percentage. A further limitation is that no validated reference values for overweight and obesity are available for body fat percentage [65], and that body fat percentage had to be computed from skin fold measurement, because the gold standard (DEXA-measurement or densitometry) is not feasible in large scale epidemiologic research in people with ID. For computing body fat percentage, Visser's equation was used based on four skinfold measurements [59]. This equation was developed and validated for the older Dutch population in 1994. We hypothesized that, although in general (as a time trend), people may have become more often overweight or obese, and thus mean body fat percentage has increased, the relation between skinfold thickness and body fat percentage did not change significantly over time. Furthermore, a recent study showed that Visser's equation is still valid in the general older population [66]. With measurement of body fat percentage, selection bias occurred due to overrepresentation of men (which will result in an underestimation of the mean body fat percentage in the total group), which is why it is best to look at gender-specific numbers. Furthermore people with mild ID were overrepresented and people with severe and profound ID were underrepresented, and people living in community based settings were underrepresented. As people with borderline ID and living independently were equally represented in the sample we conclude that skinfold measurement is possible in people with ID but can result in more resistance in people with more severe levels of ID. Since age, level of ID and independent living were not significantly correlated with body fat percentage this did not influence mean levels of body fat percentage. For the measurement of BMI, waist circumference and WHR, people with profound ID who were living in central settings were underrepresented, whereas people with mild ID and living in community settings were overrepresented. This reflects resistance to the physical examination, and may give an overestimation of the prevalence of overweight and obesity by these measures, as people with more independent functioning are more at risk.

A strength of this study was, apart from the large sample, that overweight and obesity were studied with multiple measures, fully capturing all aspects of obesity, including the best predictors for ischaemic heart disease (waist circumference and WHR) [22]. This makes our outcomes a valuable indication of an increased morbidity risk. Another strength was the large set of correlates studied, including both (ID specific) physical circumstances, and behavioural and lifestyle related factors were included. These correlates were studied

much more objectively (such as physical activity and ADL and IADL), than in a previous study in older people with ID [21].

Possible explanations for the high prevalence of overweight and obesity are, that older people with ID cannot oversee long-term effects of eating unhealthy food. Since people who are able to do groceries, prepare meals and eat by themselves are more at risk, they may not have sufficient knowledge on what is healthy and what is not, and how to prepare healthy meals. Furthermore, people may have small budgets and unhealthy meals tend to be cheaper. People with autism were more at risk of obesity. This has also been reported in adolescents [54] and may thereby be a problem since young age.

Especially the high levels of obesity as measured by waist circumference and WHR, which represent central obesity and are strongly correlated to cardiovascular disease [22], warrant concern. To treat obesity in older people with ID, especially in people with more independent functioning, education on healthy behavior is urgently needed. Knowledge and intake of healthy food should be promoted. Encouraging physical activity is very important, both to lose weight and to prevent cardiovascular disease. Older people with ID need active support in changing these behaviors and maintaining a healthy lifestyle. Furthermore, doctors should be cautious with prescribing (atypical) antipsychotics, which are frequently used off-label in people ID and have severe metabolic side-effects [35].

The results of the present study give rise to additional research questions: Is the high rate of central obesity by waist circumference and WHR an ID-population specific problem, or is this a problem in the general population as well? And does this reflect only high amounts of abdominal fat, or is there also loss of muscle mass (increased fat sarcopenia), specific for this group? Therefore we would also need to know the body fat percentage in the general population. Are older people with ID more vulnerable to obesity and subsequent cardiovascular disease than the general older population? These questions need to be answered prospectively.

In conclusion, using multiple measures to assess overweight and obesity in older adults with ID reveals a huge problem in this population. High prevalence rates of overweight and obesity not only influence individual health in older adults with ID, but increase the risk of cardiovascular conditions, and practice as well as policy should be aware of these avoidable consequences for health care costs and quality of life.

3

Cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia and metabolic syndrome) in older people with intellectual disability: results of the HA-ID study

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ABSTRACT

Hypertension, diabetes, hypercholesterolemia and the metabolic syndrome are important risk factors for cardiovascular disease (CVD). In older people with intellectual disability (ID), CVD is a substantial morbidity risk. The aims of the present study, which was part of the Healthy Aging in Intellectual Disability (HA-ID) study, were (1) to determine the prevalence of CVD risk factors in older people with ID and to compare this with the prevalence in the same-aged general population, (2) to determine how many risk factors had not been previously diagnosed, and (3) to identify correlates of CVD risk factors (gender, age, level of ID, Down syndrome, independent living, activities of daily living, mobility, instrumental activities of daily living, physical activity, use of atypical antipsychotics, central obesity), using logistic regression analyses. In this cross-sectional study, 980 people with borderline to profound ID participated. Hypertension (53%), diabetes (14%) and metabolic syndrome (45%) were present similarly as in the general Dutch population. Hypercholesterolemia was present less often (23%). Fifty percent of the people with hypertension had not been not previously diagnosed with this condition. Percentages for diabetes, hypercholesterolemia, and the metabolic syndrome were 45, 46 and 94 respectively. People who were more at risk for CVD risk factors were women, older people, people with obesity, people who lived more independently and people who were able to do groceries or prepare a meal independently. Policy on prevention, detection and treatment of CVD risk factors is urgently needed.

3.1 INTRODUCTION

Hypertension, hypercholesterolemia and diabetes mellitus are directly related to cardiovascular disease (CVD), and are major risk factors for causes of death not only in high income countries, but worldwide [49]. The metabolic syndrome, a complex of these risk factors and abdominal overweight with insulin resistance as a possible underlying mechanism, leads to CVD [67].

Cardiovascular disease can also be expected to become a major burden of disease and cause of death in older people with intellectual disability (ID), because of increasing longevity, as well as a high prevalence of obesity [68] and a sedentary lifestyle [28, 31, 32]. Moreover, cardiovascular disease is associated with certain genetic syndromes (such as Bardet-Biedl syndrome [69], Prader-Willi syndrome [70], sex-chromosomal abnormalities, Werner's syndrome, as well as mitochondrial defects and congenital rubella syndrome[71]). Evidence on CVD in people with ID is scarce. In two studies, combined prevalence of coronary artery disease and cerebrovascular accidents in older people with ID was 3.2% [8] and 5.7% [9], which was not different from prevalence in the general population. However, more cerebrovascular accidents were reported than myocardial infarctions[9]. This indicates that the latter diagnosis might be missed, because people with ID may be less able to communicate pain or other signs of myocardial infarction, leading to an under estimation of the prevalence [9].

CVD risk factors (diabetes, hypertension and hypercholesterolemia) have been insufficiently investigated in older people with ID. Until now, studies have only been performed in small or biased populations [20, 21, 23-25], or were based on questionnaires [26-28] and results have been inconclusive. CVD risk factors were reported to occur less frequent [26, 29], similar [21, 23, 24, 30] or more frequent [21, 25] than in the general population. We have studied overweight and obesity as part of the HA-ID study and found a higher prevalence of obesity by body mass index than in the general population. Moreover, similar to the general population there were very high rates of abdominal obesity, which gives an increased risk of CVD [68].

Several subgroups have been reported to have more CVD risk factors. People with a less severe ID [21, 25], more independent living and functioning [68] and less physical activity [72] are more at risk. Moreover, there is a widespread use of (atypical) antipsychotics [35], which is associated with metabolic changes [73]. Smoking is associated with CVD risk factors [74, 75], but this association has not been investigated in older people with

ID. However, smoking is an increasing problem among people with ID [16]. In contrast, people with Down syndrome are suggested to be less at risk for CVD risk factors [76].

Underdiagnosis of CVD risk factors has been suggested to be an important pitfall [26, 77]. To justify an active CVD prevention policy, it is necessary to determine the prevalence of CVD risks in older people with ID. We hypothesize that many risk factors remain undiagnosed in this group, which would require an active approach for detecting these risk factors. Studying related factors aids in focusing on groups that are more at risk and making strategies to promote health in these specific groups. Therefore the aims of the present study were:

1. To determine the prevalence of hypertension, diabetes mellitus, hypercholesterolemia and metabolic syndrome in older people with ID, using formal ID services, and to compare this with the prevalence in the general older Dutch population.
2. To determine how many new diagnoses of CVD risk factors are found.
3. To identify correlates of cardiovascular risk factors (gender, age, smoking, level of ID, Down syndrome, residential setting, activities of daily living, mobility, instrumental activities of daily living, physical activity, use of atypical antipsychotics, central obesity).

3.2 METHODS

3.2.1 Design

This study is part of a large cross-sectional study, titled 'Healthy Ageing and Intellectual Disability' (HA-ID) [5]. Three care-providing organisations in the Netherlands participated in the study. These organizations offer low to high level specialised support and care to people with ID. Subthemes in this study are: (1) Physical activity and fitness, (2) Nutrition and nutritional state, and (3) Mood and anxiety [5]. Assessment of blood pressure, serum glucose, serum cholesterol and components of the metabolic syndrome was part of the subtheme concerning nutrition and nutritional state. Ethical clearance has been provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care-providing organisations. The study adheres to the Declaration of Helsinki for research involving human subjects [56].

3.2.2 Participants

A full description of details about design, recruitment and representativeness of the sample, as well as diagnostic methods, has been published elsewhere [5]. Of the three participating organisations, 2150 clients aged 50 years and over were invited to participate. Informed consent was provided by 1069 clients or their legal representatives, of whom 1050 clients participated in the assessments. This study population was almost representative for the total Dutch older ID population receiving formal care or support: only people living independently and people aged 80 years and over were underrepresented, women were slightly overrepresented [5].

3.2.3 Data collection

Gender and age were collected from the records of the care-providing organisations. Participant characteristics were obtained from medical files and files of the behavioural therapists. General practitioners and specialized physicians for people with ID recorded etiology (Down syndrome yes /no), cardiovascular risk factors, cardiovascular disease and use of medication. Use of blood pressure lowering drugs (antihypertensives C02, beta-blockers C07, ACE-inhibitors C09, diuretics C03, selective angiotensin II antagonists C09, calcium channel blockers C08), glucose lowering drugs A10, lipid lowering drugs C10 and atypical antipsychotic medication (olanzapine N05AH03, risperidone N05AX08 and quetiapine N05AH04) was noted.

Participants underwent physical examination and vena puncture by specially trained medical assistants. If people showed any kind of (unusual) resistance, measurements were immediately stopped and people were considered as non-participants. Blood pressure was measured twice using the Omron M7, after at least two minutes of rest in seated position. Hypertension was defined as a mean systolic blood pressure ≥ 140 mmHg and/ or a mean diastolic blood pressure ≥ 90 mmHg [78] and/ or the use of blood pressure lowering drugs (if a participant used diuretics, diagnosis was checked in the medical file, to differentiate between hypertension and heart failure).

Waist circumference was measured over the unclothed abdomen at the narrowest point between the costal margin and iliac crest [68]. For men waist circumference ≥ 102 cm was classified as obesity, as was ≥ 88 cm for women [79].

Vena puncture was performed after an overnight fast. Serum was transported frozen, stored at -80 degrees Celsius and analyzed at the laboratory of the Erasmus Medical Center, which is a reference laboratory, with specific expertise in serum lipid analysis. Reference values of the Erasmus Medical Center were used. Diabetes mellitus was defined as a fasting serum glucose > 6.1 mmol/l and/or the use of glucose lowering drugs. Hypercholesterolemia was defined as a fasting serum total cholesterol > 6.5 mmol/l and/or the use of lipid lowering drugs. Metabolic syndrome was defined according to the criteria of the joint interim statement 2009 [67]. Metabolic syndrome was present if at least three of the following five criteria were met: a serum fasting glucose ≥ 5.6 mmol/l and/or the use of glucose lowering drugs, serum fasting triglycerids ≥ 1.7 mmol/l and/or the use of lipid lowering drugs, serum fasting HDL cholesterol ≤ 1.0 mmol/l in men and ≤ 1.3 mmol/l in women and/or the use of lipid lowering drugs, waist circumference (measured using non-stretchable standard tapes, waist circumference ≥ 94 cm in men and ≥ 80 cm in women (reference values for overweight in Europeans), and blood pressure ≥ 130/≥ 85 and/or use of antihypertensive drugs.

To be able to compare our data with previous studies we also present the prevalence of metabolic syndrome defined according to the NCEP-ATP III criteria: as the presence of at least 3 of the following 5 symptoms: abdominal obesity (waist circumference for men > 102 cm, women > 88 cm), insulin resistance (serum fasting glucose ≥ 6.1 mmol/l), hypertriglyceridemia (≥ 1.7 mmol/l), low HDL cholesterol (< 1.0 mmol/l in men, < 1.3 mmol/l in women) and hypertension (blood pressure systolic ≥ 130 and diastolic ≥ 85 mmHg) [80].

Physical activity was assessed by wearing pedometers for at least four days [32]. We classified a minimum of 7500 steps/day as sufficient physical activity [32]. People who were not able to participate in pedometry because they were bound to a wheelchair or were unable to walk independently, were also classified as physically inactive. Professional caregivers were asked about smoking (minimum 1/day), activities of daily living (ADL) by Barthel index [61] and Instrumental Activities of Daily Living by Lawton and Brody [53, 62].

Comparable data of the Dutch general population are published by the National Institute for Public Health and the Environment[81]. A sample of 4513 people, aged 30-70 years, underwent physical examination and vena puncture. Data are published age and gender specific. Data were extracted for the group aged 50-70, and compared to results from the HA-ID study population aged 50-70.

3.2.4 Statistical analysis

Data were analysed using IBM SPSS Statistics 17.0. Descriptive statistics are provided. With chi-square analysis we tested if there were any differences between the study participants and the total HA-ID study population in gender, age (age groups 50-59, 60-69, 70-79, 80+), level of ID (borderline, mild, moderate, severe, profound) and residential setting (central setting, community based or independent with ambulatory support, with relatives). Descriptive statistics were used to report prevalence rates of CVD risk factors (aim 1), and to compare between measurements in the study, and data from the medical files (aim 2).

To explore associations between hypertension, diabetes, hypercholesterolemia and metabolic syndrome (dependent variables) and participant characteristics (correlates); gender, age, level of ID, diagnosis of Down syndrome, smoking, residential setting, (I) ADL items and total score, physical activity, use of atypical antipsychotics and obesity by waist circumference (independent variables), univariate logistic regression analyses were performed. If an independent variable showed a significant association ($p < 0.05$) with the dependent variable, it was subsequently entered into a multivariate logistic regression analysis. Items of ADL and IADL were all entered separately in the univariate analyses. From ADL and IADL the separate item or total score that correlated strongest was entered in the multivariate model (to prevent multicollinearity). Independent variables were entered into the multivariate regression equation simultaneously. Independent variables were checked for multicollinearity, using Pearson's correlation coefficient. If a reasonably high correlation existed (> .400), we entered the variables separately in the models, to see if any change in associations with the dependent variable or explaining value of the model occurred. If this happened, we presented both models in the results section. People with missing data on hypertension, diabetes, hypercholesterolemia or metabolic syndrome in physical examination or vena puncture were excluded from analysis in that particular model.

3.3 RESULTS

3.3.1 Study population

Of the 1050 participants in the total cohort, 980 participated in physical examination and/or vena puncture. Mean age was 61.5 years (range 50-93). Characteristics of the study population are shown in Table 3.1. Representativeness of the groups of participants of physical examination (n = 815), vena puncture (n = 724) and those who fulfilled all

Table 3.1 Characteristics of the study population

	N	%
Gender (n = 980)		
Male	503	51.3
Female	477	48.7
Level of ID (n = 980)		
Borderline	30	3.1
Mild	210	21.4
Moderate	476	48.6
Severe	157	16.0
Profound	85	8.7
Unknown	22	2.2
Down syndrome (n = 861)	139	16.1
Smoking (n = 931)	190	20.4
Use of atypical antipsychotics (n = 866)	51	5.9

assessments of metabolic syndrome (n = 584) are shown in Table 3.2. In the physical examination group, people with severe and profound ID, living in central settings were underrepresented, whereas people with mild ID, living in community settings were overrepresented. This may reflect resistance to or misunderstanding of physical assessments and physical disabilities. Moreover, men were very slightly overrepresented. In the vena puncture group, people living in central settings were overrepresented and people living in community settings and living independently were underrepresented. This was due to the fact that some people who did not live in central locations had to travel to the nearest (local) laboratory for vena puncture, and some people declined for this reason. The sample of people who participated in all assessments required for the diagnosis of metabolic syndrome was representative with the exception of an underrepresentation of people with profound ID.

Table 3.2 Differences between the current study sample and the total HA-ID population

	Blood pressure Chi-square (dF)	Vena puncture Chi-square (dF)	Metabolic syndrome Chi-square (dF)
Gender	4.1* (1)	.2 (1)	3.6 (1)
Residential setting	35.9*** (3)	19.6*** (3)	3.8 (3)
Age	2.3 (5)	.9 (5)	2.8 (4)
Level of ID	40.4*** (5)	11.6* (5)	12.3* (5)

* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

3.3.2 Prevalence of cardiovascular risk factors

Prevalence of hypertension, diabetes mellitus, hypercholesterolemia and metabolic syndrome is presented in Table 3.3. Prevalence of metabolic syndrome defined according to the joint interim statement was 44.7% (95% CI 40.7-48.7%) (Table 3.3), whereas defined according to the NCEP-ATP III criteria, prevalence was 24.8% (95% CI 21.3-28.3%). Prevalence of CVD risk factors in the HA-ID population as compared to the general Dutch population [81], both aged 50-70, is presented in Table 3.4. Hypertension and metabolic syndrome are less prevalent in men with ID and more prevalent in women with ID than in the general population (as determined by the absence of overlap between 95% confidence intervals). Diabetes is more prevalent in women with ID. The overall hypertension, diabetes and metabolic syndrome prevalence does not differ between populations. Hypercholesterolemia is less prevalent in men, women and the overall ID population, as compared to the general population. To give a complete overview of CVD risk factors, prevalence of overweight and obesity (which has been published before [68]) is also shown, as compared to the general population aged 50-70 years [81] (Table 3.4).

Table 3.3 Prevalence of cardiovascular risk factors

	Prevalence %	95% CI
Hypertension		
Men (n = 432)	49.8	45.1-54.5
Women (n = 383)	56.7	51.7-61.6
Total (n = 815)	**53.0**	**49.6-56.4**
Diabetes mellitus		
Men (n = 375)	11.7	8.5-15.0
Women (n = 349)	15.8	11.9-19.6
Total (n = 724)	**13.7**	**11.2-16.2**
Hypercholesterolemia		
Men (n = 375)	16.5	12.8-20.3
Women (n = 349)	30.1	25.3-34.9
Total (n = 724)	**23.1**	**20.0-26.1**
Metabolic syndrome		
Men (n = 315)	36.5	31.2-41.8
Women (n = 269)	54.3	48.3-60.2
Total (n = 584)	**44.7**	**40.7-48.7**

Table 3.4 Prevalence of cardiovascular risk factors

	ID population aged 50-70 (95% confidence interval)		General population aged 50-70 (95% confidence interval)	
Hypertension	Men (n = 366)	45.4% (40.3-50.5)	Men (n = 1104)	55.1% (52.1-58.0)*
	Women (n = 319)	53.9% (48.5-59.4)	Women (n = 1160)	44.0% (41.1-46.8)*
	Total (n = 685)	**49.3% (45.6-53.1)**	**Total (n = 2264)**	**49.4% (47.3-51.4)**
Diabetes	Men (n = 320)	10.0% (6.7-13.3)	Men (n = 1063)	10.2% (8.3-12.0)
	Women (n = 291)	15.5% (11.3-19.6)	Women (n = 1110)	8.0% (6.4-9.6)*
	Total (n = 611)	**12.6% (10.0-15.2)**	**Total (n = 2173)**	**9.1% (7.9-10.3)**
Hypercholesterolemia	Men (n = 320)	15.6% (11.7-19.6)	Men (n = 1088)	36.2% (33.4-39.1)*
	Women (n = 291)	28.9% (23.7-34.1)	Women (n = 1130)	40.2% (37.3-43.0)*
	Total (n = 611)	**21.9% (18.7-25.2)**	**Total (n = 2218)**	**38.3% (36.3-40.3)***
Metabolic syndrome**	Men (n = 269)	27.5% (22.2-32.9)	Men (n = 1074)	44.8% (41.8-47.8)*
	Women (n = 223)	46.2% (39.6-52.7)	Women (n = 1160)	36.6% (33.8-39.4)*
	Total (n = 492)	**36.0% (31.7-40.2)**	**Total (n = 2186)**	**40.6% (38.6-42.7)**
Overweight (Body Mass Index 25-30 \ kg/m^2)	Male (n = 387)	39.3% (34.4-44.1)	Male (n = 1105)	50.7% (47.7-53.6)*
	Female (n = 374)	36.4% (31.5-41.2)	Female (n = 1158)	35.8% (33.0-38.5)
	Total (n = 761)	**37.8% (34.4-41.3)**	**Total (n = 2263)**	**43.0% (41.0-45.1)**
Obesity by Body Mass Index (≥ 30 kg/m^2)	Male (n = 387)	12.1% (8.9-15.4)	Male (n = 1105)	13.9% (11.9-16.0)
	Female (n = 374)	37.2% (32.3-42.1)	Female (n = 1158)	17.5% (15.3-19.7)*
	Total (n = 761)	**24.4% (21.4-27.5)**	**Total (n = 2263)**	**15.8% (14.3-17.3)***
Central obesity (waist circumference)	Male (n = 392)	24.0% (19.8-28.2)	Male (n = 1104)	37.0% (34.2-39.9)*
	Female (n = 375)	64.3% (59.4-69.1)	Female (n = 1162)	50.5% (47.6-53.4)*
	Total (n = 767)	**43.7% (40.2-47.2)**	**Total (n = 2266)**	**43.9% (41.9-46.0)**

* Confidence intervals do not overlap between ID population and general population.
** Metabolic syndrome defined according to the joint interim statement criteria [67], but with abdominal obesity instead of abdominal overweight (waist circumference ≥ 102 cm in men and ≥ 88 cm in women).

3.3.3 New diagnoses of cardiovascular risk factors

For 715 of the 815 participants in the physical examination group, medical file data were available. Of these 715 persons, 385 met the criteria for hypertension in this study, of which 191 (50%) had not been previously diagnosed with hypertension (neither in medical file nor receiving medication). Of 724 participants in serum glucose measurement, medical file data were available for 654 persons, of whom 91 met the criteria for diabetes mellitus in this study. Of these 91 persons, 41 (45%) had not been previously diagnosed with diabetes (neither in medical file nor receiving medication). Out of 724 participants in serum lipid measurement, with 651 with available medical file data, 157 met the criteria for hypercholesterolemia in this study. There were 73 persons (46%) with a new diagnosis of hypercholesterolemia (neither in medical file nor receiving medication). For 518 of the 584 participants in metabolic syndrome assessments, medical file data were available. Of these, 241 met the criteria for metabolic syndrome according to the joint interim statement definition. No mention was made of metabolic syndrome in the medical files in 226 participants (94%).

3.3.4 Associations with cardiovascular risk factors

Univariate and multivariate associations between client characteristics and hypertension, diabetes, hypercholesterolemia and metabolic syndrome are presented in Table 3.5.

3.3.4.1 Associations with hypertension

Independent variables included in the multivariate logistic regression model with hypertension were gender, age, level of ID, Down syndrome, (semi-) independent living, being able to prepare a meal independently and obesity by waist circumference. Possible multicollinearity existed between level of ID, independent living and being able to prepare a meal independently. Level of ID and preparing a meal independently were subsequently entered in separate models, together with gender, age, Down syndrome and obesity (Table 3.5). The proportion explained variance of the model (R^2) was 0.18 (Table 3.5) and did not increase with this intervention, whereas significance and ORs of the other variables did not change significantly either.

The following groups were significantly more at risk of having hypertension: people with higher age, people with other causes of ID than Down syndrome, people who lived more independently, people who were able to do groceries independently and people who were obese.

Table 3.5 Logistic regression analyses (univariate and multivariate)

	Hypertension			Diabetes			Hypercholesterolemia			MS	
	Uni	Multi	Sep	Uni	Multi	Sep	Uni	Multi	Sep	Uni	Multi
Female (Gender n = 980)	*	1.2 (0.8-1.7)		-			***	1.8 (1.1-2.8)*		***	2.8 (1.9-4.1)***
Higher age (n = 980)	***	1.6 (1.3-2.0)***		**	1.2 (0.9-1.7)		*	1.2 (0.9-1.5)		***	1.3 (1.0-1.7)*
Less severe level of ID (n = 958)	**	1.0 (0.8-1.3)	1.2 (1.0-1.4)†[1]	***	1.3 (0.9-1.8)	1.5 (1.1-2.0)**†[3]	***	1.1 (0.8-1.4)	1.4 (1.1-1.7)**†[5]	***	1.3 (1.0-1.6)*
Absence of Down Syndrome (n = 861)	***	3.1 (1.7-5.4)***		*	3.1 (0.9-10.6)	3.6 (1.1-11.9) *†[3]	*	1.5 (0.7-3.0)		***	3.1 (1.5-6.1)**
Smoking (n = 931)	-			-			-			-	
More independent living (Residential setting n = 980)	***	1.6 (1.3-2.2)**		-			*	1.3 (0.8-1.9)	1.7 (1.2-2.3)**†[6]	-	
Mobility (ADL) (n = 937)	-			-			-			-	
ADL total (n = 937)	-			-			**			-	
ADL eating (n = 937)	-			-			**	1.1 (0.7-2.0)	1.8 (1.2-2.8)**†[7]	-	

IADL total (n = 937)	**			**			***			***	
IADL groceries (n = 937)	-			**	1.6 (0.9-2.8)	1.9 (1.1-3.2)*†[4]	***	1.9 (1.1-3.2)*	2.4 (1.5-3.7)***†[8]	***	1.8 (1.1-2.9)*
IADL preparing meal (n = 937)	**	1.3 (0.8-2.3)	1.7 (1.1-2.8)* †[2]	*			**			**	
Atypical Antipsychotics (n = 866)	-			-			*	2.0 (0.9-4.5)		-	
PA < 7500 steps (n = 359)	-			-			-			-	
Obesity (n = 898)	***	1.9 (1.3-2.8) ***		**	1.7 (1.0-2.9)		***	2.1 (1.3-3.3)**			

R^2: Hypertension model: 0.18, Diabetes model: 0.10, Hypercholesterolemia model: 0.15, metabolic syndrome model: 0.19.
- = univariate not significant; * = p < 0.05; ** = p < 0.01; *** = p < 0.001; † = Results from multiple logistic regression analysis in a separate model, because multicollinearity seemed to be a problem.
[1] = Gender, age, Down syndrome, obesity and level of ID were entered in the model; [2] = Gender, age, Down syndrome, obesity and preparing meal independently (IADL) entered in the model; [3] = Age, Down syndrome, obesity and level of ID entered in the model; [4] = Age, Down syndrome, obesity and doing groceries independently entered in the model; [5] = Gender, age, Down syndrome, use of atypical antipsychotics, obesity and level of ID entered in the model; [6] = Gender, age, Down syndrome, use of atypical antipsychotics and independent living entered in the model; [7] = Gender, age, Down syndrome, use of atypical antipsychotics and eating independently entered in the model; [8] = Gender, age, Down syndrome, use of atypical antipsychotics and doing groceries independently entered in the model.

3.3.4.2 Associations with diabetes mellitus

Independent variables included in the multivariate logistic regression model with diabetes were age, level of ID, Down syndrome, being able to do groceries independently (IADL) and obesity by waist circumference. Possible multicollinearity existed between level of ID and being able to do groceries independently. These two independent variables were subsequently entered in separate models, together with age, Down syndrome and obesity. The proportion explained variance of the model (R^2) was 0.10 (Table 3.5) and did not change significantly with this intervention. The OR of 'absence of Down syndrome' changed if 'being able to do groceries independently' was left out of the analysis. Other independent variables did not change significantly.

Significantly more at risk of having diabetes were people with a less severe ID, people with other causes of ID than Down syndrome and people who were able to do groceries independently.

3.3.4.3 Associations with hypercholesterolemia

Independent variables included in the multivariate logistic regression model with hypercholesterolemia were gender, age, level of ID, Down syndrome, (semi-)independent living, being able to eat independently (ADL), being able to do groceries independently (IADL), use of atypical antipsychotics and obesity by waist circumference. Possible multicollinearity existed between level of ID, independent living, being able to eat independently (ADL) and being able to do groceries independently (IADL). These four independent variables were subsequently entered in separate models, together with gender, age, Down syndrome, use of atypical antipsychotics and obesity. The proportion explained variance of the model (R^2) was 0.15 (Table 3.5) and did not increase with this intervention, and significance and ORs of the other variables did not change significantly.

The following groups were significantly more at risk of having hypercholesterolemia: females, people with a less severe ID, people who lived more independently, people who were able to eat (ADL) or do groceries (IADL) independently and people who were obese.

3.3.4.4 Associations with the metabolic syndrome

Independent variables included in the multivariate logistic regression model with the metabolic syndrome were gender, age, level of ID, Down syndrome and being able to do groceries independently (IADL). Bivariate correlations between the independent

variables did not indicate risk of multicollinearity. The proportion explained variance of the model (R^2) was 0.19 (Table 3.5).

Significantly more at risk of having the metabolic syndrome were females, people with higher age, a less severe ID, with other causes of ID than Down syndrome and people who were able to do groceries (IADL) independently.

3.4 DISCUSSION

This study into cardiovascular risk factors of 980 older people with intellectual disabilities (ID) in a near-representative population showed that hypertension (53.0%), diabetes (13.7%), hypercholesterolemia (23.1%) and metabolic syndrome (44.7%) are significant problems within this population. In the study population, individual cardiovascular risk factors had not been previously diagnosed in 45-50%, whereas the metabolic syndrome had not been diagnosed in 94%. People who are more at risk, apart from females, people with higher age and people with obesity, are people with other causes of ID than Down syndrome, people with less severe ID, people who live more independently and are able to do groceries and prepare a meal by themselves. Surprisingly, we did not find a correlation with the use of atypical antipsychotics. The proportion explained variances (R^2) of the models of all CVD risk factors was very low, which means that the population risk is not fully explained by the correlates included in the models, and there may be other influences that we did not take into account in the present study (for example diet and genetic influences).

Prevalence of hypertension, diabetes and metabolic syndrome does not differ from prevalence in the general Dutch population of the same age. However, more females were affected in the ID population than in the general population, and the reverse was true for males [81]. In the general population, 23% of people with diabetes in the study were not previously diagnosed with this condition [81], whereas in people with ID there were almost twice as much missed diagnoses (45%). Hypercholesterolemia was present less often than in the general population [81].

The prevalence of hypertension was higher than the 36.8% (95% CI 32.3-41.3) found in our previous study in 470 older people with ID receiving care by specialized ID physicians from three care providing organizations, and prevalence of diabetes was similar (8.8%, 95% CI 6.2-11.4) [21]. In the present study we found a lower prevalence of hypercholesterolemia

than in the previous study (31.9%, 95% CI 27.6-36.1). However, in that study blood samples had been analyzed in three laboratories and women were overrepresented [21], whereas we have shown that women have a higher risk. This warrants concern about hypercholesterolemia in older women with ID. Other studies in older people with ID showed an equal [20, 28] or lower [26, 27] prevalence of hypertension, diabetes or hypercholesterolemia, but these studies were all based on chart reviews or interviews, which unavoidably results in an underestimation of the prevalence, due to underdiagnosis. No previous studies have been published, investigating the prevalence of metabolic syndrome according to the joint interim statement criteria in older people with ID. Also, effects of metabolic syndrome according to these new criteria on CVD morbidity and mortality has not yet been evaluated in long term cohort studies. Prevalence according to the NCEP-ATP III criteria was exactly comparable to the only previous study [25].

Strengths of the present study are the large sample size and the presence of all levels of ID in the sample. The fact that all blood samples were analyzed in one reference laboratory with specific expertise in serum lipid analyses is an additional strength. Furthermore, included correlates were studied extensively and according to current statistical insights.

Weakness of the present study is that we draw conclusions on hypertension based on two consecutive measurements on the same day, whereas in clinical practice, a single elevated blood pressure outcome would require repeated measurement a few days later, before a diagnosis of hypertension would be made. This could have resulted in an over estimation of the prevalence of hypertension due to stress-related high blood pressure, caused by the test environment or procedure. However, in other studies this method has been used before [21, 81, 82]. Another limitation was that we compared our data to published data from the general population and we did not have comparable data for the group aged over 70 years.

In conclusion, cardiovascular risk factors occur as much in older people with ID as in older people in the general population in the Netherlands, but these risk factors remain more often unnoticed. This serious population risk has important implications for cardiovascular disease prevention policy.

First of all, detection of cardiovascular risk factors is currently insufficient. The high amount of missed diagnoses shows that people with ID are not able to address their symptoms (in case of diabetes) or worries adequately. Professional caregivers, who know these people best, should be educated on cardiovascular risk factors, in order to support

clients in their need for help. Moreover, physicians should actively screen this group for CVD risk factors. We recommend that physicians screen all people with ID aged 50 years and over at least once in five years for CVD risk factors, and are aware of the diagnosis of metabolic syndrome, which warrants a very active treatment policy. Treatment of CVD risk factors should occur according to current standards.

Prevention of CVD risk factors is the second important issue. Lifestyle could be improved in many cases. Since physical activity level is extremely low in older people with ID [32], care-providing organisations should promote physical activity through education and supporting programs. Furthermore, teaching people about healthy diets and supporting them in choosing healthy food and preparing healthy meals is needed. We have shown that people who live and function more independently in these areas, are specifically at risk, and therefore deserve to be supported.

We did not find an association with the use of atypical antipsychotics, probably because of lack of statistical power, and also because we did not have information on the duration of treatment. Indeed, we have observed in clinical practice that there may be an association between use of atypical antipsychotics and the metabolic syndrome. Physicians should be very cautious in prescribing atypical antipsychotics in older people with ID for other reasons than psychosis (e.g. challenging behavior, and behavioral problems in people with autism) [35].

Policy for future research is needed. Explained variance in the analyses of the investigated CVD risk factors was very low, which means that not all influences were identified in the present study. We did not study familiar occurrence of CVD risk factors, but genetic factors may very well be an important factor. Further fundamental research is needed to explore the origin of the CVD risk in older people with ID. Another question that remains unanswered in the present study is what the presented cardiovascular risk factors, and the two measures of metabolic syndrome, as part of the total risk profile, mean for future morbidity and mortality in older people with ID. This question needs to be answered prospectively.

Joint effort of policy makers, clinicians, caregivers and scientists is needed in order to effectively prevent, detect and treat CVD risk factors and consequent morbidity and mortality in older people with ID.

4

Peripheral arterial disease in older people with intellectual disability in The Netherlands using the ankle-brachial index: results of the HA-ID study

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ABSTRACT

Older people with an intellectual disability (ID) have been shown to have similar to increased cardiovascular risks as compared to the general population. Peripheral arterial disease (PAD), atherosclerosis distal from the aortic bifurcation, is associated with increased cardiovascular morbidity and mortality. The prevalence of PAD has not been investigated in this population. Therefore, the aim of the present study was to determine the prevalence of PAD in older people with ID in The Netherlands, the rate of prior diagnoses, and correlations with participant characteristics, and to compare the prevalence with PAD in the general Dutch population. 771 people aged 50 years and over participated in ankle-brachial index (ABI) measurement as part of a multi-centre cross-sectional study (HA-ID study). PAD was defined as an ABI < 0.9. After excluding those, who met the exclusion criteria, 629 participants remained. PAD was present in 20.7% of the participants and 97% had not been diagnosed before. People with higher age, smokers and people who lived in central settings, walked with support and were more dependent in activities of daily living were more at risk of PAD. Prevalence of PAD is higher than in the general population (17.4% of 562 eligible participants with ID, as compared to 8.1% of 917 Dutch participants of the PANDORA study, a pan-European study into the prevalence of PAD) through all age groups. Because the high prevalence of PAD implies a serious health risk for older people with ID, we recommend that ankle-brachial index measurement is to be routinely performed as part of the cardiovascular risk management in this group.

4.1 INTRODUCTION

With increasing longevity, older people with an intellectual disability (ID) have been shown to have similar to increased cardiovascular risks as compared to the general population [8, 9, 21, 25, 68]. A low ankle-brachial index (ABI) indicates peripheral arterial disease (PAD), atherosclerosis distal from the aortic bifurcation. PAD also indicates generalized atherosclerosis [41]. Although PAD is often asymptomatic [83, 84], longitudinal studies have proven an increased risk of cardiovascular morbidity, cardiovascular mortality and total mortality [41-43].

Risk factors for peripheral arterial disease are smoking, obesity, hypertension, hypercholesterolemia, metabolic syndrome, physical inactivity and impaired lower extremity functioning [85-87]. Smoking among people with ID increases [16]. In the HA-ID study, 20% of the participants smoked, which is exactly as much as in the same aged general population in The Netherlands [81]. Furthermore, the metabolic syndrome and it's components occur as much as in the general population [21, 24, 25, 88]. Obesity is present more often than in the general population, probably due to lifestyle related factors and use of medication (i.e. atypical antipsychotic drugs) [68]. Moreover, physical activity levels are very low in older people with ID [31, 32] and impaired mobility is often present, either from early age on, as part of the genetic syndrome or cause of the ID, or acquired later in life [53]. Thus, PAD may be expected to occur similarly or more often than in the general population, which can cause current disease symptoms, but can also indicate a future morbidity and mortality risk. Until now PAD has not been studied in people with ID.

Therefore, we studied prevalence of PAD using the ABI in older people with ID, how often these cases had been diagnosed before this study, and its associations with participant characteristics that are related to cardiovascular disease risks (gender, age, level of ID, Down syndrome, mobility, residential setting, (instrumental) activities of daily living, smoking, physical activity, use of atypical antipsychotics, obesity, hypertension, diabetes, hypercholesterolemia and metabolic syndrome) [68, 88]. Furthermore, prevalence of PAD in older people with ID was compared to the prevalence of PAD in the older general Dutch population.

4.2 METHODS

This study is part of a large cross-sectional study, titled 'Healthy Ageing and Intellectual Disability' (HA-ID). A full description of details about design, recruitment and

representativeness of the sample, as well as diagnostic methods, has been published elsewhere [5]. Of three Dutch care-providing organisations, 1050 clients participated in the study. This study population was nearly representative for the total older ID population receiving formal care or support. Ethical clearance was provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care providing organizations. The study adheres to the Declaration of Helsinki for research involving human subjects [56].

Participants underwent physical examination by specially trained medical assistants or specially trained nurses. People sitting in wheelchairs were excluded, because they could not be examined in the supine position. Systolic blood pressure was measured at rest once, using the Omron M7 on the left arm in the supine position. The blood pressure at the anterior or tibial posterior arteries was measured once at both ankles using a Doppler ultrasonic instrument with an 8-MHZ vascular probe (Boso classico and Huntleigh MD II). ABI was calculated by dividing the mean of the two ankle measurements by the arm measurement [89, 90]. PAD was classified as an ABI <0.9, whereas an ABI 0.9-0.99 was considered as borderline PAD [41, 91]. Participants with an ABI ≥1.3 were excluded from further analysis, because this is an indication of poor arterial compressibility, resulting from arterial stiffness or calcification, which could be related to diabetes [41, 91].

Data were analyzed using IBM SPSS Statistics 17.0. With a chi-square test we explored the representativeness of the participants in ABI measurements as compared to the total HA-ID study population in gender, age (age groups 50-59, 60-69, 70-79, 80+), level of ID (borderline, mild, moderate, severe, profound) and residential setting (three groups: central setting, community based, independent with ambulatory support or living with relatives).

Associations between PAD (dependent variable) and the following participant characteristics were explored: gender, age, level of ID, diagnosis of Down syndrome, smoking, residential setting, (instrumental) activities of daily living ((I)ADL) total score and individual item scores of ADL eating and IADL preparing meal and IADL doing groceries, physical inactivity (less than 7500 steps/day), use of atypical antipsychotics, abdominal obesity, hypertension, diabetes, hypercholesterolemia and metabolic syndrome (independent variables). Diagnostic methods and criteria of independent variables have been published elsewhere [32, 53, 68, 88]. Independent variables showing a significant association ($p < 0.05$), or trend ($p = 0.05$) towards significance with the dependent variable in a univariate regression analysis, were simultaneously entered into a multivariate logistic

regression analysis. Independent variables were checked for multicollinearity, using Pearson's correlation coefficient (with a correlation > 0.4 between independent variables indicating possible multicollinearity).

For comparison with the general population, aggregated data of Dutch participants of the PANDORA-study were used. In the PANDORA study, a cross-sectional European study, the prevalence of PAD was studied in people with ≥ 1 cardiovascular risk factor, but without a prior diagnosis of PAD or cardiovascular disease [92]. Inclusion criteria for participants in the PANDORA study were: men aged 45 years and over and women aged 55 years and over, with at least one of the following cardiovascular risk factors: cigarette smoking, hypertension, low high-density-lipoprotein-cholesterol or high low-density-lipoprotein-cholesterol, family history of premature coronary heart disease or elevated waist circumference. Participants were excluded if they had symptoms of PAD identified by the physician, diabetes mellitus or cardiovascular disease or equivalents (transient ischaemic attacks, stroke, aortic aneurism) [92]. In order to compare the data of HA-ID participants with the Dutch PANDORA participants, the same exclusion criteria were applied to the HA-ID population for this analysis. The HA-ID population also included participants without cardiovascular risk factors, and for the HA-ID population no data were available on family history. Comparison between the prevalence of PAD in the HA-ID population and the aggregated data of the Pandora study was performed using confidence intervals [93].

4.3 RESULTS

Of the 1050 HA-ID participants, 771 clients participated in ankle-brachial measurement. Forty-eight were excluded from the analyses because of an ABI ≥1.3, indicating arterial stiffness, and 105 were excluded because they were in a wheelchair, resulting in 629 study participants with a mean age of 61.5 years (range 50-93). Participant characteristics are presented in Table 4.1. As compared to the total HA-ID population, people living in community settings were overrepresented and people living in central settings underrepresented. Furthermore, people with borderline, mild ID and moderate ID were overrepresented whereas people with severe and profound ID were underrepresented. This reflects varying cooperation in physical examination of people with more severe ID and the exclusion of people in wheelchairs, which means that a functionally more able group participated in the study. Gender and age-groups were equally represented as in the total HA-ID population.

Table 4.1 Prevalence of PAD according to participant characteristics

		PAD	
Participant characteristic (n = data available)	(N) Percentage of total study population	Prevalence of PAD	95% CI
Total study population (n = 629)	(629) 100%	20.7%	17.5-23.8%
Gender (n = 629)			
Male	(337) 53.6%	21.1%	16.7-25.4%
Female	(292) 46.4%	20.2%	15.6-24.8%
Age (n = 629)			
50-59	(300) 47.7%	17.0%	12.8-21.3%
60-69	(220) 35.0%	20.9%	15.5-26.3%
70-79	(95) 15.1%	29.5%	20.3-38.6%
80+	(14) 2.2%	35.7%	10.6-60.8%
Down syndrome (n = 541)	(69) 12.8%	18.8%	9.6-28.0%
Level of ID (n = 610)			
Borderline	(25) 4.1%	24.0%	7.3-40.7%
Mild	(152) 24.9%	20.4%	14.0-26.8%
Moderate	(323) 53.0%	20.4%	16.0-24.8%
Severe	(82) 13.4%	20.7%	12.0-29.5%
Profound	(28) 4.6%	21.4%	6.2-36.6%
Residential setting (n = 629)			
Central setting	(283) 45.0%	24.7%	19.7-29.8%
Community based	(305) 48.5%	17.4%	13.1-21.6%
Independent or with relatives	(41) 6.5%	17.0%	5.6-28.6%
Mobility (n = 600)			
Walking independently	(504) 84.0%	19.0%	15.6-22.5%
Walking with support	(96) 16.0%	33.3%	23.9-42.8%
Smoking (n = 599)	(151) 25.2%	28.5%	21.3-35.7%
Use of atypical antipsychotics (n = 547)	(34) 6.2%	35.3%	19.2-51.4%
Physical inactivity (n = 300)	(219) 73.0%	22.4%	16.9-27.9%

4.3.1 Prevalence of PAD

Total prevalence of PAD was 20.7% (95% CI 17.5-23.8), whereas borderline PAD was found in 25.4% (95% CI 22.0-28.8). The total prevalence of PAD and prevalence for each participant characteristic is shown in Table 4.1. For 517 participants medical file data were available, of whom 112 were found to have PAD in this study. Three out of these 112 participants, (2.6%) had been diagnosed with PAD prior to the study, which means that there were 97.4% previously unidentified cases.

4.3.2 Associations of PAD

Independent variables included in the multivariate logistic regression model were age, residential setting, smoking, mobility, ADL score and use of atypical antipsychotics (Table 4.2). Possible multicollinearity existed between residential setting, mobility and ADL score. Therefore, residential setting, mobility and ADL score were subsequently entered

Table 4.2 Univariate and multivariate logistic regression analysis of PAD

Independent variable (n = participants in measurement)	Univariate	Multivariate OR (95% CI)	Multivariate separate models OR (95% CI)
Gender (n = 629)	-		
(Higher) age (n = 629)	**	1.33 (1.03-1.71)*	
(Less severe) level of ID (n = 610)	-		
Presence of Down Syndrome (n = 541)	-		
Residential setting (higher risk for people in central settings) (n = 629)	*	1.28 (0.86-1.91)	1.46 (1.00-2.13)* †[1]
Smoking (n = 599)	*	1.20 (1.05-1.38)*	
Less independent mobility (walking with support) (n = 600)	**	1.57 (0.93-2.65)	1.89 (1.18-3.02)** †[2]
ADL total score (less independent functioning) (n = 600)	*	1.04 (0.98-1.10)	1.07 (1.02-1.13)** †[3]
ADL eating (n = 600)	-		
IADL total score (n = 600)	-		
IADL groceries (n = 600)	-		
IADL preparing meal (n = 600)	-		
Atypical antipsychotics (n = 547)	p = 0.052	1.85 (0.86-4.01)	
Physical inactivity (n = 300)	-		
Obesity (waistcircumference) (n = 624)	-		
Hypertension (n = 608)	-		
Hypercholesterolemia (n = 474)	-		
Diabetes (n = 474)	-		
Metabolic syndrome (n = 474)	-		

R^2: 0.73; - = univariate not significant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
† = Results from multiple logistic regression analysis in a separate model, because multicollinearity was a problem in the first multivariate model.
[1] = Age, smoking, use of atypical antipsychotics and living less independently were entered in the model; [2] = Age, smoking, use of atypical antipsychotics and less independent mobility (walking with support) were entered in the model;
[3] = Age, smoking, use of atypical antipsychotics and functioning less independently (ADL) were entered in the model.

in separate models, together with age, smoking and use of atypical antipsychotics. The proportion explained variance of the model (R^2) was 0.73 (Table 4.2) and did not change with this intervention, whereas odds ratios of the other variables in the analysis did not change significantly either. Groups that were significantly more at risk of PAD, were people with higher age, people who smoked, people who lived in central settings, people who walked with support and people with less independent functioning on ADL score.

4.3.3 Comparison with the general population

After excluding 105 people in a wheelchair, 63 people with diabetes and 41 people with established PAD or cardiovascular disease, 562 HA-ID participants remained (of the original 771) for comparison with the data of 917 Dutch PANDORA participants aged 50 years and over [86]. For the total group and the age groups 50-59, 60-69 and 70-79 prevalence of PAD was significantly higher in the ID population than in the general population (Table 4.3). The group aged 80 years and over of the HA-ID population was too small to draw conclusions.

Table 4.3 Prevalence of PAD in the HA-ID population without established PAD or cardiovascular disease as compared to the prevalence in the Dutch PANDORA participants [86], according to age

	HA-ID		PANDORA	
	n	PAD prevalence (95% CI)	n	PAD prevalence (95% CI)
50-59	284	15.9% (11.6-20.1)*	213	6.6% (3.2-9.9)
60-69	198	17.2% (11.9-22.4)*	388	7.5% (4.9-10.1)
70-79	70	24.3% (14.2-33.3)*	237	9.3% (5.6-13.0)
80+	10	20.0%	49	16.33% (6.0-26.7)
Total	562	17.4% (14.3-20.6)*	917	8.1% (6.3-9.8)

* Confidence intervals do not overlap between ID population and general population.

4.4 DISCUSSION

This is the first study to investigate peripheral arterial disease (PAD) in older people with intellectual disability (ID) in The Netherlands, using the ankle-brachial index (ABI). With a total prevalence of 20.7%, PAD is highly present. It had not been diagnosed prior to the study in 97% of the cases. People with higher age, smokers and people living in

central settings, walked with support and were more dependent in activities of daily living (ADL) were more at risk. No association was found with other cardiovascular disease (CVD) risk factors.

The prevalence of PAD in older people with ID is significantly higher than in the general Dutch population through all age groups. Possible explanations for the increased prevalence are the high amount of people with impaired mobility among this group [31, 32], the widespread unhealthy lifestyle [21], and subsequent obesity [17-19, 68], which leads to vascular disease later in life. It has been shown that frailty in people with ID aged 50-64 occurs as much as in the general population aged 65 and over [94]. Moreover sarcopenia is highly prevalent [95]. Thus, due to metabolic changes in muscle tissue and an accumulation of adverse conditions, higher occurrence of PAD might be conceivable. But PAD may also be one of the causes of these conditions.

Most cases of PAD had remained unrecognized. Although PAD is often asymptomatic, the high rate of new diagnoses suggests that people who did experience pain or discomfort but were unable to communicate that, had remained undiagnosed too.

As could be expected, people with higher age and people who smoked were more at risk of PAD [86, 87]. People living in central settings, with impaired mobility and less independent ADL functioning were also more at risk. These are probably people with declining health, who for this reason are less able to take care of themselves in the community, and have moved to residential settings with a higher level of support. Cardiovascular disease may be a part of their physical problems, but PAD may also result from the declined mobility and low levels of physical activity [85]. Because of the cross-sectional design of the study, it is not possible to provide information about the direction of the causal relationship between impaired mobility and PAD.

The use of atypical antipsychotics was not significantly related to PAD, possibly due to lack of statistical power, because the univariate analysis was near-significant. We do expect atypical antipsychotics to be associated with PAD, because these are a relevant causal factor for the metabolic syndrome and increased CVD risk factors [73]. This has an implication for clinical practice, since use of (atypical) antipsychotics is high [35], and discontinuation significantly improves metabolic changes [40]. Unexpectedly, other CVD risk factors (obesity, hypertension, diabetes, hypercholesterolemia, metabolic syndrome) could not be proven to be correlated to PAD in this study. Some risk factors may be treated adequately, as there was no information on duration of treatment.

Strengths of the present study were the relatively large sample and the inclusion of a complete set of correlates, which led to a high proportion explained variance ($R^2 = 0.73$). Limitations were the exclusion of people in wheelchairs, which is the most vulnerable group, and low participation of the eldest group, which could lead to an underestimation of the total population prevalence. For comparison with the general population we used aggregated data from the Pandora study. We chose to compare with the data from the Dutch participants of the Pandora study only, because the Pandora study shows us that there are large differences of the prevalence of PAD between countries within Europe, possibly due to differences in ethnicity, culture and lifestyle [86]. There were two differences in inclusion between the HA-ID study and the Pandora study. In the HA-ID study also people without CVD risk factors had been included, in contrast to the PANDORA participants with at least one known CVD risk factor. This makes the estimation in the HA-ID population more conservative. Moreover, in the group aged 50-59, the Pandora study did not include women aged 50-54. This could give an overestimation of the prevalence in this age-group in the Pandora study, as compared to the HA-ID study. However, in the HA-ID study, we did not find a significant difference between the prevalence of PAD in men and women. Both these differences in inclusion might only underestimate the increased prevalence in the ID population as compared to the general population.

In conclusion, PAD is highly prevalent among older people with ID and is clearly more prevalent than in the general Dutch population of comparable age. This implies a serious health risk for older people with ID. Apart from people with higher age and people who smoke, older people with impaired mobility and less independent functioning are more at risk, and require intensive medical attention and effort to improve their mobility. We recommend that ABI measurements are performed as part of the cardiovascular risk management in people with ID, especially because most people with PAD were not previously diagnosed. Longitudinal research should address the consequences for cardiovascular morbidity and mortality of PAD diagnosed in this group.

5

Associations of symptoms of anxiety and depression with diabetes and cardiovascular risk factors in older people with intellectual disability

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ABSTRACT

Background: Depression, anxiety, diabetes and cardiovascular risk factors are frequent health problems among older people with intellectual disability (ID). These conditions may be bidirectionally related. Depression and anxiety may have biological effects causing glucose intolerance, fat accumulation and also lifestyle changes causing metabolic syndrome. But also the effects of diabetes, metabolic syndrome and subsequent cardiovascular disease may affect mood and anxiety. This study investigated the association between depression, anxiety and diabetes and cardiovascular risk factors in older people with intellectual disabilities.

Methods: The healthy ageing in intellectual disability-study (HA-ID study) is a cross-sectional study among people aged 50 years and over with ID, receiving formal ID care. Screening instruments for symptoms of anxiety and depression were completed and physical examination and vena-puncture were performed to establish components of the metabolic syndrome, peripheral arterial disease and c-reactive protein.

Results: Of the 990 people who participated, 17% had symptoms of depression and 16% had symptoms of anxiety. Type I diabetes was present in 1%, type II diabetes in 13% of the study population. Metabolic syndrome, central obesity, hypercholesterolemia and hypertension were present in 45%, 48%, 23% and 53% respectively. In a multivariate logistic regression analysis a significant association was found between increased anxiety symptoms and diabetes only (OR 2.4, 95% CI 1.2-4.9).

Conclusions: Increased anxiety symptoms and diabetes are related in older people with ID. This association may be bidirectional. No other associations of depression and anxiety symptoms with cardiovascular risk factors could be proven to be significant. Therefore, more research is needed to unravel the mechanisms of stress, mood disorders and cardiovascular disease in older people with ID. To provide comprehensive care for older people with ID, screening for diabetes and components of the metabolic syndrome in people with anxiety or mood disorders, and screening for symptoms of anxiety or depression in people with diabetes is warranted.

5.1 INTRODUCTION

Depression, anxiety, diabetes and cardiovascular disease (CVD) risks are major health challenges among older people with intellectual disabilities (ID) [68, 88, 96]. The relationships between these conditions were not studied before in the ID population. In the general older population, these conditions have been shown to be related. Depression is bidirectionally related to diabetes [44], CVD [46] and the metabolic syndrome (a combination of CVD risk factors: abdominal obesity, insulin resistance, hypercholesterolemia –a high serum cholesterol- and hypertension –high blood pressure-) [47]. Effects of cardiovascular pathology on mood and vice versa can be identified on different levels, from depressing effects of preclinical pathology such as inflammation, atherosclerosis and disturbed glucose homeostasis to psychological effects of lifestyle, obesity, diabetes and cardiac disease. The underlying mechanism is that depression causes neuro-endocrine effects (e.g. dysregulation of the hypothalamic-pituitary-adrenal cortex axis and sympathetic nervous system activation), resulting in abdominal fat accumulation, impaired glucose tolerance and high blood pressure [44, 46, 47]. Moreover, people with depression tend to have poor health behavior (e.g. unhealthy diet, smoking, sleep disturbance and low physical activity) [44, 47]. In the opposite direction, increased levels of inflammatory cytokines (proteins involved in the inflammatory response), such as c-reactive protein, through atherosclerotic plaques in the blood vessels may be involved in depressed mood [44, 47]. Disturbed glucose homeostasis [47] and vascular damage may also lead to mood disturbance [44, 47]. Further, obesity and a sedentary lifestyle may result in low self-esteem and depression [47], whereas diabetes and cardiovascular disease may result in fear and a sense of loss. Moreover, changes in lifestyle, which are necessary to avoid further health complications, may be difficult to accept and to include in daily life [44, 46]. Similar mechanisms have been suggested for anxiety, but this has been investigated less thoroughly and results are more inconclusive [97-100]. Especially diabetes may occur more often in people with anxiety symptoms [45].

Research in this area among people with ID is very scarce and limited to conflicting results on obesity and depression. Adolescents with ID and obesity were more likely to experience depression than those with a healthy weight [54]. The prevalence of depression and low self-esteem seemed to be higher among overweight adolescents [101]. However, no association was found between depression and obesity in a cohort of adults with ID [102]. The relationship between depression and other CVD risk factors, or diabetes has not been investigated. The same applies to the relationship between anxiety and CVD

risk factors and diabetes. Although CVD risk factors increase with age, no studies on these associations are available for older people with ID. Moreover, the mediating role of use of antipsychotic drugs, which are widely used among older people with ID and can have metabolic side-effects [35], such as obesity and diabetes [55], has not been taken into account in these mechanisms.

In (older) people with Down syndrome, different mechanisms may affect these relationships. Although people with Down syndrome are more often obese [68] and have higher body fat percentages from early age on [103, 104], they have less other CVD risk factors [88] and less often atherosclerotic CVD [105] than people with other causes of ID. Moreover, Down syndrome is associated with early dementia [106], in which symptoms can resemble depressive symptoms.

Therefore, the aim of the present study was to explore the relationship between symptoms of anxiety and depression, and cardiovascular risk factors (obesity, body fat percentage, diabetes, hypercholesterolemia, hypertension, metabolic syndrome, smoking, c-reactive protein, and peripheral arterial disease) in older people with ID.

5.2 METHODS

5.2.1 Design

This study is part of a large cross-sectional study, titled 'Healthy Ageing and Intellectual Disability' (HA-ID) [5]. Three care-providing organizations in the Netherlands participated in the study. These organizations offer low to high level specialized support and care to people with ID. Subthemes in this study are: (1) Physical activity and fitness, (2) Nutrition and nutritional state, and (3) Mood and anxiety [5]. Assessment of associations between depression, anxiety and cardiovascular risk factors was part of themes two and three.

5.2.2 Participants

There were 2322 clients aged 50 years and over in the three participating organizations, of whom 2150 were invited to participate (178 were not invited to participate, because 5 were seriously ill, 86 passed away, 39 moved and from 42 data were incomplete at start). Informed consent was provided by 1069 clients or their legal representatives (856 people

did not give consent and consent was missing for 225 people). 1050 clients participated in the assessments of the HA-ID study (19 clients did not participate, because 13 passed away, 2 were seriously ill and for 4 clients consent was received too late) [5]. Subsequently, 990 participants completed the mood and anxiety assessments (as required for the present study).

5.2.3 Data collection

Participant characteristics were obtained from medical files. General practitioners and specialized ID physicians completed a questionnaire on their clients health issues and also recorded etiology (Down syndrome yes /no) and use of medication (for diabetes, hypercholesterolemia, hypertension, and atypical antipsychotic drugs: olanzapine, risperidone and quetiapine). Behavioural therapists recorded level of ID from their files.

Depression and anxiety have been defined as increased depressive or anxiety symptoms measured with screening tools. We have not used psychiatric diagnoses, because those were not available for the complete study population. Depressive symptoms were measured using two screening instruments. Participants capable of self-report completed the Inventory of Depressive Symptomatology Self Report (IDS-SR) [107]. For participants who were not capable of self-report, professional care-givers who knew the participant for at least three months, completed the Dutch informant-report Signalizing Depression List (SDL-ID) [108]. In people with ID, the IDS-SR has a good internal consistency and test-retest reliability ($\alpha = 0.89$ and ICC = 0.91), and the validity is satisfactory (sensitivity 71% and specificity 54%) [109]. Its score ranges from 0 to 84. We used a cut-off score of ≥ 18 [110]. The SDL-IDs internal consistency and interrater reliability in older people with ID are good ($\alpha = 0.77$ and $r = 0.87$) [111]. The score on the SDL-ID ranges from 18 to 72. We used a cut-off score of ≥ 35 [112]. In a pilot study, the IDS-SR and SDL-ID were completed both for 23 participants, showing 100% correspondence for the used cut-off scores.

Screening of anxiety symptoms was performed using three screening instruments [96]. All participants were screened with an informant-report instrument, the Anxiety, Depression, And Mood Scale (ADAMS) (the whole instrument was completed, but for the present study only the general anxiety subscale was used) [113]. This subscale's internal consistency, test-retest reliability and interrater reliability are good ($\alpha = 0.88$, ICC = 0.86 and ICC = 0.74) and its validity is satisfactory (sensitivity 80-82% and specificity 65-78%) in older people with ID [114]. The score on the general anxiety subscale ranges from

0 to 21. We used cut-off scores ≥ 10 for people without autism and ≥ 14 for those with an autism spectrum disorder [114]. In addition to the ADAMS, participants who were capable of self-report were screened with the Glasgow Anxiety Scale for People with an Intellectual Disability (GAS-ID) [115] and the Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) [31, 116]. The internal consistency and reliability of the GAS-ID are good (α = 0.86 and ICC = 0.89) and its validity sufficient (sensitivity 84% and specificity 52%) [115]. Its score ranges from 0 to 54. We used a cut-off score of ≥ 17 [117]. The HADS-A has fair to good psychometric properties [118, 119]. Its score ranges from 0 to 21, we used a cut-off score of ≥ 8 [119]. Anxiety was defined as a score above cut-off on at least one of the anxiety questionnaires [96].

Participants underwent physical examination to assess blood pressure [88], ankle-brachial index [120], waist-to-hip ratio (WHR) and body fat percentage [68]. Methods of physical examination are in Table 5.1.Vena puncture was performed after an overnight fast, to assess serum glucose, serum cholesterol and c-reactive protein (crp) [88]. Serum was transported frozen, stored at -80 degrees Celcius and analyzed at the laboratory of the Erasmus Medical Center. Reference values of the Erasmus Medical Center were used for cut-off scores for glucose and cholesterol in serum. Diabetes mellitus was defined as a fasting serum glucose > 6.1 mmol/l and/or the use of glucose lowering drugs. Hypercholesterolemia was defined as a fasting serum total cholesterol > 6.5 mmol/l and/

Table 5.1 Methods of physical examination

Outcome	Method	Cut-off score
Central obesity	Waist to hip ratio (WHR): measurement of waist circumference and hip circumference	WHR ≥ 0.90 was classified as overweight and ≥ 1.00 as obese for men, and WHR ≥ 0.80 was classified as overweight and ≥ 0.88 as obese for women [58, 68].
Body fat percentage	Skinfold measurement of the triceps, biceps, subscapular and suprailiacal	The sum of four skinfolds was used to calculate body density using the Visser equation [59]. Body fat percentage was calculated from body density using Siri's equation [60].
Hypertension	Blood pressure measurement	Systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg [78] and/ or the use of blood pressure lowering drugs [88].
Peripheral arterial disease (atherosclerosis distal from the aortic bifurcation)	Ankle-brachial index measurement	Ankle-brachial index < 0.9 [120].

or the use of lipid lowering drugs. Metabolic syndrome was defined using the criteria of the joint interim statement 2009 [67]. Metabolic syndrome was present if at least three of the following five criteria were met: a serum fasting glucose ≥ 5.6 mmol/l and/or the use of glucose lowering drugs, serum fasting triglycerids ≥ 1.7 mmol/l and/or the use of lipid lowering drugs, serum fasting HDL cholesterol ≤ 1.0 in men and ≤ 1.3 mmol/l in women and/or the use of lipid lowering drugs, and waist circumference ≥ 94 cm in men and ≥ 80 cm in women (reference values for overweight in Europeans, as this is a European Caucasian sample).

5.2.4 Statistical analysis

All analyses were done with the Statistical Package for the Social Sciences 17.0. First, non-response analyses were done using a t-test for age and chi-square-tests for gender and residential setting. Univariate associations between depression and anxiety and cardiovascular risk factors were performed using Pearson's point-biserial correlation coefficient. Those cardiovascular risk factors that correlated significantly, or with a trend towards significance ($p = 0.05$), with depression or anxiety were subsequently entered in a multivariate logistic regression analysis, together with age, gender, level of ID, Down syndrome and anxiety or depression respectively (because of overlapping symptoms). Associations were checked for possible multicollinearity using the variance inflation factor (VIF) of linear regression analysis.

5.2.5 Ethics

Ethical clearance has been provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care providing organizations. The study adheres to the Declaration of Helsinki for research involving human subjects [56].

5.3 RESULTS

The screening questionnaires for anxiety and depression were completed for 990 participants with a mean age of 61.1 years (SD = 8.2). Of the sample, 48.7% were females. The majority (54.1%) lived on a central location of the care-providing organizations (in a sheltered environment with surrounding health facilities (e.g. physician, dentist,

movement therapy centre), whereas 40.7% lived in an accommodation in the community and 5.1% lived with their family or independently. Non-participants (n = 1332) and participants were not significantly different with respect to age (t = 0.27, p = 0.79), but men (chi-square = 4.72, p < 0.05) and people living independently (chi-square = 44.22, p < 0.05) were slightly underrepresented in the sample. Because not all participants completed all assessments from physical examination and vena-puncture, associations were computed for those available. Characteristics of the study population are shown in Table 5.2. Of the 990 participants, 16.8% had symptoms of depression and 16.3% had symptoms of anxiety. Diabetes was present in 97 people (13.8%), 9 had type I diabetes,

Table 5.2 Characteristics of the study population (n = 990)

	n	%
Gender		
Male	508	51.3
Female	482	48.7
Level of ID		
Borderline (IQ = 70-84)	31	3.1
Mild (IQ = 50-69)	211	21.3
Moderate (IQ = 35-49)	471	47.6
Severe (IQ = 20-34)	165	16.7
Profound (IQ < 20)	89	9.0
Unknown	23	2.3
Residential setting		
Central location	536	54.1
Community home	403	40.7
Living with family	7	0.7
Independent living	44	4.4
Symptoms of depression	166	16.8
Symptoms of anxiety	161	16.3
Smoking (n = 974)	194	19.6
Alcohol misuse (≥ 5 glasses/day) (n = 988)	3	0.3
Central obesity (waist to hip ratio) (n = 796)	385	48.4
Hypertension (n = 780)	412	52.8
Hypercholesterolemia (n = 702)	162	23.1
Diabetes (n = 702)	97	13.8
Metabolic syndrome (n = 568)	254	44.7
Peripheral arterial disease (n = 601)	127	21.1
Use of atypical antipsychotic drugs (n = 870)	55	6.3

the others type II. metabolic syndrome, central obesity, hypercholesterolemia and hypertension in 44.7%, 48.4%, 23.1% and 52.8% respectively. 19.6% of the sample smoked and 21.1% had peripheral arterial disease. Atypical antipsychotic drugs were used by 6.3% of the participants. Additional information on aetiology of ID and comorbidity of the study population is shown in Table 5.3.

Table 5.3 Information on aetiology of ID and co-morbidity and polypharmacy (n = 1050)

	n	%
Aetiology (n = 927)		
No diagnosis of a genetic syndrome	653	70.7
Down syndrome	150	16.2
Fragile-X syndrome	9	1.0
Prader-Willi syndrome	1	.1
Rett syndrome	2	.2
Angelman syndrome	3	.3
Other genetic syndrome	58	6.3
Unknown	48	5.2
Autism (n = 1032)	178	17.2
Immobility (in a wheelchair) (n = 989)	107	10.8
Visual impairment (n = 924)	203	22.0
Hearing impairment (n = 924)	410	44.2
Epilepsy (n = 924)	196	21.2
Hypothyroidism (n = 924)	134	14.5
Hyperthyroidism (n = 924)	11	1.2
History of alcohol and/or substance misuse (n = 988)	26	2.6
Polypharmacy (≥ 4 types of medication) (n = 924)	487	52.7

There was no multicollinearity; all VIFs were between 1.01 and 1.92. In addition, relationships between the use of atypical antipsychotics and CVD risk factors was explored using Pearson's point biserial correlation coefficient. There were no significant correlations between the use of atypical antipsychotics and central obesity (Pearson = .04, p = 0.24), body fat percentage (Pearson = -.005, p = 0.90), diabetes (Pearson = .01, p = 0.67), hypercholesterolemia (Pearson = .07, p = 0.08), hypertension (Pearson = .03, p = 0.49) and the metabolic syndrome (Pearson = .01, p = 0.80). Therefore, the use of atypical antipsychotics was not entered into the multivariate analyses as a possible confounder.

Table 5.4 Univariate associations between symptoms of depression and anxiety and cardiovascular risk factors, using Pearson's point-biserial correlation coefficient

	Down	Smoking	Central obesity	Body Fat percentage	Hyper tension	Hyper cholester olemia	Diabetes	Metabolic syndrome	Peripheral arterial disease	C-reactive protein
Depression	.08 (p = 0.29)	.04 (p = 0.29)	-.04 (p = 0.32)	-.02 (p = 0.65)	-.01 (p = 0.84)	-.02 (p = 0.56)	-.06 (p = 0.15)	.01 (p = 0.75)	.05 (p = 0.28)	.07 (p = 0.05)
Anxiety	-.09 (p = 0.001)	.11 (p = 0.001)	.11 (p = 0.002)	.08 (p = 0.04)	0.00 (p = 0.95)	.10 (p = 0.009)	.16 (p = 0.000)	.04 (p = 0.32)	.06 (p = 0.18)	.05 (p = 0.23)

5.3.1 Associations between depression and cardiovascular risk factors

Univariate associations between depression and cardiovascular risk factors are shown in Table 5.4. There were no significant correlations, only a trend towards significance for the correlation between crp and depression (p = 0.05). In the multivariate logistic regression analysis, people with Down syndrome were almost three times more likely to have depressive symptoms. Older people's likelihood of depressive symptoms was only slightly (but significantly) elevated compared to younger people. Anxious people were ten times more likely to be depressive than people without anxiety symptoms (Table 5.5). The explaining value of this model is calculated with R^2, as the percentage of variance explained by the model. R^2 of the present depression model is 0.21, indicating a moderate amount of explained variance.

5.3.2 Associations between anxiety and cardiovascular risk factors

Univariate associations between anxiety and cardiovascular risk factors are shown in Table 5.4. There were significant correlations for anxiety and smoking, central obesity (by waist to hip ratio), body fat percentage, hypercholesterolemia and diabetes. In the multivariate logistic regression analysis, people with mild ID were almost four times more likely, and people with moderate ID almost three times more likely to experience anxiety symptoms, as compared to people with severe and profound ID. People with symptoms of depression were ten times more likely to also experience anxiety symptoms, than people without depressive symptoms. People with diabetes were almost two and a half times more likely to experience anxiety symptoms than people without diabetes

Table 5.5 Odds ratios (OR) from a multiple logistic regression analysis with symptoms of depression as a dependent variable (n = 626)

	OR	95% confidence interval	p-value
Gender	1.07	.67-1.71	0.77
Mild ID	.59	.28-1.23	0.16
Moderate ID	.96	.55-1.67	0.88
Down syndrome	2.93	1.59-5.41	0.001
Age	1.03	1.00-1.06	0.03
Anxiety	10.19	5.87-17.70	0.000
C-reactive protein	1.01	.99-1.02	0.37

R^2 = .21.

Table 5.6 Odds ratios (OR) from a multiple logistic regression analysis with anxiety symptoms as a dependent variable (n = 524)

	OR	95% confidence interval	p-value
Gender	1.03	.56-1.91	0.92
Mild ID	3.82**	1.48-9.88	0.006
Moderate ID	2.67*	1.11-6.47	0.03
Age	1.00	.96-1.04	0.96
Down syndrome	.36	.11-1.21	0.10
Depression	10.35***	5.42-19.75	0.000
Smoking	1.60	.84-3.03	0.15
WHR obesity	1.49	.80-2.78	0.21
Diabetes	2.42*	1.19-4.90	0.01
Hypercholesterolemia	1.57	.83-2.95	0.16

R^2 = .27.

(Table 5.6). R^2 of the anxiety model is 0.27, which is a moderate amount of explained variance.

5.4 DISCUSSION

This is the first study into the associations between depression, anxiety and cardiovascular risk factors in older people with ID. There was a significant association between increased anxiety symptoms and diabetes. No other associations with CVD risk factors could be proven to be significant. This study contributes to the yet very small body of knowledge on the interactions between psychosocial variables and physical illness indicators—more specifically: risk factors for cardiovascular disease—in people with ID. These findings may give rise to formulating recommendations for the improvement of clinical practice for older people with ID, and management (possibly prevention) of conditions that account for excess economic costs.

People with diabetes may encounter a lot of stress and medical visits in their lives. By frequent finger pricking, blood sugars are monitored, and regular vena-puncture is part of the health screening of people with diabetes. These measures may be frightening, especially for (older) people with ID. Also, complications of diabetes and hospitalizations may cause a lot of stress leading to anxiety. A disturbed glucose homeostasis, elevated

inflammatory cytokines (which are likely in the case of diabetic complications) and vascular damage may give rise to symptoms of anxiety too [44, 47]. Because of its neuro-endocrine effects (dysregulation of the hypothalamic-pituitary-adrenal cortex axis), anxiety might also contribute to an impaired glucose tolerance [44].

Other relations between anxiety and cardiovascular risk factors could not be proven in the multivariate analysis. Smoking, central obesity, a high body fat percentage and hypercholesterolemia were all significantly correlated to anxiety univariately, but these relations disappeared if they were entered in the multivariate analysis. This may be due to the fact that these are all related to a more mild level of ID (as does anxiety) [68, 88, 96], and this may be the mediator in the association.

No correlations between depression and cardiovascular risk factors were found. The lack of correlation between depression and obesity confirms the findings of the earlier study in adults with ID [102]. Several explanations for the absence of associations may come to mind. The first is that we screened for increased depressive symptoms. Correlations might have been stronger in case of a diagnosis of major depression. Furthermore, one of the suggested mechanisms is that people worry about their cardiovascular risks, causing a depressed mood [46, 47]. People with ID might worry less about long-term consequences of their cardiovascular risks and may even lack the cognitive ability to understand their health risks.

The lacking correlation between depression and biological factors also raises the question whether depression is the same state of body and mind in people with ID as in the general population. Whereas in the general population depression and stress induce a cascade of hormonal changes, resulting in CVD (risk factors), this could not be proven in our study population of older people with ID. Do depressive symptoms in older people cause the same stress cascade in the brain as in the general population? Or are depressive symptoms an expression of a different process?

Strengths of the present study were that both psychological factors and cardiovascular risk factors were actually measured in a large sample and were not derived from file data. Moreover all somatic factors were objectively measured and not obtained using questionnaires as in the only previous study in adults with ID [102].

Weaknesses of the study were that information of those participants who were incapable of self-report, is based on information by proxy, which possibly makes associations more difficult to detect. Although the used instruments are valid for this population

[96], measurements by proxy always (slightly) differ from subjective measurements, depending on how subjective the investigated concept is. Moreover we used screening tools for symptoms of depression and anxiety. For a small proportion of the participants diagnostic interviews were available, but statistical power was too small to use these for the analyses. People with ID may express these symptoms not only when they have a true depression or anxiety disorder (as defined in the ICD-10), but also when they experience pain, discomfort or distress from other physical or social conditions [121], which could be possible confounders of the relationship we studied. Furthermore, we did not control for dementia which has some similar symptoms as depression which is also reflected in the higher proportion of people with Down syndrome and depressive symptoms (as dementia is highly prevalent in older people with Down syndrome). Not all participants completed all physical assessments, which increases the threat of selection bias. However the analyses showed that selection bias was only mild.

In future prospective studies the causal relationship between mood disorders as well as cardiovascular risk factors and cardiovascular disease could be elucidated. Cortisol levels should be measured to unravel the mechanism of stress, depression and biological consequences in older people with ID.

The main contribution to the field of this article is the establishment of the association between anxiety and diabetes. This finding suggests a potential importance of screening for anxiety in older people with ID and diabetes. This might become part of the standard health watch for diabetes in people with ID. Moreover people with ID and anxiety or mood disorders should be screened for diabetes and components of the metabolic syndrome [122]. Thus, prevention measures can be taken for those who present with diabetes or pre-diabetes (defined by impaired fasting glucose and/or impaired glucose tolerance), as recommended by the International Diabetes Federation [123]. Screening is necessary to provide comprehensive care for people with ID who are at risk of depressive or anxiety disorders and cardiovascular disease.

6

Chronic kidney disease in older people with intellectual disability: results of the HA-ID study

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ABSTRACT

With increasing longevity and cardiovascular events, chronic kidney disease may also become a significant problem in older people with intellectual disability (ID). We studied prevalence and associations of chronic kidney disease as part of the Healthy Ageing and Intellectual Disability (HA-ID) study, a large Dutch cross-sectional study among people with ID aged 50 years and over, using creatinine and cystatin-C measurement in plasma. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Equations based on creatinine (as the MDRD equation) may underestimate kidney dysfunction in people with sarcopenia, because low muscle mass leads to a low creatinine production. Therefore, also prevalence of chronic kidney disease was studied in the sarcopenic group, using different GFR equations. Prevalence of chronic kidney disease, among 635 participants, was 15.3%, which equals prevalence in the general Dutch population. In the group of participants with sarcopenia (n=82), the CKD-EPI equation based on creatinine and cystatin-C gave a higher prevalence of chronic kidney disease than did the MDRD equation, but confidence intervals were very wide. Chronic kidney disease was associated with higher age, Down syndrome, obesity, hypercholesterolemia and hypothyroid disease.

GFR should be measured in all older people with ID and polypharmacy, and in older people with ID and Down syndrome as part of the regular health checks. Moreover, if sarcopenia is present and information on GFR is required, this should not be measured based on creatinine only, but additional measures, such as cystatin-C, should be taken into account.

6.1 INTRODUCTION

Chronic kidney disease is a major health problem, especially in older people and in people with cardiovascular disease, diabetes or hypertension. It can proceed into kidney failure and also contributes to increased morbidity and mortality from cardiovascular disease. As people with intellectual disability (ID) tend to get older, chronic diseases and polypharmacy become increasingly prevalent in this group. Eighty percent of people with ID aged 50 years and over have two or more chronic diseases [124], whereas 52% use four or more types of medication [125]. In these conditions renal functioning should be taken into account.

There are several reasons to suspect that people with ID are at risk of renal dysfunction. Some genetic syndromes are associated with renal dysfunction. In a study among 66 children with Down syndrome, eight percent had congenital kidney disease or glomerulopathy. Of these children, 4.5% had renal failure [126]. In another study among 103 persons with Down syndrome aged 1-57 years, a significantly lower excretion of creatinine in urine was found as compared to non-ID controls. The authors suggest that this might be due to oxidative stress, which also leads to premature aging in Down syndrome [127, 128]. Some more rare genetic syndromes are associated with congenital kidney diseases. Renal anomalies are present in 46% of people with Bardet-Biedl syndrome, mostly hyperechoic kidneys and cystic dysplasia. Many people with this syndrome (70%) develop chronic renal failure and 10-30% require kidney replacement therapy. People with Lowe syndrome have a specific tubulopathy. In Joubert syndrome people have, depending on the genetic mutation, nephronophtisis (chronic tubule-interstitial nephritis) [129]. In Williams syndrome, renal anomalies may occur, such as hypoplastic kidneys and renal artery stenosis [130].

In a large Taiwanese study among adolescents with ID by heterogeneous causes a significantly increased prevalence of renal dysfunction was found [48]. Information about patient characteristics was limited, which reduces insight into possible selection bias or other underlying mechanisms for an increased risk on renal dysfunction. Although the authors did not mention sarcopenia (low muscle mass), which results in underestimation of renal dysfunction with the used diagnostic methods, the significantly lower prevalence in the subgroup with underweight points in this direction, and suggests that the prevalence published in this study was an underestimation of the actual amount of renal dysfunction in this group.

Risk factors for renal damage are (as they are in the general population) the presence of diabetes, hypertension, smoking and use of lithium. These risk factors were studied in the Healthy Ageing and Intellectual Disability (HA-ID) study, a large Dutch cross-sectional study into health of people with ID aged 50 years and over. There is an increased risk on the development of diabetes, whereas hypertension and smoking occur as frequently as in the general population [88]. Peripheral arterial disease (atherosclerosis distal from the aortic bifurcation) indicates atherosclerosis and thus is a risk for microvascular renal damage. The increased risk on diabetes is probably due to metabolic changes based on muscular inactivity in people with an impaired mobility and in the large group with a sedentary lifestyle [32], and to the widespread use of antipsychotic drugs [35]. We have recently shown that also the risk on peripheral arterial disease is increased as compared to the general population [120]. Moreover renal functioning is directly influenced by thyroid hormones, as these induce glomerular filtration [131]. Hypothyroid disease is also a significant problem in people with ID [132]. These are reasons to expect that renal dysfunction can be a relevant problem in older people with ID.

Sarcopenia (loss of muscle mass) is highly prevalent (14%) in older people with ID [95].It is unknown if sarcopenia occurs more often than in the general population, but the presence of motor disabilities from early age on in addition to the age-related motor problems support this hypothesis [95]. The, inherent to sarcopenia, low creatinine production can lead to underestimation of renal dysfunction. This means that creatinine measurement, although it is the most widely used technique, may not be the most reliable indicator of renal damage. Cystatin-C is a protease inhibitor produced by nearly all cells in the body. This protein is, after filtration by the glomerulus, metabolised in the proximal tubular epithelial cells. It may be a good indicator for renal dysfunction in older people, as it is not influenced by the muscle metabolism [133]. Both creatinine and cystatin-C can be used to calculate the estimated glomerular filtration rate (eGFR), the measure for kidney functioning. Most widely used in clinical practice is the Modification of Diet in Renal Disease (MDRD) study equation for calculating the eGFR [134]. However, this equation is not reliable for the normal range of GFR and tends to over-estimate kidney disease, which is why a new equation to predict GFR, based on serum creatinine, was developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI creatinine equation) [135]. This equation more accurately classified people into GFR categories than did the MDRD [136]. Because of the better performance in people with low muscle mass, GFR estimating formulas have also been designed based on cystatin-C (CKD-EPI cystatin C

equation), but the most reliable estimation is based on both creatinine and cystatin-C (CKD-EPI creatinine-cystatin-C equation) [137].

To our knowledge, there has been no research into renal dysfunction in older people with ID. Therefore, the aims of the present study were:

1. To determine the prevalence of chronic kidney disease in older people with ID
2. To determine the prevalence of chronic kidney disease in the sarcopenic group based on different GFR equations (MDRD and CKD-EPI using creatinine and cystatin-C measurement).
3. To identify correlates of renal dysfunction in older people with ID (gender, age, level of ID, mobility, Down syndrome, diabetes, hypertension, obesity, hypercholesterolemia, smoking, peripheral arterial disease, use of antipsychotic drugs, sarcopenia, hypothyroid disease).

6.2 METHODS

6.2.1 Design

This study is part of the large cross-sectional HA-ID study [5]. Three care-providing organisations in the Netherlands participated in the study. These organisations offer low to high level specialised support and care to people with ID. Ethical approval has been provided by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC 2008-234) and by the ethics committees of the participating care-providing organisations. The study adheres to the Declaration of Helsinki for research involving human subjects [56].

6.2.2 Participants

A full description of details about design, recruitment and representativeness of the sample, as well as diagnostic methods, has been published elsewhere [5]. Of the three participating organisations, 2150 clients aged 50 years and over were invited to participate. Informed consent was provided by 1069 clients or their legal representatives, of whom 1050 clients participated in the assessments. This study population was almost representative for the total Dutch older ID population receiving formal care or support: only people living

independently and people aged 80 years and over were underrepresented, women were slightly overrepresented [5]. Only those 637 participants of the total HA-ID population who had participated in vena-puncture and from whom remained enough material for the present analysis could be included in the present study. There were no other exclusion criteria.

Although all participants (clients or their representatives) had given their consent for storage and further analyses from frozen plasma, a second round of informed consent was asked for new analyses from frozen plasma, for which two participants denied consent, which finally resulted in 635 participants in this study.

6.2.3 Data collection

Gender and age were collected from the records of the care-providing organisations. Participant characteristics were obtained from medical files. Behavioural therapists and psychologists completed checklists with the level of ID from their files (borderline, mild, moderate, severe, profound). General practitioners and specialized physicians for people with ID recorded etiology (Down syndrome yes /no), presence of thyroid disease and use of medication. Smoking was reported by a personal caretaker. Obesity (by body mass index) [68], hypertension, hypercholesterolemia, diabetes [88], peripheral arterial disease [120], mobility [53] and sarcopenia [95] were part of the physical and laboratory assessments. Sarcopenia was measured using muscle mass by calf circumference, muscle strength by grip strength and muscle performance by comfortable walking speed. Sarcopenia was defined as having low muscle mass combined with low muscle strength and/or low muscle performance [95]. Peripheral arterial disease was measured using the ankle-brachial index, using a cut off score < 0.9 for the diagnosis. Participants underwent venapuncture by specially trained medical assistants after an overnight fast between November 2008 and July 2010. If people showed any kind of (unusual) resistance, measurements were stopped. Serum was transported frozen and stored at -80 degrees Celsius at the Erasmus Medical Center. Participants of whom no serum had been obtained were excluded from this study. Blood samples were analysed in June 2013 at the laboratory of the Erasmus Medical Center. Creatinine and cystatin-C were measured using the Cobas 8000 Modular Analyzer from Roche Diagnostics AG (Rotkreuz, Swiss). GFR was calculated using the MDRD study equation [134], the CKD-EPI creatinine equation [135], the CKD-EPI cystatin-C equation and the CKD-EPI creatinine-cystatin-C equation [137]. A GFR < 60 ml/min/1.73m^2 was considered as chronic kidney disease (CKD), as recommended by the National Kidney Foundation [138].

6.2.4 Statistical analysis

Data were analysed using IBM SPSS Statistics 17.0. Descriptive statistics are provided for gender, age, aetiology and level of ID. With chi-square analysis we tested if there were any differences between the present study participants and the total HA-ID study population in gender, age (age groups 50-59, 60-69, 70-79, 80-89, 90+) and level of ID Descriptive statistics were used to report prevalence rates of CKD based on the four GFR-equations for both the total study population (aim 1) and the sarcopenic subgroup (aim 2). To explore associations (aim 3) univariate logistic regression analyses were performed between chronic kidney disease (dependent variable), based on GFR as calculated by the CKD-EPI creatinine-cystatin-C equation, and participant characteristics (correlates); gender, age, level of ID, diagnosis of Down syndrome, mobility, diabetes, hypertension, hypercholesterolemia, body mass index (categorised as normal, overweight or obesity), smoking, peripheral arterial disease, use of atypical antipsychotic drugs, hypothyroid disease and sarcopenia (independent variables). If an independent variable showed a significant association ($p < 0.05$) with the dependent variable, it was subsequently entered into a multivariate logistic regression analysis. People with missing data on any of the variables were excluded from the logistic regression analysis. Odds Ratios (OR) were provided for those variables included in the logistic regression analysis. Associations were checked for possible multicollinearity using the variance inflation factor (VIF) of linear regression analysis.

6.3 RESULTS

For analysis of kidney functioning, serum was available from 635 out of 1050 HA-ID participants. Participant characteristics are presented in Table 6.1. As compared to the total HA-ID population, men were slightly overrepresented (chi-square 4.9, $p = .02$). Age and level of ID-groups were similarly represented as in the total HA-ID population.

6.3.1 Prevalence of chronic kidney disease

Prevalence of CKD in the total study population according to the different equations are shown in Table 6.2. Eighty-two participants met the criteria for sarcopenia [95]. Prevalence of CKD in this subgroup, according to the different equations (aim 2), is also shown in Table 6.2.

Table 6.1 Participant characteristics

		n	%
Gender (n=635)	Male	343	54.0%
	Female	292	46.0%
Aetiology (n=570)	Down	88	15.4%
Level of ID (n=629)	Borderline ID	13	2.1%
	Mild ID	132	21.1%
	Moderate ID	321	51.2%
	Severe ID	102	16.3%
	Profound ID	59	9.4%
Age (n=635)	Mean 61.7 years	Range 50-92	SD 8.1
Serum creatinine (n=635)	Mean 75.19	Range 31-219	SD 19.91
Serum cystatin-C (n=635)	Mean 1.05	Range .41-2.46	SD .26

SD = standard deviation.

Table 6.2 Prevalence of chronic kidney disease

Equation	Number of CKD in the total study population (n=635)	% CKD in total study population	95% CI	% in the sarcopenic group (n=82)	95% CI in the sarcopenic group
MDRD	68	10.7%	8.3-13.1	4.9%	0.2-9.5
CKD-EPI creatinine equation	48	7.6%	5.5-9.6	3.7%	0-7.7
CKD-EPI cystatin-C equation	171	26.9%	23.5-30.4	30.5%	20.5-40.5
CKD-EPI creatinine-cystatin-C equation	97	15.3%	12.5-18.1	12.2%	5.1-19.3

CI = confidence interval.

6.3.2 Associations of chronic kidney disease

Results of the univariate and multivariate analyses are presented in Table 6.3. Independent variables included in the multivariate logistic regression model were gender, age, mobility, Down syndrome, hypercholesterolemia, obesity, peripheral arterial disease and hypothyroid disease (Table 6.3). There were 398 participants included in the multivariate logistic regression model, after excluding participants with missing values on any of the independent variables. The proportion explained variance of the model (R^2) was 0.27. There was no multicollinearity; all VIFs were between 1.02 and 1.29. Groups that were significantly more at risk of CKD, were people with higher age (OR 2.38 for each ten

Table 6.3 Logistic regression analysis of chronic kidney disease by CKD-EPI creatinine-cystatin-C equation

	Univariate analyses	Multivariate analysis Odds Ratio (n=398)	95% CI
Gender (n=635)	1.9**	.95	.48-1.87
Age (10 year categories) (n=635)	1.9***	2.38***	1.58-3.58
Level of ID (n=627)	-		
Mobility (n=616)	1.3*	.89	.50-1.59
Down syndrome (n=570)	3.4***	6.86***	2.70-17.40
Diabetes (n=635)	-		
Hypertension (n=539)	-		
Hypercholesterolemia (n=635)	1.7*	2.65**	1.33-5.29
Obesity (body mass index categories) (n=566)	1.7***	1.74**	1.15-2.64
Smoking (n=611)	-		
Peripheral arterial disease (n=488)	1.9*	1.89	.96-3.70
Use of atypical antipsychotic drugs (n=572)	-		
Hypothyroid disease (n=561)	4.3***	3.14**	1.43-6.90
Hyperthyroid disease (n=558)	-		
Sarcopenia (n=565)	-		

* $p < .05$, ** $p < .01$, *** $p < .001$.
- = no significant correlation; CI = confidence interval.

year category), Down syndrome (OR 6.86), hypercholesterolemia (OR 2.65), obesity (OR 1.74) and hypothyroid disease (OR 3.14). From 88 participants with Down syndrome, 33.0% (95% CI 23.1 - 42.8) met the criteria for CKD disease according to the CKD-EPI-creatinine-cystatin-C equation.

6.4 DISCUSSION

This study is, until now, the only internationally published epidemiologic study into renal dysfunction in older people with ID. We found a prevalence of 15.3% (95% CI 12.5 - 18.1) of CKD using the CKD-EPI creatinine-cystatin-C equation. Unfortunately, no published epidemiological studies in the general population, using this equation, were available for comparison. Using the MDRD equation (10.7%, 95% CI 8.3 - 13.1) the prevalence of CKD is the same as in the general same aged Dutch population (12.2%, 95% CI 11.4 - 13.5) [139]. In participants with sarcopenia, the lower prevalence as established with the MDRD

equation than that established with the CKD-EPI creatinine-cystatin-C equation, suggests an underestimation of the prevalence of CKD using the routine formula. As was to be expected, and comparable to the distribution in the general population, CKD was associated with higher age [140], hypercholesterolemia [141], obesity [142] and hypothyroid disease [131]. Down syndrome gave an almost seven times increased risk on CKD, which was the only association specific for the ID population. There was no difference in prevalence of CKD between men and women. In a large epidemiological study in the general population, stage 5 CKD (eGFR < 15 ml/min/1.73 m^2) was significantly more prevalent in men in the group without diabetes, and stage 3 CKD (eGFR 30 - 59 ml/min/1.73 m^2) was more prevalent in women irrespective of the presence of diabetes [140]. Prevalence figures were not comparable to our study data due to differences in study design and methods. The proportion explained variance of our regression model was not high (R^2 = 0.27), which means that there are more (unstudied) associated factors explaining the population risk.

As could be expected CKD was independently associated with correlates of atherosclerosis. Many of these cardiovascular risk factors remain undiagnosed in people with ID: 45-50% of cases with hypertension, diabetes and hypercholesterolemia [88] and 97% of cases with peripheral arterial disease [120] had not been previously diagnosed with these conditions in our study into these conditions. People with ID are not always capable of or supported in addressing their symptoms, asking questions about their health, or being aware of long term health consequences. This warrants concern for renal dysfunction in this group. If cardiovascular risk factors or diseases are overlooked, this may as well occur with (beginning) renal dysfunction, especially when cardiovascular risk management (which includes screening for kidney disease) is not performed. Therefore, chronic kidney disease may proceed into more advanced stages before it is detected.

Down syndrome was highly associated with CKD, independent of hypothyroid disease, and even though they are at lower risk of atherosclerosis [143] and (components of) the metabolic syndrome [88]. Although there were some indications, mostly from smaller studies in children and adolescents [127], for renal dysfunction, these were mostly based on congenital disorders, as established with GFR and renal ultrasound. This is the first time that an increased risk on chronic kidney disease in older people with Down syndrome has been shown. This leaves questions in regard to the underlying pathophysiology. One theory could be that free radicals and increased oxidative stress [127, 128], as a result of an impaired DNA-repair system [144], or the recently discovered impaired somatic stem cells (tissue resident cells that self renew throughout life to repair damaged cells) [145],

could directly damage the kidneys as part of premature aging. Another theory would be that increased circulating proteins in plasma, such as β-amyloid, which is deposited extracellular and plays a crucial role in the development of Alzheimer dementia, could lead to microvascular damage and reduced renal functioning. Such a mechanism would particularly affect people with Down syndrome, due to the triplication of chromosome 21, leading to over expression of the amyloid precursor protein [146-148] and neopterin (a marker for cell-mediated immune activation and inflammation) [149, 150].

Limitations of the present study were that we did not use the gold standard for measuring GFR, the collection of 24-hours urine. This method is not feasible for larger epidemiological studies in this vulnerable group of participants. Also, additional information on kidney disease, through measurement of proteins in urine, was not available. Another limitation is that there were no comparison groups available in the literature, where GFR was studied using the CKD-EPI creatinine-cystatin-C equation. The group participants with sarcopenia was rather small, which makes it difficult to draw firm conclusions on GFR measurement in this group. However, conclusions are supported by current research, which implies that GFR estimations based on creatinine alone do not perform well, especially in groups with low muscle mass, and that the combined creatinine-cystatin-C equation may be useful as a confirmatory test [137]. Strengths of the present study are the innovative character in the population with ID, this major health issue has hardly ever been studies in this population. Furthermore, given the population, the sample size is large, and both creatinine and cystatin-C are used for calculating GFR.

Implications for clinical practice are that renal functioning measurement using the MDRD equation in older people with ID and sarcopenia is not reliable. If information on GFR is required in this group additional determinants should be measured, such as cystatin-C, or albumin in urine to gain more information on chronic kidney disease. Moreover, in patients with Down syndrome, kidney functioning should be measured, as part of the current healthwatch for people with Down syndrome. Also, in all older people with ID and polypharmacy kidney functioning should be measured. For future insight into the pathophysiology of chronic kidney disease in people with Down syndrome, more fundamental research is required. This study showed that chronic kidney disease is a significant problem in older people with ID and that there are several implications for monitoring renal functioning in this group, in order to detect renal functioning at early stage and to prevent it from proceeding into more severe forms of kidney disease and eventually kidney failure.

7

General discussion

The Healthy Ageing and Intellectual Disability (HA-ID) study aimed at gaining knowledge on healthy ageing by studying health and health risks in an older population of people with intellectual disabilities. In this thesis, an overview of cardiovascular disease risk factors is presented, covering prevalence, associations, resulting atherosclerosis and comorbidity. Thereby it contributes to the knowledge on one of the most prominent aging diseases of this time, cardiovascular disease, which will become increasingly prevalent in people with intellectual disabilities, given their improved longevity in the last decades.

Principal findings

We have established that some important cardiovascular disease risk factors, which are also a burden of disease by themselves: peripheral arterial disease, diabetes and obesity (in women), occur more often among aging people with intellectual disability than in the same aged general population. Other risk factors, hypertension, metabolic syndrome and obesity in men, occur as frequently as in the general population, which is a reason to worry, as cardiovascular risk factors in the general population also are a major problem. Chronic kidney disease, which may result from atherosclerosis of kidney vessels, occurs as frequently as in the general population. We were able to compare our data to the general population, because in the same period in which the HA-ID study was performed, the National Institute for Public Health conducted and published a comparable cross-sectional study on cardiovascular disease risk factors using identical outcome measures [81]. For peripheral arterial disease comparable data were available from the Dutch participants of the Pandora study [86], and for chronic kidney disease we could compare our data with those of a large representative epidemiologic study among older people, the Rotterdam study [139].

Associations and mechanisms

Within the intellectually disabled population, mostly people who live more independently, people with mild intellectual disability who are able to make their own choices on lifestyle, like doing groceries and cooking meals independently, are more at risk of developing obesity, hypertension, hypercholesterolemia, diabetes and the metabolic syndrome. This represents the lifestyle-related part of the risk factors, which can be a target for intervention programs, such as education and training programs for healthier diets, physical activity and smoking cessation. In the intellectually disabled population, these targets (diet,

physical activity and smoking) are even more important to address, as the HA-ID study also showed that physical inactivity and a sedentary lifestyle are very widespread problems among older people with intellectual disability [32]. Smoking occurs as much as in the same-aged general population (unpublished data from the HA-ID study).

The people with peripheral arterial disease represent a partly different subgroup of the population with intellectual disability. They are more dependent on others in daily life. This association may be bidirectional. Some of them have been functionally disabled and more dependent in daily activities from a younger age onwards. Inactivity contributes to the development of peripheral arterial disease. Later in life, the functional disability is possibly due to, or worsened by (multi-)morbidity, of which cardiovascular disease can be one of the causes.

There are several other possible mechanisms that can lead to a disturbed metabolic homeostasis, resulting in increased cardiovascular disease risk factors in the population with intellectual disability (Figure 7.1). First of all, there is the widespread use of psychotropic drugs [36], of which especially (but not only) the atypical antipsychotic agents cause obesity and the metabolic syndrome. In psychiatric patients this has

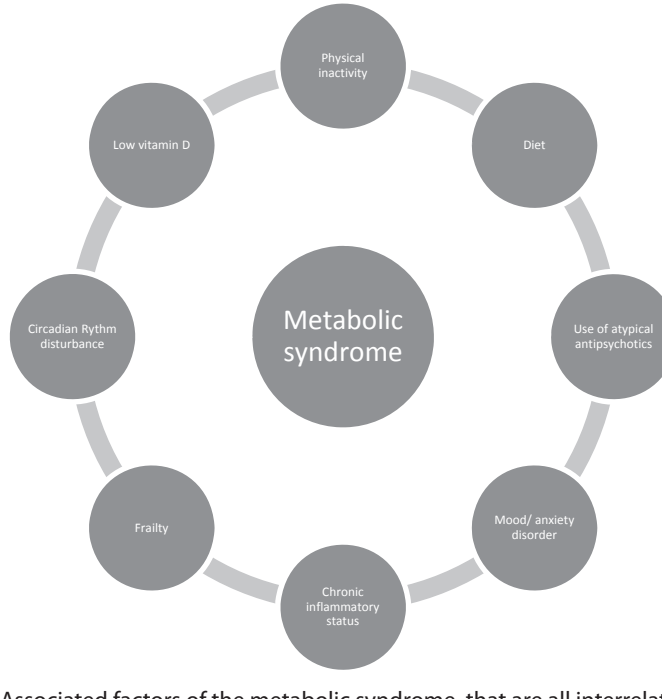

Figure 7.1 Associated factors of the metabolic syndrome, that are all interrelated.

been shown to lead to significantly increased cardiovascular mortality [38, 39]. In people with intellectual disability, atypical antipsychotics are usually used off-label for challenging behavior (such as aggression or self-injurious behavior) [35], and significant improvement of metabolic parameters has been shown when doses are lowered or when the antipsychotic drug is discontinued [40].

A second possible mechanism is the influence of a disturbed circadian rhythm on metabolic homeostasis. The HA-ID study showed that sleep-wake rhythm was less stable and more fragmented in older people with intellectual disability as compared to a control group from the general older population [151]. The suprachiasmatic nucleus paces sleep-wake rhythm as a reaction to daylight. It degenerates with aging, which is a cause of a disturbed sleep-wake rhythm in older people. A disturbed sleep-wake rhythm leads through different pathways to a disturbed glucose metabolism. The pituitary gland influences glucose metabolism, through cortisol, growth hormones and other regulatory hormones. The autonomic nervous system influences the production of insulin and thus glucose both directly and through the pancreatic-β cells, but influences also other cardiovascular risk factors. Finally the pineal gland affects glucose metabolism through the production of melatonin [152]. We know that melatonin production is often disturbed in people with intellectual disability [153, 154]. Moreover, in some cases, the brain alterations inherent to the cause of the intellectual disability may be additive to the natural degeneration of the suprachiasmatic nucleus, which could explain the increased circadian rhythm problems [151] and the resulting metabolic disturbances.

Linked to the extremely low levels of physical activity is the possibility of lack of daylight exposure and thus low levels of vitamin D. Although in some groups this is supplemented, many older people with intellectual disability have vitamin D deficiency [155]. Vitamin D is related to cardiovascular risk factors and cardiovascular disease on multiple levels. Obesity reduces serum vitamin D levels, by sequestrating vitamin D into adipose tissue. It can be released during weight loss. Correction of vitamin D deficiency may improve β-cell functioning, and reduce inflammation mediated β-cell apoptosis, in insulin resistance [156]. Vitamin D may be associated with serum lipid levels and the metabolic syndrome independent of weight status [156, 157]. Moreover vitamin D suppletion may improve type II diabetes and the outcome of cardiovascular disease, but confounding factors, such as physical inactivity, make this relationship unsure [156].

Another mechanism linked to the low levels of physical activity is the metabolic effect of inactivity of the large muscles. The large (leg) muscles metabolize body glucose. With

a sedentary lifestyle, this counts for a dysfunctioning metabolizing organ and thereby it contributes to the development of diabetes [33].

Another possible cause of cardiovascular disease risks are the high amount of anxiety and mood disorders and stress resulting from frequent life-events among older people with intellectual disabilities [96, 158]. These conditions mutually affect each other through lifestyle, inflammatory and neuro-endocrine changes (the hypothalamic-pituitary-adrenal cortex axis and sympathetic nervous system activation). The association between anxiety and diabetes was confirmed in this thesis.

Chronic inflammation is a key feature of obesity, type II diabetes and the metabolic syndrome. In obesity, inflammatory cytokines are more expressed, and adipocytes are infiltrated by macrophages. Inflammatory cytokines cause disruption of insulin action and mediate insulin resistance at the enzyme, activator and receptor level, thus blocking the signaling pathways [159]. As a result to stress (which can be nutrient excess or deficiency, inflammation, infection or hypoxia) peptide mediated pathways (inflammatory cytokines, chemokines and receptors) or lipid mediated pathways (lipids, fatty acids, metabolic enzymes and receptors) can be induced, which both lead to activation of signaling cascades and then to metabolic disease clusters [159]. Older people with intellectual disability have been shown to be at risk of several conditions in which chronic inflammation play a crucial role. Multimorbidity [124], sarcopenia [95] (or obesity sarcopenia [160]) and frailty [94, 161] are frequently encountered health problems in the intellectual disabled population, associated with an increased inflammatory state [162].

Frailty is a geriatric syndrome associated with high vulnerability for adverse health outcomes. Both the phenotype (slow walking speed, impaired grip strength, low activity levels, unintended weight loss and exhaustion) and the multifactorial definition (a combination of signs and symptoms of chronic physical conditions, social circumstances and mental health) are applicable to the population of older people with intellectual disability [94, 161, 163]. In the HA-ID study it has been shown that people with intellectual disability aged 50 years and over had frailty index scores comparable to older people from the general population aged 75 years and over [161]. Cardiovascular disease risks and the metabolic syndrome may have common underlying mechanisms and may also contribute to (the progression of) frailty. Several components, such as obesity, hypertension, diabetes, peripheral arterial disease and cardiovascular disease are included in the frailty index for older people with intellectual disability as contributing deficits to the concept of frailty [161]. Not only are they disabling conditions and general health threats, the hypothesized common underlying pathways

may play a crucial role in the development of frailty. A poor nutritional state (through the development of (obesity-)sarcopenia, loss of muscle mass accompanied by increased fat mass), inflammatory pathway dysregulation (as measured by increased inflammatory markers such as c-reactive protein, interleukin-6 and tumor necrosis factor α), endocrine dysregulation (low insulin-like growth factor 1, which is associated with frailty and insulin resistance), hematocoagulation system activation (in frailty research, D-dimer, factor VIII and fibrinogen are studied as biomarkers, which are also studied as newer risk markers for cardiovascular disease [139]) and insulin resistance in itself (both by hyperglycemia and by increase in adipose tissue mass and loss of lean mass) all cause or increase frailty [164].

Cardiovascular disease

The significant amount of cardiovascular disease risk factors leads to an increased risk of peripheral atherosclerosis. However, the evidence on the effect of the risk factors on incidence of myocardial infarction and cerebrovascular accidents in people with intellectual disability remains scarce. Cardiovascular morbidity is insufficiently studied, as the only internationally published studies are two limited Dutch studies [8, 9]. Retrospectively studied, it has been suggested that prevalence and incidence of myocardial infarction and stroke in older people with intellectual disability do not differ from the general population. However, myocardial infarctions were underreported, which suggests that this diagnosis may be missed due to atypical presentation of symptoms and complaints [9]. This underdiagnosis may have led to an underestimation of the prevalence and incidence of cardiovascular disease in the group with intellectual disabilities. This resembles the underdiagnosis of cardiovascular disease risk factors and peripheral arterial disease that we found in this thesis. In two older studies on reported causes of death among people with intellectual disabilities, cardiovascular disease was a major cause of death [165, 166]. There was an increased risk of death due to (ischaemic) cardiovascular disease as compared to the general population, and, as was shown with the cardiovascular disease risk factors in this thesis, women were more at risk than men [166].

Recommendations for policy and practice

This study has shown that everyone who works with or for older people with intellectual disabilities should be well aware of the cardiovascular disease risk. An anticipating preventive policy should be embedded in the whole care for people with intellectual

disability, both by care providing organizations and by the municipality, which is responsible for the support of people with intellectual disability who need lower levels of care and support. This includes education on healthy lifestyle for personal care givers and for people with mild levels of intellectual disability. Furthermore, care providing organizations should incorporate targeted health promotion programs in daily care and activities. As part of the HA-ID study such a program has been started [167] and has proven to be effective on improving physical activity and health parameters. Further evidence-based interventions are now being designed within the HA-ID consortium. Only recently policy makers have started to recommend health promotion for this population. Chronic healthcare insurance companies (as supervised by the Dutch Healthcare Authority, NZa) now ask care providing organizations to design and justify their preventive health policy. This is a trend following the general population where preventive health campaigns have been conducted for many years now. People using formal care of some care providing organization may benefit from this policy. However, there are many people with mild or borderline intellectual disability who do not make use of any form of formal care or support from care organizations, and will not benefit from such interventions. Moreover, it is well-known that the lower the level of education, the lower the effect of large-scale preventive campaigns on change of behavior. This warrants concern for the group with borderline intellectual disability, as these are also the people who are most at risk for developing cardiovascular risks factors, according to findings of this study.

Currently, diagnosis and treatment of cardiovascular risk factors occurs according to the standard of the Dutch College of General Practitioners 'Cardiovascular risk management' [168]. A cardiovascular risk profile, including age, gender, smoking, family history, diet, use of alcohol, physical activity, blood pressure, body-mass index, serum lipids and glucose and estimated glomerular filtration rate, is composed for people with known cardiovascular disease, diabetes and rheumatoid arthritis. Treatment of risk factors is based on the subsequent 10-year risk of cardiovascular morbidity and mortality. A cardiovascular risk profile can also be composed for people asking for a risk assessment, or with a known positive family history, smoking or obesity. Moreover people with hypertension, hypercholesterolemia and chronic kidney disease should be screened for cardiovascular risk factors. The standard has not been designed for active and systematic detection of risk factors. A major problem with implementing cardiovascular risk management in this population is that people with intellectual disability generally do not

ask for risk assessment by themselves. As we know from this study, many cardiovascular risk factors remain undiagnosed, which leads to under treatment if the present standard is applied to this group, too. Prevention in people without present cardiovascular disease is more effective than prevention in people with manifest cardiovascular disease. For the active screening and detection of undiagnosed risk factors, the Dutch College of General Practitioners has designed the standard "Prevention Consult", which consists of a questionnaire that patients are supposed to fill in themselves [169]. However, this questionnaire is not designed for people with intellectual disabilities and they are not included as a separate risk group [169]. Therefore, general practitioners and specialized physicians for people with intellectual disabilities (ID-physicians) should perform pro-active cardiovascular risk management, starting before the client is aged 50 years. This includes screening for and treatment of cardiovascular risk factors, peripheral arterial disease and kidney dysfunction. Moreover, through medication reviews, atypical antipsychotics should be discontinued when there is no appropriate indication.

When the preventive stadium is passed, risk factors have proceeded into causing cardiovascular disease. Despite high quality medicine for people with intellectual disability, cardiovascular morbidity may remain underdiagnosed. Where cerebrovascular accidents are relatively easy to recognize through the physical symptoms, and are probably diagnosed adequately, angina pectoris, peripheral arterial disease and myocardial infarction may be missed [9]. These conditions should be considered in case of atypical signs, such as behavioral changes or delirium. Active treatment of cardiovascular disease should be considered. From clinical practice, it appears that invasive cardiac surgery (such as percutaneous coronary intervention and coronary artery bypass grafting) is rarely performed in this group [9], which leaves questions with regard to supposed feasibility of these treatments. Under treatment of these conditions in this population should be considered an indesirable health inequity.

Recommendations for research

We have well established that cardiovascular disease risk factors are a significant health issue among older people with intellectual disabilities. However, questions remain on explaining mechanisms and on the effect on cardiovascular morbidity and mortality. Is the observed cardiovascular risk profile merely a result of lifestyle and use of medication in this group, or are there fundamental differences between the aging group with intellectual disabilities and the general population, e.g. in the genetic predisposition or inherent to

the cause of the intellectual disability. Because of the cross-sectional character of the HA-ID study, causality could not be studied. Moreover, more complex measurements should be performed, that may not all be feasible for use in large scale epidemiologic research among this vulnerable group of participants.

To unravel mechanisms, fundamental research should be combined with prospective outcome studies. Mechanisms from which the direction now is unclear, or where the magnitude of the effect in this population is yet unknown are those of inflammation, circadian rhythm, the endocrine cascade and the role of mood and stress of environmental factors.

In a representative population, baseline examinations should be performed in some detail, like in the HA-ID study. Not only people receiving formal care of an organization should be included, but also people with borderline intellectual disability who live independently in the community. Additionally, in targeted subgroups, inflammatory cytokines could be measured. Hormone function can be measured to differentiate between eating behavior effects (leptin and ghrelin) and insulin resistance effects (also mediated by inflammation). Day curves of melatonin levels from saliva can provide information on mechanisms behind circadian rhythm problems. Also from saliva, cortisol levels could provide information on the role of mood disorders and stress. To improve prediction of cardiovascular disease, newer risk markers such as amino-terminal pro-B-type natriuretic peptide (NT-Pro-BNP), high sensitive C-reactive protein and lipoprotein-associated phospholipase A2, but also non-invasive measurements of atherosclerosis such as carotid intima thickness, and coronary calcium score could be included [6, 139].

When in a longitudinal cohort study among adults and older people with ID, ideally for at least 10 years, not only these baseline measures are determined, but also well-defined and measured outcome data are gathered, more insight into the pathology that is specific for the population with intellectual disability would be created. Moreover, reliable epidemiological information on incidence of cardiovascular disease could emerge from such a design. This would lead to the possibility of designing more specific evidence based interventions, that are effective and that will result in significant health and quality of life improvement.

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Summary

Chapter 1 General introduction

There is an increasing group of older people with intellectual disability in The Netherlands, reaching almost the same life expectancy as the general population. Age-related diseases, such as cardiovascular disease, cancer and dementia are now the most encountered diseases and causes of death in older people with intellectual disabilities. Although cardiovascular disease is a major risk for older people with intellectual disabilities, no reliable information was available on cardiovascular disease risk factors, nor attention for prevention of cardiovascular disease was present prior to the start of the Healthy Ageing and Intellectual Disability (HA-ID) study. The HA-ID study aimed at gaining knowledge on healthy ageing by studying health and health risks in an older population of people with intellectual disabilities. Three large care organizations and two university departments participated in this study. Subthemes in the HA-ID study were: (1) Physical activity and fitness, (2) Nutrition and nutritional state, and (3) Mood and anxiety. By studying these themes and the interrelationships, a comprehensive concept of health and health-needs in aging people with intellectual disability would be created. Through physical examination, laboratory examination, and use of screening and diagnostic psychiatric interviews, data were collected on 1050 participants, aged 50 years and over with borderline to profound intellectual disability, which was a near-representative sample for the total older population using formal intellectual disability care. This study was performed to give more insight into the prevalence and associations of cardiovascular risk factors, and the subsequent development of atherosclerosis, in older people with intellectual disability in a large unbiased population sample.

Chapter 2 Overweight and obesity

As obesity is a major health problem associated with increased cardiovascular disease risks, the prevalence of overweight, obesity and body fat percentage in older people with intellectual disability through measurement of Body Mass Index (BMI), waist circumference, waist to hip ratio and skin fold thickness was studied and compared with prevalence of overweight and obesity in the general population. Associations of overweight and obesity with participant and treatment characteristics (gender, age, level of intellectual disability, Down syndrome, autism, independent living, smoking, (instrumental) activities of daily living, physical activity and use of atypical antipsychotic medication) were studied using regression analyses. Among 945 participants, overweight and obesity were highly prevalent, with more obesity (26%) than in the general Dutch older population (10%) as

measured by BMI, and 46-48% obesity as measured by waist circumference and waist to hip ratio respectively. Women, people with Down syndrome, higher age, less severe ID, autism, people who are able to eat independently, preparing meals and doing groceries independently, people with physical inactivity and use of atypical antipsychotics were significantly more at risk of being overweight or obese.

Chapter 3 Hypertension, hypercholesterolemia, diabetes and the metabolic syndrome

Hypertension, hypercholesterolemia and diabetes are important cardiovascular disease risk factors. Together with abdominal obesity they form the metabolic syndrome, which indicates metabolic disturbances, consisting of insulin resistance and accounting for a severe risk of cardiovascular disease. We determined the prevalence of cardiovascular risk factors and compared this with the prevalence in the same-aged general population. Furthermore we determined how many risk factors had not been previously diagnosed, and identified correlates of CVD risk factors (gender, age, level of ID, Down syndrome, independent living, activities of daily living, mobility, instrumental activities of daily living, physical activity, use of atypical antipsychotics, central obesity), using logistic regression analyses. Ninehundred-eighty people participated in this study. Hypertension (53%), diabetes (14%) and metabolic syndrome (45%) were present similarly as in the general Dutch population. Hypercholesterolemia was present less often (23%). Fifty percent of the people with hypertension had not been not previously diagnosed with this condition. Percentages for diabetes, hypercholesterolemia, and the metabolic syndrome were 45, 46 and 94 respectively. People who were more at risk for CVD risk factors were women, older people, people with obesity, people who lived more independently and people who were able to do groceries or prepare a meal independently.

Chapter 4 Peripheral arterial disease

Peripheral arterial disease, atherosclerosis distal from the aortic bifurcation, is associated with increased cardiovascular morbidity and mortality. We determined the prevalence of peripheral arterial disease, the rate of prior diagnoses, and correlations with participant characteristics, and compared the prevalence with peripheral arterial disease in the general Dutch population. Peripheral arterial disease was defined as an ankle-brachial index < 0.9. After excluding those, who met the exclusion criteria, 629 participants

remained. Peripheral arterial disease was present in 20.7% of the participants and 97% had not been diagnosed before. People with higher age, smokers and people who lived in central settings, walked with support and who were more dependent in activities of daily living were more at risk of peripheral arterial disease. The prevalence is higher than in the general population (17.4% of 562 eligible participants with ID, as compared to 8.1% of 917 Dutch participants of the PANDORA study, a pan-European study into the prevalence of peripheral arterial disease) through all age groups.

Chapter 5 Association with anxiety and depression symptoms

Depression and anxiety may be bidirectionally related to cardiovascular disease risk factors. Depression and anxiety may have biological effects causing glucose intolerance, fat accumulation and also lifestyle changes causing metabolic syndrome. But also the effects of diabetes, metabolic syndrome and subsequent cardiovascular disease may affect mood and anxiety. We studied the association between symptoms of anxiety and depression, among 990 participants who completed the screening instruments, with components of the metabolic syndrome, peripheral arterial disease and c-reactive protein. Of the 990 people who participated, 17% had symptoms of depression and 16% had symptoms of anxiety. In a multivariate logistic regression analysis a significant association was found between increased anxiety symptoms and diabetes only (OR 2.4, 95% CI 1.2-4.9).

Chapter 6 Chronic kidney disease

Prevalence and associations of chronic kidney disease were studied using creatinine and cystatin-C measurement in plasma. Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Equations based on creatinine (as the MDRD equation) may underestimate kidney dysfunction in people with sarcopenia, because low muscle mass leads to a low creatinine production. Therefore, also prevalence of chronic kidney disease was studied in the sarcopenic group, using different glomerular filtration rate equations. Prevalence of chronic kidney disease, among 635 participants, was 15.3%, which equals prevalence in the general Dutch population. In the group of participants with sarcopenia (n = 82), the CKD-EPI equation based on creatinine and cystatin-C gave a higher prevalence of chronic kidney disease than did the MDRD equation, but confidence intervals were very wide. Chronic kidney disease was associated

with higher age, Down syndrome, obesity, hypercholesterolemia and hypothyroid disease. Glomerular filtration rate should be measured in all older people with ID and polypharmacy, and in older people with ID and Down syndrome as part of the regular health checks. Moreover, if sarcopenia is present and information on GFR is required, this should not be measured based on creatinine only, but additional measures, such as cystatin-C, should be taken into account.

Chapter 7 General discussion

Some important cardiovascular disease risk factors, which are also a burden of disease by themselves: peripheral arterial disease, diabetes and obesity (in women), occur more often among aging people with intellectual disability than in the same aged general population. Other risk factors, hypertension, metabolic syndrome, obesity in men and chronic kidney disease, occur as frequently as in the general population. People who live more independently are more at risk for cardiovascular disease risk factors, which reflects lifestyle related factors, such as physical inactivity and unhealthy diet choices. Other possible related factors in the intellectually disabled population (such as use of atypical antipsychotics, mood and anxiety disorders, circadian rhythm disturbances, low vitamin D, effects of inactivity of the large muscles, chronic inflammation and frailty) are discussed. This study has shown that everyone who works with or for older people with intellectual disabilities should be well aware of the cardiovascular disease risk. An anticipating preventive policy should be embedded in the whole care for people with intellectual disability. This includes education on healthy lifestyle for personal care givers and for people with mild levels of intellectual disability. Furthermore, care providing organizations should incorporate targeted health promotion programs in daily care and activities. General practitioners and specialized physicians for people with intellectual disabilities should perform pro-active cardiovascular risk management, starting before the client is aged 50 years. This includes screening for and treatment of cardiovascular risk factors, peripheral arterial disease and kidney dysfunction. Recommendations for future research are provided to improve knowledge and care on cardiovascular disease risk factors and subsequent cardiovascular disease for older people with intellectual disabilities.

Samenvatting

Hoofdstuk 1 Algemene Inleiding

Er is een toenemende verouderende groep mensen met een verstandelijke beperking in Nederland die inmiddels bijna dezelfde levensverwachting hebben als de algemene populatie. Verouderingsziekten, zoals cardiovasculaire ziekten, kanker en dementie zijn nu de meest voorkomende ziekten en doodsoorzaken onder mensen met een verstandelijke beperking. Hoewel het risico op hart- en vaatziekten groot is onder mensen met een verstandelijke beperking, bestond er geen betrouwbare informatie over het voorkomen van de risicofactoren en over preventie van hart- en vaatziekten, voor aanvang van de GOUD (Gezond ouder met een verstandelijke beperking) studie. De GOUD-studie was er op gericht om kennis over gezonde veroudering te verwerven, door de gezondheid en gezondheidsrisico's te bestuderen in een oudere populatie verstandelijk gehandicapten. Drie grote zorgorganisaties en twee universitaire afdelingen participeerden in het onderzoek. Subthema's binnen het onderzoek waren: (1) Fysieke activiteit en fitheid, (2) Voeding en voedingstoestand en (3) Stemming en angst. Door deze thema's en de onderlinge relaties te onderzoeken zou een totaalbeeld van de gezondheid en gezondheidsbehoeften van ouderen met een verstandelijke beperking worden gecreëerd. Met behulp van lichamelijk onderzoek, bloedonderzoek en het gebruik van screenende en diagnostische psychiatrische interviews werden gegevens verzameld van 1050 deelnemers van 50 jaar en ouder met zwakbegaafdheid of een lichte tot zeer ernstige verstandelijke beperking. Dit was een bijna representatieve steekproef van de totale populatie ouderen met een verstandelijke beperking die gebruik maken van enige vorm van zorg of ondersteuning van een zorgaanbieder voor verstandelijk gehandicapten. Dit onderzoek werd uitgevoerd om meer inzicht te verwerven in de prevalentie en associaties van cardiovasculaire risicofactoren en de hierop volgende ontwikkeling van atherosclerose in een grote representatieve steekproef ouderen met een verstandelijke beperking.

Hoofdstuk 2 Overgewicht en obesitas

Obesitas is een ernstig gezondheidsprobleem, geassocieerd met een verhoogd risico op hart- en vaatziekten. Daarom werd de prevalentie van overgewicht en obesitas en het vetpercentage in het lichaam onderzocht bij ouderen met een verstandelijke beperking door middel van meting van de Body Mass Index (BMI), middelomtrek, middelheupratio en huidplooidikte. Prevalenties werden vergeleken met die van de algemene oudere populatie. Middels regressie-analyses werden geassocieerde factoren bestudeerd (geslacht, leeftijd, mate van de verstandelijke beperking, Down syndroom, autisme, mate van zelfstandig

wonen, roken, (instrumentale) activiteiten van het dagelijks leven, fysieke activiteit, en gebruik van atypische antipsychotica). Onder de 945 deelnemers aan de huidige metingen waren overgewicht en obesitas een veel voorkomend probleem. Gemeten met de BMI was er meer obesitas (26%) dan in de algemene Nederlandse oudere bevolking (10%). Met de middelomtrek en middelheupratio hadden respectievelijk 46-48% obesitas. Risicogroepen voor obesitas waren vrouwen, mensen met Down syndroom, mensen op hogere leeftijd, met een minder ernstige mate van de verstandelijke beperking, autisme, mensen die in staat waren om zelfstandig te eten, maaltijden te bereiden en boodschappen te doen, mensen die weinig fysiek actief waren en mensen die atypische antipsychotica gebruikten.

Hoofdstuk 3 Hypertensie, hypercholesterolemie, diabetes en het metabool syndroom

Hypertensie, hypercholesterolemie en diabetes zijn belangrijke cardiovasculaire risicofactoren. Zij vormen samen met centrale obesitas het metabool syndroom, wat wijst op metabole ontregeling bestaande uit insulineresistentie, en wat een sterk verhoogd risico geeft op hart- en vaatziekten. In deze studie werden de prevalentie van deze cardiovasculaire risicofactoren bepaald en vergeleken met de prevalentie in de algemene populatie. Verder werd onderzocht hoeveel van deze risicofactoren nog niet eerder gediagnosticeerd waren en wat de geassocieerde factoren van deze cardiovasculaire risicofactoren waren (geslacht, leeftijd, mate van verstandelijke beperking, Down syndroom, mate van zelfstandig wonen, (instrumentale) activiteiten van het dagelijks leven, mobiliteit, gebruik van atypische antipsychotica en centrale obesitas), met behulp van logistische regressie-analyses. Er namen 980 mensen deel aan de metingen. Hypertensie (53%), diabetes (14%) en het metabool syndroom (45%) kwamen even vaak voor als in de algemene Nederlandse populatie. Hypercholesterolemie kwam minder vaak voor (23%). De helft van de mensen met hypertensie was hiermee niet eerder gediagnosticeerd. Voor diabetes, hypercholesterolemie en het metabool syndroom was dat respectievelijk 45, 46 en 94 procent. Mensen die vaker cardiovasculaire rsicofactoren hadden waren vrouwen, mensen op hogere leeftijd, mensen met obesitas, mensen die zelfstandiger woonden en mensen die zelfstandig boodschappen konden doen of zelf een maaltijd konden bereiden.

Hoofdstuk 4 Perifeer arterieel vaatlijden

Perifeer arterieel vaatlijden, atherosclerose distal van de aortabifurcatie, is geassocieerd met een verhoogd risico op morbiditeit en mortaliteit ten gevolge van hart- en vaatziekten. De prevalentie van perifeer arterieel vaatlijden, het aantal diagnoses hiervan voorafgaande aan de studie en de geassocieerde factoren werden onderzocht. De prevalentie werd vergeleken met die in de algemene Nederlandse populatie. Perifeer arterieel vaatlijden was gedefinieerd als een enkel-armindex < 0.9. Na exclusie van mensen in een rolstoel bleven er 629 deelnemers over. Van hen voldeed 20.7% aan de criteria voor perifeer arterieel vaatlijden. 97% van de mensen met perifeer arterieel vaatlijden waren niet eerder met deze aandoening gediagnosticeerd. Risicogroepen waren mensen op hogere leeftijd, mensen die rookten, mensen die op een centrale locatie woonden, mensen die liepen met een hulpmiddel en mensen die afhankelijker waren in hun vaardigheden betreffende de activiteiten van het dagelijks leven. De prevalentie was hoger dan in de algemene bevolking (17.4% van 562 vergelijkbare deelnemers, vergeleken met 8.1% van 917 Nederlandse deelnemers aan de PANDORA studie, een pan-Europese studie naar de prevalentie van perifeer arterieel vaatlijden) in alle leeftijdscategorieën.

Hoofdstuk 5 Associatie met symptomen van angst en depressie

Depressie en angst zijn bidirectioneel gerelateerd aan cardiovasculaire risicofactoren. Depressie en angst hebben mogelijk biologische effecten die glucose-intolerantie, vetophoping en leefstijlveranderingen die tot het metabool syndroom leiden, mede veroorzaken. Maar ook kunnen het metabool syndroom, diabetes en de hierop volgende hart- en vaatziekten de stemming en angst beïnvloeden. De relaties tussen symptomen van angst en depressie, onder de 990 deelnemers bij wie de screeningsinstrumenten waren afgenomen, en componenten van het metabool syndroom, perifeer arterieel vaatlijden en c-reactive protein werden bestudeerd. 17% van de deelnemers had symptomen van depressie en 16% had symptomen van angst. Met een logistische regressie-analyse werd alleen een significante associatie gevonden tussen aanwezigheid van symptomen van angst en het hebben van diabetes (OR 2.4, 95% CI 1.2-4.9).

Hoofdstuk 6 Chronische nierziekte

De prevalentie en geassocieerde factoren van chronische nierziekte werden onderzocht door bepaling van kreatinine en cystatine-C in plasma. De glomerulaire filtratiesnelheid werd berekend met de "Modification of Diet in Renal Disease" (MDRD) formule en met de verschillende "Chronic Kidney Disease Epidemiology Collaboration" (CKD-EPI) formules. Formules gebaseerd op kreatinine (zoals de MDRD-formule) kunnen nierfunctiestoornissen onderschatten bij mensen met sarcopenie, omdat de lage spiermassa leidt tot een lage kreatinineproductie. Daarom werd ook de prevalentie van nierfunctiestoornissen onder de deelnemers met sarcopenie onderzocht, waarbij de verschillende formules vergeleken werden. De prevalentie van chronische nierziekte onder 635 deelnemers was 15.3%. Chronische nierziekte kwam even vaak voor als in de algemene Nederlandse bevolking. Bij de 82 deelnemers met sarcopenie gaf de CKD-EPI-formule gebaseerd op kreatinine en cystatine-C een hogere prevalentie van chronische nierziekte dan de MDRD-formule, maar de betrouwbaarheidsintervallen waren erg breed. Mensen met een hogere leeftijd, Down syndroom, obesitas, hypercholesterolemia en hypothyreoidie hadden een verhoogde kans op chronische nierfunctiestoornissen. De glomerulaire filtratiesnelheid zou bij alle ouderen met een verstandelijke beperking en polyfarmacie gemeten moeten worden en bij mensen met Down syndroom als onderdeel van de reguliere healthwatch. Als er sprake is van sarcopenie en de nierfunctie moet onderzocht worden, dan zou die niet alleen gebaseerd moeten worden op de glomerulaire filtratiesnelheid op basis van het kreatinine, maar zouden ook aanvullende bepalingen, zoals cystatine-C, gedaan moeten worden.

Hoofdstuk 7 Algemene discussie

Een aantal cardiovasculaire risicofactoren die zelf ook een ziektelast kunnen zijn, namelijk perifeer arterieel vaatlijden, diabetes en obesitas (bij vrouwen) komen vaker voor onder ouderen met een verstandelijke beperking dan in de algemene oudere Nederlandse bevolking. Andere risicofactoren, hypertensie, metabool syndroom, obesitas bij mannen en chronische nierziekte komen even vaak voor als in de algemene bevolking. Mensen die zelfstandiger wonen hebben een hoger risico op cariovasculaire risicofactoren, wat veroorzaakt wordt door de leeftstijlgerelateerde factoren, zoals fysieke inactiviteit en ongezonde dieetkeuzes. Andere mogelijke gerelateerde factoren in de verstandelijk gehandicapte populatie (zoals het gebruik van atypische antipsychotica, stemmings- en angststoornissen, circadiane ritmestoornissen, een laag vitamine D-gehalte, effecten van

inactiviteit van de grote spieren, chronische inflammatie en geriatrische kwetsbaarheid) worden bediscussieerd. Deze studie heeft aangetoond dat iedereen die werkzaam is in de zorg voor of ondersteuning van mensen met een verstandelijke beperking, zich bewust moet zijn van de risico's op hart- en vaatziekten. Er zou een anticiperend preventief beleid moeten worden ingebed in de totale zorg voor mensen met een verstandelijke beperking. Dit bestaat onder andere uit onderwijs over een gezonde leefstijl voor zorgverleners en mensen met een lichte verstandelijke beperking. Verder zouden zorgorganisaties doelgerichte gezondheidsbevorderende programma's onderdeel moeten laten uitmaken van de dagelijkse zorg en activiteiten. Huisartsen en artsen voor verstandelijk gehandicapten zouden pro-actief cardiovasculair risicomanagement moeten aanbieden en uitvoeren, te beginnen voor de cliënt 50 jaar oud is. Dit omvat het screenen voor en behandelen van cardiovasculaire risicofactoren, perifeer arterieel vaatlijden en chronische nierziekte. Er worden aanbevelingen gedaan voor verder onderzoek om de kennis en zorg te verbeteren voor ouderen met een verstandelijke beperking en cardiovasculaire risicofactoren en daarop volgende ziekten.

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Schoon-famiglia, con voi la vita e molto bella. Vi amo. Voi ricevete da me il "Nobel-price for being".

En dan mijn fotomodellen natuurlijk. Want voor de duidelijkheid, de mensen op de omslag zijn de slimste mensen die ik ken. Mijn opa is er helaas niet meer bij. Hij was een voorbeeld voor iedere wetenschapper, als uitvinder van de pil, maar bovendien een van de meest sensitieve mensen die ik kende. En lieve oma wat ben ik blij dat jij er bent! Lief en zorgzaam, mijn kinderen hebben je niet voor niets omgedoopt tot oma TIEN!

Lieve Ilja, wat is het belangrijk om een broer te hebben. Om elkaar uit te dagen, plezier te hebben en te begrijpen. En dan heb ik nog wel zo'n lieve broer als jij! Wat een geluk heb ik toch!

De kinderen van de fietsenmaker hebben rammelende fietsen. En de kinderen van de schoenmaker lopen met gaten in hun schoenen. Dan moet het met de kinderen van een hoogleraar pedagogiek en een consultatiebureauarts wel heel rampzalig aflopen… Niet dus! Lieve pap en mam, waar zou ik zijn zonder jullie. Jullie zijn de liefste ouders die ik me kan wensen. Jullie hebben ons altijd gestimuleerd om te doen wat we kunnen en willen, altijd vanuit de warme thuisbasis. En nog steeds staan jullie altijd voor ons klaar. Nu ook als super-oma en partici-opa van onze schatjes. Jullie zijn geweldig!

Niek, mijn liefielief! Je vond me bij de Albert Heijn tussen de groente. Toen als studenten, nu als groot gezin. Wat onveranderd blijft is ons plezier samen, onze interesses en de liefde. En wat is er mooier dan dat delen met Luïsa, Jonah en Leander, onze drie mooiste en liefste kindertjes van de hele wereld?

About the author

CURRICULUM VITAE

Channa Femke de Winter werd geboren op 30 augustus 1980 in Utrecht. Na het behalen van haar VWO diploma aan de Werkplaats Kindergemeenschap in Bilthoven in 1998 begon zij aan haar studie geneeskunde in Utrecht. Tijdens haar studie deed ze onderzoek naar hormonale effecten op het cognitief functioneren bij de afdeling endocrinologie. In 2005 behaalde zij haar artsexamen. Daarna werkte ze als arts-assistent psychiatrie bij Altrecht, afdeling Wier, waar zij naast haar klinische werkzaamheden wetenschappelijk onderzoek deed naar psychiatrische problematiek bij verstandelijk gehandicapten. In 2006 startte zij met de opleiding tot arts voor verstandelijk gehandicapten (AVG) aan het Erasmus MC, met als werkplekken achtereenvolgens zorgaanbieders Bartiméus en Abrona. Ze werkte in deze periode in opdracht van het CCE aan het onderzoek naar somatische oorzaken van probleemgedrag. In 2009 rondde zij de opleiding tot AVG af en werkte vervolgens als AVG bij Bartiméus en Wier. Sinds februari 2011 is zij werkzaam als AVG en bopz-arts binnen Reinaerde en in maart 2011 startte zij daarnaast met haar promotieonderzoek binnen de Leerstoel Geneeskunde voor Verstandelijk Gehandicapten aan het Erasmus MC te Rotterdam, waarvan het huidige proefschrift het resultaat is. Sinds 2012 is zij tevens opleider binnen Reinaerde voor artsen in opleiding tot AVG.

Channa woont samen met Niek Verwey en zij zijn trotse ouders van Luïsa (2008), Jonah (2010) en Leander (2013).

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