CARDIOVASCULAR DISEASE IN OLDER ADULTS WITH INTELLECTUAL DISABILITIES

Prevalence, incidence, and risk factors

Marleen de Leeuw

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Prevalence, incidence, and risk factors

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CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Compared to the extensive research in the general population, epidemiological studies on the cardiovascular health of adults with intellectual disabilities (ID) remain in their early stages. As a clinical epidemiologist, I recognise the significant importance of longitudinal research in understanding and improving long-term health outcomes. This PhD trajectory provided me with the opportunity to explore the cardiovascular health of older adults with ID through the Healthy Ageing and Intellectual Disabilities (HA-ID) study. This chapter provides background information on intellectual disabilities, the organisation of care for people with ID, the HA-ID study, cardiovascular diseases (CVD), and its risk factors. It then reviews current evidence on the prevalence, incidence, and risk factors of CVD in adults with ID, emphasising the importance of longitudinal data collection. Finally, the potential role of objective measurements, such as electrocardiography (ECG), in this population is discussed, followed by the aims and outline of this thesis.

Intellectual disabilities

ID are defined by a combination of limitations in intellectual functioning (intelligence quotient (IQ)<70) and adaptive behaviour, encompassing everyday social and practical skills, that manifest before the age of 22 [1]. The severity of ID is categorised as borderline (IQ=70-80), mild (IQ=55-70), moderate (IQ=35-55), severe (IQ=25-35), and profound (IQ<25) [2]. The global prevalence of ID is estimated to be between 1% and 1.5% of the population [3]. This prevalence appears to be similar in the Netherlands, though precise epidemiological data are lacking [4]. In the Netherlands, people with ID, live either at home (with or without support) or in small group homes within specialised care facilities. They have access to standard healthcare services, including municipal care, informal care and primary care provided by general practitioners (GPs). GPs play a central role in the Dutch healthcare system, serving as the primary point of contact for accessing medical care. When needed, people with ID can also receive specialised care under the Dutch Long-Term Care Act (Wlz). This care is provided in residential facilities or through outpatient clinics by multidisciplinary teams including ID physicians, behavioural experts, and specialised therapists. The level of support and care is determined by care intensity packages, a system with eight levels for ID-specific care. In 2018, over 111000 people with ID received care or support under the Wlz [5]. In 2019 healthcare costs for people with ID accounted for 9.9% (9.6 billion euros) of the total healthcare expenditure in the Netherlands, with 97% covered by the Wlz [6]. In recent years, the demand for care and support for people with ID has risen significantly. In the Netherlands, between 2012 and 2016, the number of people with ID undergoing assessments for more intensive forms of long-term residential care

increased by an average of 7% per year [7]. Factors such as digitalisation, the decline of low-skilled jobs, reduced opportunities for practical education, greater diversity in care options, and more and earlier diagnoses have been identified as key drivers of this rapid growth in demand [8]. Currently, approximately 2.3 million people in the Netherlands have borderline ID, with an estimated 730000 (31.7%) facing significant challenges in social adaptation qualifying them for specialised ID care [5]. As modern society becomes more complex, people with mild and borderline ID, are expected to increasingly require specialised ID care due to the growing demands for intellectual, practical, and social skills [8].

Healthy Ageing and Intellectual Disabilities study (HA-ID study)

In response to the increasing longevity of people with ID [9-11] and the lack of epidemiological data about their health and health risks at older ages, the HA-ID study was initiated [12]. The HA-ID study is a prospective multicentre cohort study on physical and mental health of older adults with ID who use formal ID care and support. The study was conducted collaboratively by three Dutch ID care organisations (Abrona, Amarant, and Ipse de Bruggen) in partnership with the Department of General Practice, Intellectual Disability Medicine Research at Erasmus MC, University Medical Center Rotterdam. The data collection was conducted in the three participating care organisations, which provide support to a wide spectrum of people with borderline to profound ID in different ID care settings across the Netherlands. All adults with ID who received formal care or support from one of these care organisations, and who were 50 years or older on September 1, 2008, were invited to participate. Of the 2322 invitees, 1050 (45.2%) agreed to participate in the baseline measurements in 2009-2010, resulting in a study population that was nearly representative of the Dutch older ID population receiving formal care or support [12].

The HA-ID study started with a focus on physical activity and fitness, nutrition and nutritional state, and mood and anxiety. Baseline measurements comprised an extensive set of measurements, such as physical examinations, laboratory assessments, medical, psychological, and dental record reviews, physical fitness tests, measurements of physical activity with pedometers, swallowing observations, questionnaires regarding daily functioning, mobility, and falls, food intake diaries, and depression and anxiety screenings. A detailed description of the rationale and design of the baseline measurements can be found elsewhere [12]. After three and five years, new research topics were introduced, including cardiovascular diseases (CVD), frailty, mortality, and causes of death. The 3- and 5-year follow-up measurements included medical record reviews for health conditions, mortality and cause of death, as well as questionnaires on daily functioning, mobility, and falls.

All 429 participants who still received care or support from one of the participating care organisations on July 1, 2020 and consented to be contacted for participation were invited for the 10-year follow-up measurements. Of these, 278 (64.8%) provided consent to participate. Data were collected between October 2020 and July 2023, using an updated version of the comprehensive baseline measurements, with several new measurements added, including ECG. Based on findings from the baseline, 3- and 5-year follow-up, the 10-year follow-up study focused on five research themes: 1) CVD; 2) physical activity, fitness and musculoskeletal disorders; 3) psychological problems and psychiatric disorders; 4) nutrition and nutritional state; and 5) frailty. A detailed description of the 10-year follow-up study can be found in Chapter 3 of this dissertation. This follow-up will provide deeper insight into health trajectories and risk factors for health problems in older adults with ID, including the progression of CVD and associated risk factors over time.

Cardiovascular diseases

CVD are a group of diseases affecting the heart and blood vessels [13]. This dissertation specifically focuses on atherosclerotic CVD, thereby excluding congenital CVD. CVD, including coronary artery disease, heart failure, cerebrovascular disease, and other conditions [13], account for nearly one-third of all deaths worldwide [13] and are associated with significant long-term impacts on quality of life [14, 15] and health care costs [16, 17]. CVD are not only an important health issue for the population at large; they are also associated with high morbidity and mortality in adults with ID [18, 19]. A recent Danish cohort study reports that people with ID had a significantly higher overall risk of early-onset CVD of 24% than the general population [20]. Extensive research and attention are given to CVD in the general population, forming the basis for both prevention and early treatment [21]. In contrast, this focus is a lot less prevalent for adults with ID. Despite some existing longitudinal studies [22, 23], including the HA-ID study, longitudinal research on CVD and its risk factors in adults with ID remains limited.

Research specifically in the ID population is needed because adults with ID face syndrome-specific vulnerabilities that elevate their CVD risk, such as those seen in Prader-Willi syndrome [24, 25] and cerebral palsy [26]. The high prevalence of psychotropic drug use, including antipsychotics, compounds this risk [27, 28]. These medications are frequently prescribed off-label, primarily for managing behavioural problems like aggression or self-injurious behaviour [27], despite limited evidence of efficacy [29]. Psychotropic drugs can delay cardiac repolarisation, leading to QTc prolongation [30], which increases the risk of ventricular arrhythmias and CVD [31]. Atypical antipsychotics, in particular, are known to cause significant side

effects, including weight gain and the development of metabolic syndrome [32, 33]. Additionally, CVD risk is strongly influenced by lifestyle factors, including an unhealthy diet, physical inactivity, smoking, and alcohol consumption [21]. Several lifestyle related CVD risk factors, such as hypertension [20, 34], type 2 diabetes [34, 35], obesity [34, 36], metabolic syndrome [37, 38], and physical inactivity [39], are more prevalent in adults with ID than in the general population. For example, Thorsted et al. (2025) reported that adults with ID had more than double the risk of type 2 diabetes compared to age-matched peers from the general population (HR 2.15, 95%CI 2.09-2.20) [35]. Wallén et al. (2018) found a significantly higher prevalence of obesity in people with ID compared to the general population with an age-adjusted OR of 3.0 to 3.4 [34]. Additionally, de Winter et al. (2011) reported a prevalence of metabolic syndrome of 25.1% in adults with ID aged 50 and older, which was significantly higher than the 15.7% observed in their peers from the general population [37]. Lifestyle related CVD risk factors are particularly present among those with mild ID, who live more independently and make their own lifestyle choices [40]. Physical inactivity is often observed among adults with ID [39, 41]. Only 9% of adults with ID meet the minimum physical activity recommended by public health guidelines [42]. Finally, the increasing life expectancy of people with ID [9-11] leads to a growing burden of age-related CVD in this population, making it increasingly important to understand and address their heightened CVD risk.

Cardiovascular diseases in adults with intellectual disabilities

In addition to growing evidence of the high CVD risk in adults with ID [19], there is a strong need for accurate and up-to-date understanding of the prevalence and incidence of CVD and associated risk factors in this specific population. As this population ages, too little is known about the trajectory of their cardiovascular health, the changes in their health status over time, and early indicators of cardiovascular problems. This knowledge is vital for ID and primary care providers, public health planners, and policymakers [43, 44], as it supports the optimisation of healthcare delivery [45] and ensures the effective allocation of healthcare resources [46]. Several epidemiological studies previously assessed the prevalence, and to a lesser extent the incidence, of CVD in adults with ID. However, systematic reviews on this topic are limited. This makes correct understanding and interpretation of CVD prevalence and incidence in adults with ID complex. Existing reviews summarising CVD prevalence or incidence in adults with ID used narrative review methods rather than systematic review methodology [47]. These reviews also had methodological limitations, such as the absence of methodological quality assessment of the included articles, the lack of subgroup analyses [48], the lack

of targeted CVD search terms and focusing on a broad range of physical health conditions with less focus on CVD [49], or being concentrated on specific groups [50]. Therefore, there's a need for a comprehensive systematic review examining the prevalence and incidence of CVD in the population of adults with ID.

Data on the predictive value of risk factors for CVD morbidity and mortality in this group also remains limited. The HA-ID study [51] previously identified obesity (OR 3.0; 95%CI 1.02-7.64; p=0.04), atypical antipsychotic use (OR 8.90; 95%CI 1.12-70.77; p=0.04), chronic kidney disease (OR 5.53; 95%CI 1.26-24.22; p=0.02), and history of heart failure (OR 10.03; 95%CI 2.63-38.21; p=0.001) and stroke (OR 4.46; 95%CI 1.21-16.49; p=0.03) as associated risk factors over a 3-year follow-up period, but at that time noted limited statistical power, emphasising the need for larger study populations or longer follow-up periods. Understanding the predictive value of CVD risk factors is important to determine CVD risk profiles and high risk groups for adults with ID, and whether they differ from the general population. If this is the case, current CVD prevention guidelines should be adapted to better serve this group. Targeted research on CVD risk factors in adults with ID is therefore essential.

An important CVD risk factor worth investigating is physical fitness. Research in the general population showed that lack of physical fitness [52, 53], especially cardiorespiratory fitness [54-56], is an important risk-factor of CVD. In the general population, cardiorespiratory fitness levels have consistently been shown to predict CVD events, with each increase in metabolic equivalent of task (MET) associated with an 11% reduction in CVD risk and a 19% reduction in the risk of heart failure [56]. Additionally, in the general population, slow gait speed [57, 58] and low grip strength [59, 60] are predictive for a higher risk of CVD and CVD-related mortality. Very low physical fitness levels have been observed in older adults with ID [61-63]. In the HA-ID cohort, Hilgenkamp et al. (2012) found that physical fitness levels among adults with ID aged 50 years and older were comparable to, or even lower than, those of adults in the general population who were 20 years older [61]. Additionally, adults with ID frequently experience a high prevalence of comorbidities at younger ages [64]. For example, in the HA-ID cohort, a multimorbidity prevalence of 79.8% (defined as ≥ 2 chronic conditions) was reported among adults with ID aged 50 and older [65]. Given their generally low physical fitness levels and the high prevalence of comorbidities, it remains unclear whether findings from the general population can be generalised to older adults with ID. Longitudinal studies exploring the relationship between physical fitness and CVD could provide insights into whether physical fitness might be a

target for improving cardiovascular health in this population. These studies are important for building the evidence base needed to improve care and support for older adults with ID and for preparing healthcare providers for the growing elderly ID population. This knowledge can be used to reduce the occurrence of specific risk factors and identify, monitor and early treat high-risk groups. The current gap in research highlights the need for more longitudinal studies on the cardiovascular health of adults with ID.

Underdiagnosis

Longitudinal research in adults with ID faces the challenge of underdiagnosis. Diagnostic work-up in adults with ID can be complex and challenging [66], as they can experience limitations in understanding and expressing health problems, symptoms could present atypically, and cooperation or tolerance during physical examination might be limited [67]. Referral policies for this vulnerable group are made with the greatest possible care in close consultation with physicians, representatives, healthcare staff, and other stakeholders. Careful consideration is given to the potential impact of diagnostic processes on the individual's quality of life, which may sometimes result in the decision to refrain from further diagnosis [68]. As a result, this increases the likelihood of underdiagnosis in adults with ID [51, 65, 67, 69]. This is also supported by previous research on peripheral arterial disease (PAD), which showed a high rate of underdiagnosis in older adults with ID: 97% had not been previously diagnosed with PAD [70]. Similar trends of underdiagnosis have been found for CVD risk factors, with high rates of underdiagnosis reported for hypercholesterolemia (46%), hypertension (50%), diabetes (54%), and metabolic syndrome (94%) [40].

Electrocardiography

To better understand the true prevalence and incidence of CVD and to reduce underdiagnosis, it would be beneficial to use objective measures, such as ECGs. An ECG is a recording of the electrical activity of the heart measured via electrodes placed on the limbs and chest wall [71]. Despite the fact that not all abnormalities are detectable with an ECG and some findings may have limited clinical significance, an ECG allows for the detection of a wide range of cardiac abnormalities [71]. An ECG is easy to perform, low-cost, and widely applicable in the general population [72]. Due to the risk of QTc prolongation associated with antipsychotic use [30], which is commonly prescribed in adults with ID, the Dutch Multidisciplinary Guideline on Problem Behaviour in adults with ID recommends ECG monitoring when prescribing antipsychotics, particularly in those with additional risk factors [73]. The feasibility of ECG recording in older adults with ID, however, may not be

self-evident and has not been previously studied in this specific group. Lying still may be challenging due to restlessness, anxiety, tics, or limited ability to follow instructions. This may affect the feasibility and interpretability of the ECG. It may also make GPs and ID physicians more hesitant to perform it in this population. In addition, the prevalence of ECG abnormalities in older adults with ID has been sparsely studied. Most available studies enrolled children or adults, but not older adults, and specifically targeted on certain syndromes such as Down syndrome [74, 75], Prader-Willi syndrome [76], and Williams Syndrome [77, 78], or on specific groups such as those with severe motor and intellectual disabilities [79]. Nevertheless, to our knowledge, such studies are lacking in older adults with ID. More insight into the feasibility of ECG recording and the prevalence of ECG abnormalities in older adults with ID may contribute to screening, diagnostic protocols and (preventive) therapy to improve cardiovascular health in this specific group.

Aims and outline of this thesis

This thesis aims to describe the prevalence and incidence of CVD in (older) adults with ID and explore associated risk factors. To provide an overview of the existing literature on the prevalence and incidence of CVD in adults with ID, *Chapter 2* presents a systematic review that summarises reported prevalence and incidence rates, including subgroup data. Since a significant portion of this dissertation is based on findings from the HA-ID study, *Chapter 3* presents the study and its main findings to date, along with the design of the 10-year follow-up, which features a research theme specifically focused on CVD. Next, we utilised ECGs as an objective measure to study the prevalence of CVD. First, we evaluated the feasibility of ECG recording using ECGs collected during the 10-year follow-up of the HA-ID study. Additionally, we analysed these ECGs to assess the prevalence of ECG abnormalities in older adults with ID and compared their frequency with medical records (*Chapter 4*). In *Chapter 5*, we focused on physical fitness as a potential CVD risk factor. Research in the general population indicates that physical fitness is a key factor in CVD risk. To investigate this relationship in older adults with ID, we examined the differences in physical fitness levels between older adults with ID with and without CVD, using HA-ID baseline data. To gain more insight into the incidence of CVD and the predictive value of risk factors for CVD morbidity in older adults with ID, we conducted a longitudinal study using data from the HA-ID study (*Chapter 6*). *Chapter 7* reflects on the key findings of this thesis and provides recommendations for clinical practice and future research.

CHAPTER 2

Prevalence and incidence of cardiovascular disease in adults with intellectual disabilities: A systematic review

Marleen J. de Leeuw, Thessa I. M. Hilgenkamp, Dederieke A. M. Maes-Festen, Patrick J. E. Bindels, Roy G. Elbers & Alyt Oppewal (2025). Prevalence and Incidence of Cardiovascular Disease in Adults With Intellectual Disabilities: A Systematic Review. *Journal of Intellectual Disability Research*. Advance online publication. https://doi.org/10.1111/jir.13254

ABSTRACT

Background

Given the high risk of cardiovascular diseases (CVD) in adults with intellectual disabilities (ID), there is a strong need for accurate understanding on CVD prevalence and incidence in this population. This information is important to ensure optimal care and resource allocation. However, systematic reviews on this topic are limited. Therefore, this systematic review aimed to provide a comprehensive synthesis of studies on the prevalence and incidence of CVD in adults with ID, including subgroup data.

Method

We performed a systematic search in Embase, Medline ALL, Web of Science, Cochrane Central, PsycINFO, and Google Scholar up to 21 January 2025, including peer-reviewed articles on CVD prevalence or incidence in adults with ID. Article screening and data extraction were independently performed by two researchers. Data were synthesised by CVD diagnosis. When available, data were reported separately for different subgroups. The methodological quality was assessed by two independent researchers. This review followed the PRISMA guidelines.

Results

In 55 articles, prevalence and incidence rates were identified for coronary artery disease (prev 0-12.9%; inc 2.0-2.8 per 1000py), myocardial infarction (prev 0-7.9%; inc 0.3-2.8 per 1000py), heart failure (prev 0.8-18.6%; inc 12.5 per 1000py), cerebrovascular disease (prev 0.7-15.0%; inc 2.55 per 1000py), stroke (prev 1.3-17.2%; inc 2.7-3.2 per 1000py), peripheral arterial disease (prev 0.4-20.7%; inc 1.1 per 1000py), venous thrombosis (prev 0.6-12.4%; inc 0.8-4.1 per 1000py), and atrial fibrillation (prev 0.8-6.3%). Subgroup data have been reported based on age, sex, level of ID, aetiology of ID, living circumstances, CVD risk factors, data collection methods, and source populations. Overall, higher prevalence and incidence rates were reported in older people, and in studies that used physical measurements for diagnosis.

Conclusions

Due to variability in methodological quality, clinical characteristics, and high statistical heterogeneity, drawing conclusions about CVD prevalence and incidence in adults with ID is challenging. Therefore, the subgroup data presented in this review are valuable for identifying rates within specific subgroups. Longitudinal studies, along with research employing valid and reliable data collection methods (preferably objective measurements) aligned with studies in the general population, clear reporting of individual CVD diagnoses, and subgroup analyses will offer valuable additional insights in future research.

INTRODUCTION

Cardiovascular diseases (CVD), such as myocardial infarction, stroke, and heart failure, account for almost one-third of all deaths worldwide [13]. These diseases are not only an important health issue for the population at large; they are also associated with high morbidity and mortality in individuals with intellectual disabilities (ID) [18, 19]. The increasing life expectancy of individuals with ID [9, 11] leads to a growing burden of age-related CVD in this population. Additionally, adults with ID are at higher risk for CVD than their peers in the general population [19], partly due to aetiology-specific risk factors for example in Prader-Willi syndrome [24, 25] and for cerebral palsy [26]. The high prevalence of psychotropic drug use, such as antipsychotics, also increases CVD risk in adults with ID [28, 80]. In addition, compared to the general population, several CVD risk factors are more common in adults with ID, such as hypertension [20, 34], type 2 diabetes [34, 35], obesity [34, 36], metabolic syndrome [37, 38], and physical inactivity [39]. Risk factors for CVD are especially common in adults with mild ID, who live more independently and make their own lifestyle decisions [40].

In addition to growing evidence of the high CVD risk in adults with ID, there is a strong need for accurate and up-to-date understanding of the prevalence and incidence of CVD in this specific population. This information is important for ID and primary care providers, actors in public health planning, and health system policy makers [43, 44] and is a necessity in providing optimal healthcare [45] and allocation of healthcare resources [46].

Several epidemiological studies previously assessed the prevalence, and to a lesser extent the incidence, of CVD in adults with ID. However, these studies present varying and sometimes even conflicting rates [47] and systematic reviews on this topic are limited. This makes correct understanding and interpretation of CVD prevalence and incidence in adults with ID complex. Existing reviews summarising CVD prevalence or incidence in adults with ID used narrative review methods rather than systematic review methodology [47]. These reviews also had methodological limitations, such as the absence of methodological quality assessment of included articles and lack subgroup analyses [48], were focused on a broad range of physical health conditions with less focus on CVD and lack targeted CVD search terms [49], or concentrated on specific groups, such as individuals with ID in primary care settings [50]. Therefore, there is a need for a comprehensive systematic review examining the prevalence and incidence of CVD in the population of adults with ID.

To fill this gap in knowledge, this systematic review aimed to provide a comprehensive synthesis of studies on the prevalence and incidence of CVD in adults with ID, including subgroup data.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [81]. The review protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42022346126).

Search strategy

To identify eligible articles, the following databases were searched from inception to 21 January 2025: Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, PsycINFO, and Google Scholar. The search strategy was developed with the help of a medical research librarian of the Erasmus MC and consisted of a combination of the following topics: 1) intellectual disabilities, 2) cardiovascular diseases, 3) prevalence/incidence, and 4) study design (prospective and retrospective cohort studies and cross-sectional studies). To ensure that all relevant articles were identified by the search, both broad (e.g., 'cardiovascular diseases') and specific CVD terms (e.g., 'stroke') were used as index terms and free text words. The reference lists of systematic reviews that met the inclusion criteria were hand-searched to find any additional relevant articles. A detailed overview of the search strategy can be found in the Supplementary Materials (see S1, https://doi.org/10.1111/jir.13254).

Study selection

The articles included in this review had to meet the following criteria: 1) an observational study design (prospective and retrospective cohort studies and cross-sectional studies); 2) a study sample that included participants with ID, either in full or as a proportion, irrespective of the proportion's size. For comprehensiveness, all definitions of ID were considered, including borderline ID and those without strict classification or diagnostic criteria; 3) participants aged 18 years or older, either in full or as a proportion, irrespective of the proportion's size; and 4) the article reported prevalence and/or incidence rates of one or more individual CVD diagnoses, including cerebrovascular disease (stroke, transient ischemic attack), heart failure, ischemic heart disease/coronary artery disease, myocardial infarction, angina, atrial fibrillation, peripheral arterial disease and/or other CVD

diagnoses (except congenital CVD). All definitions of individual CVD diagnoses and methods of data collection, including medical file reviews, clinical examinations, self-reports, and questionnaires, were considered. Articles were excluded if they used mixed samples without presenting separate data for adults with ID aged 18 years or older, if they only reported the prevalence and/or incidence of congenital CVD, or if they were conference abstracts.

Two review authors (MJdL and TIMH) independently screened the titles and abstracts of all identified records using the selection criteria, with 99.1% agreement and a Cohen's Kappa of 0.99. Results were compared and disagreement was resolved through consensus discussion. Next, the full texts of the remaining articles were independently screened by two authors (MJdL and TIMH) and inclusion and exclusion checklists were completed for each article. Again, disagreements were resolved by consensus discussion. There was 94.9% agreement and a Cohen's Kappa of 0.87. Although a third author was available to resolve any disagreements, consensus was reached between the two reviewers, and therefore, no further consultation was required.

Data extraction

Data from the included articles was extracted using a data extraction form consisting of the following items: year of publication, author, country, study design, aim, data collection period, setting, target population, recruitment of participants, sampling method, ID ascertainment, sample characteristics (sample size, age, sex, level of ID, aetiology of ID, living circumstances, CVD risk factors, medication use, inclusion and exclusion criteria), data collection method to ascertain CVD diagnoses, and CVD prevalence and incidence. Data was extracted by two independent researchers for each article (MJdL, TIMH, RGE, AO and three co-workers mentioned in the acknowledgment section). Extracted data were compared and disagreements were resolved through consensus discussion. Although a third author was available to resolve any disagreements, consensus was reached between the two reviewers, and therefore, no further consultation was required.

Data synthesis

Extracted data were synthesised by CVD diagnosis and were reported separately for prevalence and incidence rates per 1000 person-years (py). A narrative synthesis was conducted to address the research questions, with plots used to visually support the presentation of the data. Clinical heterogeneity was assessed by comparing the following clinical characteristics: age, level of ID, aetiology of ID, data collection methods, and source populations. We discussed clinical homogeneity within the research team, and based on this discussion, we decided whether pooling of data

was appropriate. Statistical heterogeneity was assessed by visual inspection of the forest plot, the Wald test, and the I-squared statistic (I^2) was calculated. When both clinical and statistical homogeneity were observed (I^2<30%), a random-effects logistic regression model was used to pool the results in a meta-analysis. If no more than four articles were included in the meta-analysis, the robustness of the random-effects model was tested using a fixed-effect model. Sensitivity analyses were performed by methods used to ascertain the diagnosis of CVD. If clinical or statistical heterogeneity was observed, individual study results were plotted for visual purposes, but no pooled proportion was estimated. Statistical software environment R with package Meta was used for the statistical analysis [82].

Subgroup analyses

When available, the prevalence and incidence of CVD diagnoses in subgroups was reported separately based on: age (participants younger than 40 years old versus participants of 40 years and older, based on the Systematic Coronary Risk Evaluation (SCORE) model [83]), sex (male versus female), level of ID (borderline, mild, moderate, severe, profound), aetiology of ID (i.e. Down syndrome, Prader-Willi syndrome), living circumstances (i.e. residential setting, community, with family), CVD risk factors (i.e. overweight/obesity, smoking, physical inactivity), data collection methods to ascertain CVD diagnoses (i.e. medical record data, physical measurements, interviews, surveys), and source population (i.e. specialist/residential ID care, primary care, hospital, register data).

Methodological quality assessment

Two authors (MJdL and AO) independently assessed the methodological quality of the included articles using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data [84]. The checklist addresses the following criteria: 1) sample frame, 2) sampling method, 3) sample size, 4) description of study subjects, 5) coverage of identified sample, 6) valid methods to identify the condition, 7) standardised and reliable methods to identify the condition, 8) appropriate statistical analysis and 9) response rates. The criteria were rated as yes (1 point), no (0 points), not applicable (0 points), or unclear (0 points), with a total score for each article ranging from 0 to 9. Higher scores represent higher methodological quality articles. Scores from both authors were compared and disagreements were resolved through discussion. For each article, the individual scores per criterion and the total methodological quality score were presented. To differentiate the methodological quality of the articles, total scores were categorised into tertiles: the highest tertile (total scores 7-9), representing articles with the highest methodological quality scores; the second tertile (total scores 4-6); and the lowest tertile (total scores 1-3).

RESULTS

The article selection process is shown in Figure 1, with the number of articles retrieved, included and excluded at each stage. The most common reasons for exclusion of the full-text articles were not reporting the prevalence or incidence of individual CVD diagnoses, or, in case of mixed samples, not presenting data separately for adults with ID who were 18 years or older. All excluded full-text articles, including the reason for exclusion, can be found in the Supplementary Materials (see S2 https://doi.org/10.1111/jir.13254).

Article characteristics

Table 1 provides the characteristics of the 55 articles included in the data synthesis originating from a total of 47 studies. The included articles were published between 1997 and 2024 with a data collection period between 1977 and 2024. Most articles were based on studies conducted in Europe (n=33), followed by North America (n=13), Oceania (n=5), Asia (n=3), and Middle East (n=1). Thirty-three of the articles included used a cross-sectional design, 22 a longitudinal design. The sample sizes ranged from 28 to 116422 participants, the mean age of participants ranged from 28.1 to 70.7 years, and the percentage of females ranged from 26.3% to 62.9%. Most articles used medical record data (n=25), followed by health insurance data (n=6), interviews (n=5), surveys (n=3), and physical measurements (n=2, ankle-brachial index). Fourteen articles combined different types of data collection. Most articles had a source population from specialist/residential ID care (n=18), followed by hospital data (n=10), primary care data (n=6), ID register data (n=6), insurance register data (n=6), outpatient clinics (n=3), national register data (n=1), a combination of source populations (n=2), and other source populations (n=3). ID ascertainment methods varied, including recruitment from ID care (n=18), the use of ICD or ICPC codes (n=15), ID register recruitment (n=7), diagnosis recorded in medical records through registration (n=5), confirmed genetic diagnosis (n=2), recruitment via ID organisations (n=2), other methods (n=4), and unspecified methods (n=2). Eighteen articles specifically focused on one syndrome (Down syndrome (n=14) and Prader-Willi syndrome (n=4)) and the remaining articles were etiologically diverse samples of adults with ID.

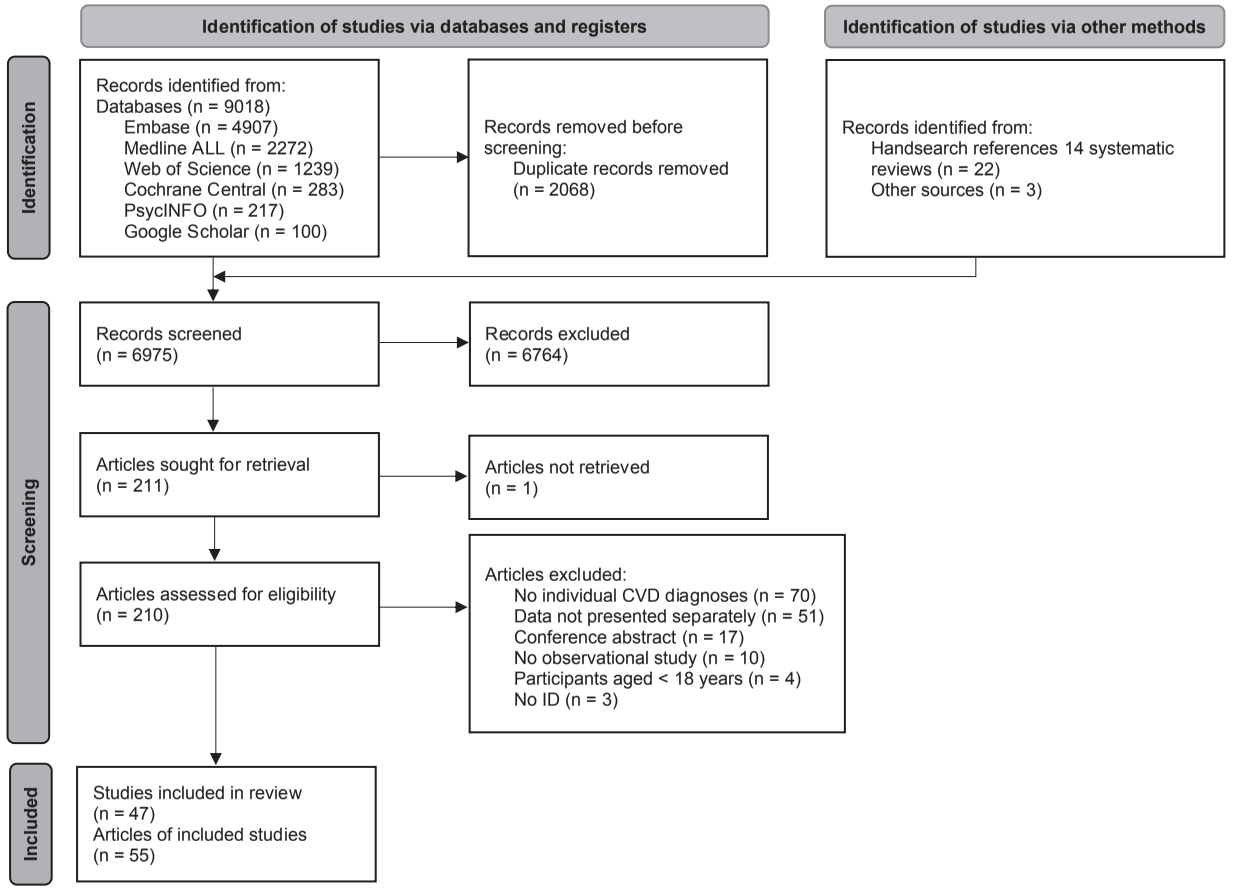

Figure 1 PRISMA flow diagram of the article selection process

CVD = cardiovascular disease; ID = intellectual disability

Table 1 Characteristics of included articles

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
Alexander et al. (2015)[85]	3803	Longitudinal	UK	2004-2013	Medical record data
Aparicio et al. (2020)[86]	3786	Cross-sectional	Spain	2005-2014	Medical record data
Aparicio et al. (2024)[18]	9879	Cross-sectional	Spain	1997-2014	Medical record data
Baksh et al. (2023)[87]	79354	Longitudinal	UK	1990-2020	Medical record data
Breia et al. (2014)[88]	209	Cross-sectional	Portugal	NR	Medical record data
Butler et al. (2020)[89]	1093	Cross-sectional	USA	2004-2014	Health insurance data
Carey et al. (2016)[90]	14751	Cross-sectional	UK	2012	Medical record data
Cho et al. (2024)[19]	3643	Longitudinal	Korea	2009-2020	Health insurance data
Cocks et al. (2016)[91]	328	Cross-sectional	Australia	2013	Interviews/surveys
Cooper et al. (1998)[92]	207	Cross-sectional	UK	NR	Interviews/medical record data
Cooper et al. (2015)[93]	8014	Cross-sectional	Scotland	2007	Medical record data
Cooper et al. (2018)[43]	721	Cross-sectional	UK	2007-2010	Medical record data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Primary care	NR, 18+ population	46.5	NR	DS in medical record	NR	100% DS
Hospital	47 (12.5; 18-96)	43.3	NR	ICD-9-CM code 758.0	NR	100% DS
Hospital	40 (12; NR)	42.8	NR	ICD-9-CM code 758.0	NR	100% DS
Primary care	NR	37.7	NR	ID/DS in medical record	NR	13.9% DS
Specialist/ residential ID care	36.3 (8.4; 20-58)	40.2	NR	Recruitment in ID care	NR	100% DS
Insurance register	NR, 18+ population	NR	NR	ICD-9 code 759.81	NR	100% PWS
Primary care	42.1 (15.7; NR)	42.1	NR	Learning disability in medical record	NR	10.7% DS, 10.3% autism spectrum disorder
Insurance register	39.1 (12.6; NR)	28.8	NR	Physician's diagnosis/IQ<70	NR	NR
ID register, specialist/ residential ID care, other (radio/news promotion)	36.6 (NR; 18-82)	40.7	NR	Varies across sample	NR	12.6% DS, 10.3% CP
ID register	61.2 (NR; 20-94)	47.3	NR	Recruitment via ID register	Mild, moderate, severe, profound	12.6% DS, 66.7% unknown
Primary care	43.1 (15.8; NR)	43.6	NR	ID in medical record	NR	NR
Primary care	44.3 (NR; 18-92)	44.8	NR	Recruitment via primary care ID register	Mild, moderate, severe, profound	13.6% DS

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
de Leeuw et al. (2023)[a][94]	684	Cross-sectional	The Netherlands	2009-2010	Medical record data
de Leeuw et al. (2024)[a][95]	200	Cross-sectional	The Netherlands	2020-2023	Medical record data / physical measurements
de Winter et al. (2013)[a][70]	629	Cross-sectional	The Netherlands	NR	Physical measurements
de Winter et al. (2016)[a][51]	1050	Longitudinal	The Netherlands	2009-2013	Medical record data/physical measurements
Evenhuis et al. (1997)[96]	70	Longitudinal	The Netherlands	1983-1993	Medical record data
Fitzpatrick et al. (2020)[97]	2342	Longitudinal	USA	1996-2016	Medical record data
Folch et al. (2019)[98]	953	Cross-sectional	Spain	2013-2016	Interviews/medical record data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Specialist/ residential ID care	61.6 (8.2; NR)	48.7	NR	Recruitment in ID care	Borderline, mild, moderate, severe, profound	14.9% DS
Specialist/ residential ID care	70.7 (5.7; NR)	49.5	NR	Recruitment in ID care	Borderline, mild, moderate, severe, profound	6.2% DS
Specialist/ residential ID care	61.5 (NR; 50-93)	46.4	NR	Recruitment in ID care	Borderline, mild, moderate, severe, profound	12.8% DS
Specialist/ residential ID care	62 (8; 50-93)	48.7	NR	Recruitment in ID care	Borderline, mild, moderate, severe, profound	14.2% DS
Specialist/ residential ID care	70.1 (NR; 60-92)	62.9	NR	Recruitment in ID care	Mild, moderate, severe, profound	1.4% DS
Hospital	NR, 18+ population	53.7	7.7% Hispanic/ Latino, 89.5% not Hispanic/ Latino, 2.9% declined	ICD-9 code 758.0 and ICD-10 code Q90.9	NR	100% DS
Specialist/ residential ID care	42.7 (15.3; 18-84)	47.6	NR	Recruitment in ID care	Mild, moderate, severe, profound	NR

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
García-Domínguez et al. (2020)[99]	1040	Cross-sectional	Spain	NR	Surveys
Gilmore et al. (2021)[100]	2054	Cross-sectional	USA	2016-2017	Health insurance data
Haider et al. (2013)[101]	897	Cross-sectional	Australia	NR	Interviews
Haveman et al. (2011)[b][102]	1253	Cross-sectional	Austria, Belgium, Finland, France, Germany, Ireland, Italy, Lithuania, the Netherlands, Norway, Romania, Slovenia, Spain, UK	NR	Interviews/surveys
Hayes et al. (2017)[103]	187	Longitudinal	USA	1995-2015	Medical record data
Hedgeman et al. (2017)[25]	66	Longitudinal	Denmark	1995-2012	Medical record data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Specialist/ residential ID care	55.3 (7.3; 44-88)	50.5	NR	Recruitment in ID care	Mild, moderate, severe, profound	NR
Insurance register	NR, 65+ population	31.2	88.8% White non-Hispanic, 8.9% Black non-Hispanic, 0.7% Hispanic, 1.7% other/ unknown	ICD-10 codes F70-F79	NR	NR
Outpatient clinic	38.4 (NR; NR)	44.5	NR	Recruitment via administrative ID database	Mild, moderate, severe, profound	NR
Other (each country identified potential participants in a geographical area representing typical living circumstances)	41 (NR; 19-90)	49	NR	NR	Mild, moderate, severe, profound	20.3% DS
Hospital	31* (NR; 21-60)	51.3	NR	Confirmed genetic diagnosis of DS	NR	100% DS
Hospital	NR, 18+ population	NR	NR	ICD-10 Danish modified code DQ871E	NR	100% PWS

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
Hermans et al. (2014)[a][65]	1050	Cross-sectional	The Netherlands	2008-2010	Medical record data/physical measurements
Ho et al. (2021)[104]	143	Cross-sectional	UK	NR	Medical record data
Hsieh et al. (2018)[105]	1381	Cross-sectional	USA	2010-2011	Surveys
Huang et al. (2015)[106]	25464	Longitudinal	Taiwan	2000-2011	Health insurance data/medical record data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Specialist/ residential ID care	NR, 50+ population	48.7	NR	Recruitment in ID care	Borderline, mild, moderate, severe, profound	14.2% DS, 0.9% Fragile X syndrome, 6.8% other, 4.6% unknown
Specialist/ residential ID care	43.3 (14.8; NR)	46.9	55.9% White, 2.1% Indian, 0.7% Pakistani, 0.7% Bangladeshi, 7.0% Other Asian, 2.1% Black Caribbean, 23.1% Black African, 8.4% other ethnic group	Recruitment in ID care	Mild, moderate, severe	NR
Other (recruitment through various organisations, e.g. Special Olympics, Easter Seals, The Arc and managed care organisations in the Midwest)	37.1 (14.4; 18-86)	44.6	NR	Recruitment via ID organisations	NR	25.8% DS
Insurance register/ national register	NR, 35+ population	NR	NR	Recruitment in disability database	NR	NR

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
Hussain et al. (2020)[107]	391	Cross-sectional	Australia	NR	Interviews
Jansen et al. (2013)[69]	510	Longitudinal	The Netherlands	2007	Medical record data
Kapell et al. (1998)[108]	278	Cross-sectional	USA	NR	Interviews/medical record data
Lefter et al. (2024)[109]	28	Cross-sectional	Romania	2022-2024	NR
Liu et al. (2023)[110]	1105	Longitudinal	Sweden	1977-2013	Medical record data
Määttä et al. (2011)[111]	104	Longitudinal	Finland	2004-2009	Medical record data
Martínez-Leal et al. (2011) b[112]	1257	Cross-sectional	Ireland, Austria, Belgium, Finland, France, Germany, Italy, Lithuania, the Netherlands, Norway, Romania, Slovenia, Spain, UK	2005-2008	Interviews

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Specialist/ residential ID care	65.2 (4.4; 60-87)	37.3	NR	Recruitment in ID care	Mild, moderate	NR
Specialist/ residential ID care	65.5 (9.6; 50-92)	44.3	NR	Recruitment in ID care	Mild, moderate, severe, profound	6.9% DS
ID register	55.1 (NR; NR)	48.6	NR	Recruitment via ID register	Mild, moderate, severe, profound	47.1% DS, 52.9% other
Hospital	28.1 (9.5; 20-55)	39.3	NR	Genetic testing (karyotyping)	NR	100% DS
National register	45 (45-45)***	NR	NR	ICD-8 codes 310-315, ICD-9 codes 317-319, and ICD-10 codes F70-F79	NR	NR
ID register	NR	NR	NR	Recruitment via ID register	Mild, moderate, severe, profound	100% DS
Other (each country identified potential participants in a geographical area representing typical living circumstances)	41.4 (NR; NR)	49.5	NR	NR	Mild, moderate, severe, profound	NR

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
McCarron et al. (2013)c[22]	753	Cross-sectional	Ireland	NR	Interviews
McCarron et al. (2017)c[44]	478	Cross-sectional	Ireland	2010	Interviews/surveys
Mendiratta et al. (2018)[113]	2134	Longitudinal	USA	2002-2012	Surveys/medical record data
Miot et al. (2023)[114]	63	Cross-sectional	France	2015-2018	Medical record data/ surveys
O'Brien et al. (2023)c[115]	58	Cross-sectional	Ireland	2019-2020	Interviews
Pemmasani et al. (2021)[116]	240	Longitudinal	USA	2014	Medical record data
Rubenstein et al. (2024)[117]	116422	Cross-sectional	USA	2011-2019	Health insurance data
Sinnema et al. (2011)[118]	102	Longitudinal	The Netherlands	NR	Interviews/medical record data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
ID register	54.8 (9.6; NR)	55	NR	Recruitment via ID register	Mild, moderate, severe, profound	NR
ID register	60 (NR; NR)	42.5	NR	Recruitment via ID register	NR	NR
Hospital	69.1 (10.3; NR)	51.7	68.9% White, 5.4% Black, 4.2% Hispanic, 2.6% other, 19.0% missing	ICD-9-CM code 758.0	NR	100% DS
Specialist/ residential ID care	46.0 (26-57)**	27.0	NR	Recruitment in ID care	NR	NR
ID register	60.7 (10.5; 41-87)	62.1	NR	Recruitment via ID register	Mild, moderate, severe/ profound	13.8% DS, 86.2% other/ unknown
Hospital	NR, 26+ population	51.7	NR	ICD-9 code 759.81	NR	100% PWS
Insurance register	NR, 18+ population	49.2	74.7% White, 14.0% Black, 1.1% Pacific Islander, 3.4% Asian, 0.9% Native American, 6.0% Multiple Races, 16.8% Hispanic/ Latino	ICD-9 and ICD-10 codes (not further specified)	NR	100% DS
Outpatient clinic	36.2 (NR; 18-66)	52.0	NR	Recruitment via PWS organisations	Borderline, mild, moderate, severe	100% PWS

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
Sobey et al. (2015)[119]	1706	Longitudinal	Australia	1993-2010	Medical record data
Tenenbaum et al. (2012)[120]	120	Longitudinal	Israel	1988-2007	Medical record data
van Allen et al. (1999)[121]	38	Longitudinal	Canada	1981-1992	Medical record data
van den Akker et al. (2006)[122]	436	Longitudinal	The Netherlands	NR	Medical record data
van den Bemd et al. (2022)[123]	18114	Cross-sectional	The Netherlands	2018	Medical record data
Wallace et al. (2008)[124]	155	Longitudinal	Australia	2002-2005	Medical record data
Wang et al. (2023)[125]	230	Cross-sectional	USA	2015-2021	Medical record data
Whitney et al. (2023)d[126]	74025	Longitudinal	USA	2011-2016	Health insurance data

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Hospital	NR, 19+ population	48.9	NR	ICD-9-CM code 7580 and ICD-10-AM code Q90	NR	100% DS
Hospital	36.3 (13.8; 18-73)	39.2	NR	DS in medical record	NR	100% DS
Specialist/ residential ID care	48.6 (NR; 30-68)	26.3	NR	Recruitment in ID care	Severe, profound	100% DS
Specialist/ residential ID care	NR, 20+ population	47.5	NR	Recruitment in ID care	Mild, moderate, severe, profound	14.9% DS, 77.8% other aetiologies, 7.3% missing
Primary care	39.0 (15.9; NR)	42.9	NR	ICPC code P85	NR	NR
Specialist/ residential ID care	50* (NR; 40-74)	47.7	NR	Recruitment in ID care	NR	16.8% DS, 12.3% other known cause, 71.0% unknown
Outpatient clinic	42 (14; 18-70)	46.1	95.2% White	ICD-8 codes 310-315 and ICD-10 codes F70-F79	NR	100% DS
Insurance register	51.5 (NR; NR)	48.3	0.9% Asian, 15.3% Black, 3.0% Hispanic, 0.8% North American Native, 78.5% White, 1.5% Other	ICD-9 codes 270.1x, 317.x-319.x, 758.0, 758.1, 759.81, 760.71, 759.83	Mild, moderate, severe/ profound	NR

Table 1 Continued

Author (year)	Sample size (N≥18year)	Study design	Country	Data collection period	Data collection method
Whitney et al. (2023)[d][127]	18549	Longitudinal	USA	2011-2016	Health insurance data
Wong et al. (2011)[128]	811	Cross-sectional	China	2010	Surveys
Zaal-Schuller et al. (2015)[129]	407	Cross-sectional	The Netherlands	NR	Medical record data/ surveys/physical measurements

CP = cerebral palsy; DS = Down syndrome; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; ID = intellectual disability; NR = not reported; PWS = Prader-Willi syndrome

[a] Articles from the Healthy Ageing and Intellectual Disability (HA-ID) study

[b] Articles from the POMONA-II project

Methodological quality assessment

Results of the methodological quality assessment are presented in the Supplementary Materials (see S3 https://doi.org/10.1111/jir.13254). The total scores ranged from 1 to 8, with higher scores representing better methodological quality. Most articles had a total score of 6 (n=16). Criterion 4 (description of study subjects) received the most 'no/unclear' scores (n=32) due to missing information on participants' age, sex, living circumstances, level of ID, and/or aetiology. This was followed by criterion 6 (valid methods to identify the condition), which was scored 'no/unclear' in nearly half of the articles (n=27) due to an unclear description of the data collection method, missing definitions or diagnostic criteria for CVD, or the use of unvalidated instruments. Also Criterion 7 (standardised and reliable methods to identify the condition) was scored 'no/unclear' in nearly half of the articles (n=26) due to insufficient descriptions of

Source population	Mean age (SD; range)	% Female	Ethnicity	ID ascertainment	Level of ID	Aetiology of ID
Insurance register	58.7 (NR; NR)	54.1	0.9% Asian, 10.0% Black, 2.7% Hispanic, 0.8% North American Native, 84.0% White, 1.6% Other	ICD-9 codes 270.1x, 317.x-319.x, 758.0, 758.1, 759.81, 760.71, 759.83	Mild, moderate, severe/ profound	NR
Specialist/ residential ID care	44 (NR; 18-79)	46.7	NR	Recruitment in ID care	Mild, moderate, severe, profound	13.2% DS, 16.7% CP
Specialist/ residential ID care	NR, 40+ population	42.0	NR	Recruitment in ID care	Mild, moderate, severe, profound	16.7% DS, 83.3% other

[c] Articles from the Intellectual Disability Supplement to the Irish Longitudinal Study on Aging (IDS-TILDA)

[d] Articles on the same study population described by Whitney et al. (2023)

*Median age

** Median age (IQR)

*** Median age (IQR) at baseline, follow-up started at the 45th birthday for all included participants

measurement procedures and data collector qualifications. The remaining criteria received 'no/unclear' scores as follows: criterion 1 (sample frame, n=22), criterion 2 (sampling method, n=10), criterion 3 (sample size, n=6), criterion 5 (coverage of identified sample, n=21), criterion 8 (appropriate statistical analysis, n=2), and criterion 9 (response rates, n=17).

Prevalence and incidence of cardiovascular disease

In 55 articles, prevalence and/or incidence rates were presented for any of the following CVD diagnoses: coronary artery disease, myocardial infarction, heart failure, cerebrovascular disease, stroke, peripheral arterial disease, venous thrombosis, and atrial fibrillation. None of the diagnoses could be pooled in a meta-analysis due to high statistical heterogeneity (range I^2 83-100%).

Coronary artery disease

Seventeen articles reported overall prevalence rates of coronary artery disease between 0% and 12.9% in adults with ID (Figure 2) and between 0.4% to 4.7% in studies within the highest methodological quality tertile (n=7). Articles exclusively focusing on the prevalence and incidence of myocardial infarction are summarised in the 'Myocardial infarction' section below. Prevalence rates of subgroups are presented in Table 2. Generally, higher prevalence rates were reported in adults aged 40 or older compared to those under 40 [118, 123]. Three articles reported the prevalence of angina (0 cases in 58 individuals (0%) [115]; 2 cases in 2342 individuals (0.1%) [97]; 3 cases in 190 individuals (1.6%) [95]).

Three articles reported overall incidence rates of coronary artery disease in adults with ID. One of them did not use person-years to describe the incidence [110]. The remaining two articles reported an incidence rate ranging from 2.0 to 2.8 per 1000py. One of them fell within the highest methodological quality tertile and reported an incidence of 2.0 per 1000py. Incidence rates and subgroup data are presented in Table 3.

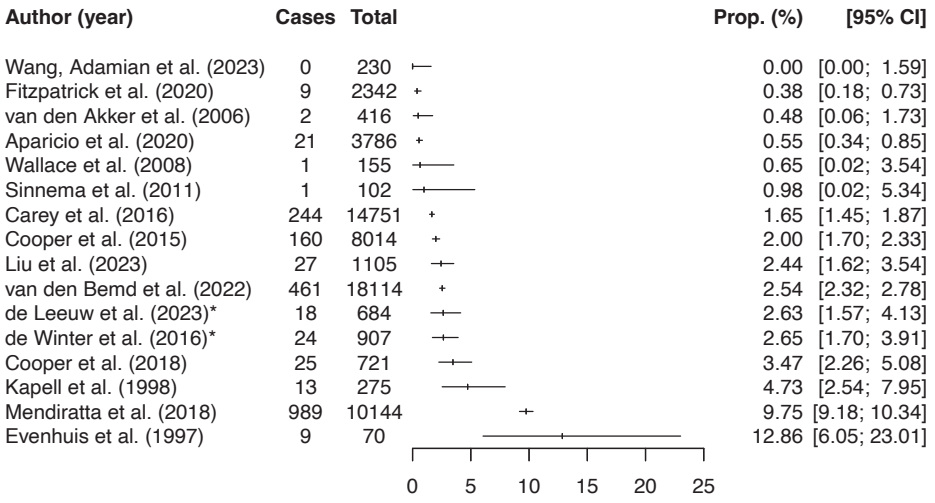

Figure 2 Prevalence coronary artery disease

Heterogeneity: I^2 = 99%

Pemmasani et al. (2020): <10 cases out of n=112 (26-39 year), <10 cases out of n=128 (40+ year)

*Articles from the Healthy Ageing and Intellectual Disability (HA-ID) study

Results were not pooled in a meta-analysis

Table 2 Prevalence subgroups coronary artery disease

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Age	<40 year	Sinnema et al. (2011)	0/50	0.0%	0.00-7.11
		van den Bemd et al. (2022)	14/13960	0.1%	0.05-0.17
		Pemmasani et al. (2021)	< 10/112	0-8.0%	-
	40+ year	Pemmasani et al. (2021)	< 10/128	0-7.0%	-
		Wallace et al. (2008)	1/155	0.6%	0.02-3.54
		Liu et al. (2023)	27/1105	2.4%	1.62-3.54
		de Winter et al. (2016)[a]	24/907	2.6%	1.70-3.91
		de Leeuw et al. (2023)[a]	18/684	2.6%	1.57-4.13
		Sinnema et al. (2011)	1/26	3.8%	0.10-19.64
		Kapell et al. (1998)	13/275	4.7%	2.54-7.95
		Mendiratta et al. (2018)	989/10144	9.7%	9.18-10.34
		van den Bemd et al. (2022)	447/4154	10.8%	9.83-11.74
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
Aetiology	Down syndrome	Wang et al. (2023)	0/230	0.0%	0.00-1.59
		Fitzpatrick et al. (2020)	9/2342	0.4%	0.18-0.73
		Aparicio et al. (2020)	21/3786	0.6%	0.34-0.85
		Kapell et al. (1998)	5/128	3.9%	1.28-8.88
		Mendiratta et al. (2018)	989/10144	9.7%	9.18-10.34
	Prader-Willi syndrome	Pemmasani et al. (2021)	<20/240	0-8.3%	-
		Sinnema et al. (2011)	1/102	1.0%	0.02-5.34
CVD risk factors	BMI <25	Sinnema et al. (2011)	0/18	0.0%	0.00-18.53
	BMI 25-30	Sinnema et al. (2011)	0/27	0.0%	0.00-12.77
	BMI >30	Sinnema et al. (2011)	1/57	1.8%	0.04-9.39
Data collection method	Medical record data	Wang et al. (2023)	0/230	0.0%	0.00-1.59
		Pemmasani et al. (2021)	<20/240	0-8.3%	-
		Fitzpatrick et al. (2020)	9/2342	0.4%	0.18-0.73
		van den Akker et al. (2006)	2/416	0.5%	0.06-1.73
		Wallace et al. (2008)	1/155	0.6%	0.02-3.54
		Aparicio et al. (2020)	21/3786	0.6%	0.34-0.85
		Carey et al. (2016)	244/14751	1.7%	1.45-1.87
		Cooper et al. (2015)	160/8014	2.0%	1.70-2.33

Table 2 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
		Liu et al. (2023)	27/1105	2.4%	1.62-3.54
		van den Bemd et al. (2022)	461/18114	2.5%	2.32-2.78
		de Winter et al. (2016)[a]	24/907	2.6%	1.70-3.91
		de Leeuw et al. (2023)[a]	18/684	2.6%	1.57-4.13
		Cooper et al. (2018)	25/721	3.5%	2.26-5.08
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
	Interviews/ medical record data	Sinnema et al. (2011)	1/102	1.0%	0.02-5.34
		Kapell et al. (1998)	13/275	4.7%	2.54-7.95
	Surveys/medical record data	Mendiratta et al. (2018)	989/10144	9.7%	9.18-10.34
Source population	Specialist/ residential ID care	van den Akker et al. (2006)	2/416	0.5%	0.06-1.73
		Wallace et al. (2008)	1/155	0.6%	0.02-3.54
		de Winter et al. (2016)[a]	24/907	2.6%	1.70-3.91
		de Leeuw et al. (2023)[a]	18/684	2.6%	1.57-4.13
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
	Primary care	Carey et al. (2016)	244/14751	1.7%	1.45-1.87
		Cooper et al. (2015)	160/8014	2.0%	1.70-2.33
		van den Bemd et al. (2022)	461/18114	2.5%	2.32-2.78
		Cooper et al. (2018)	25/721	3.5%	2.26-5.08
	Hospital	Pemmasani et al. (2021)	<20/240	0-8.3%	-
		Fitzpatrick et al. (2020)	9/2,342	0.4%	0.18-0.73
		Aparicio et al. (2020)	21/3786	0.6%	0.34-0.85
		Mendiratta et al. (2018)	989/10144	9.7%	9.18-10.34
	Outpatient clinic	Wang et al. (2023)	0/230	0.0%	0.00-1.59
		Sinnema et al. (2011)	1/102	1.0%	0.02-5.34
	ID register	Kapell et al. (1998)	13/275	4.7%	2.54-7.95
	National register	Liu et al. (2023)	27/1105	2.4%	1.62-3.54

BMI = Body Mass Index; 95%CI = 95% confidence interval; CVD = cardiovascular disease; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

[a] Articles from the same study

*No subgroups to show for sex, level of ID, living circumstances

Table 3 Incidence of cardiovascular disease (subgroups)

		Author (year)	IR (per 1000py)	95%CI
Coronary artery disease	Total	Baksh et al. (2023)	1.97	1.81-2.14
		Alexander et al. (2015)	2.80	2.02-3.78
Age	<40 year	Baksh et al. (2023)	0.29	0.19-0.44
	40+ year	Baksh et al. (2023)	3.71	3.38-4.05
Aetiology	Down syndrome	Baksh et al. (2023)	1.06	0.80-1.37
		Alexander et al. (2015)	2.80	2.02-3.78
Myocardial infarction	Total	Huang et al. (2015)	0.30	0.23-0.39
		Hedgeman et al. (2017)	1.36-1.92*	0.19-13.66
		Cho et al. (2024)	1.43	1.07-1.87
		de Winter et al. (2016)	2.82	1.13-5.81
Age	<40 year	Hedgeman et al. (2017)	1.36-1.92*	0.19-13.66
	40+ year	de Winter et al. (2016)	2.82	1.13-5.81
Aetiology	Prader-Willi syndrome	Hedgeman et al. (2017)	1.36-1.92*	0.19-13.66
Data collection method	Medical record data	Hedgeman et al. (2017)	1.36-1.92*	0.19-13.66
		de Winter et al. (2016)	2.82	1.13-5.81
	Health insurance data	Cho et al. (2024)	1.43	1.07-1.87
	Health insurance data/ medical record data	Huang et al. (2015)	0.30	0.23-0.39
Source population	Specialist/residential ID care	de Winter et al. (2016)	2.82	1.13-5.81
	Hospital	Hedgeman et al. (2017)	1.36-1.92*	0.19-13.66
	Insurance register	Cho et al. (2024)	1.43	1.07-1.87
	Insurance register/ national register	Huang et al. (2015)	0.30	0.23-0.39
Heart failure	Age 40+ year	de Winter et al. (2016)	12.50	8.49-17.74
Cerebrovascular disease	Total	Baksh et al. (2023)	2.55	2.37-2.75
Age	<40 year	Baksh et al. (2023)	0.46	0.32-0.64
	40+ year	Baksh et al. (2023)	4.74	4.37-5.13
Aetiology	Down syndrome	Baksh et al. (2023)	2.01	1.68-2.38

Table 3 Continued

		Author (year)	IR (per 1000py)	95%CI
Stroke	Total	Cho et al. (2024)	2.68	2.17-3.26
		de Winter et al. (2016)	3.23	1.39-6.35
Age	Age 40+ year	de Winter et al. (2016)	3.23	1.39-6.35
Data collection method	Health insurance data	Cho et al. (2024)	2.68	2.17-3.26
	Medical record data	de Winter et al. (2016)	3.23	1.39-6.35
Source population	Insurance register	Cho et al. (2024)	2.68	2.17-3.26
	Specialist/residential ID care	de Winter et al. (2016)	3.23	1.39-6.35
Peripheral arterial disease	Total	Baksh et al. (2023)	1.08	0.97-1.21
Age	<40 year	Baksh et al. (2023)	0.59	0.43-0.79
	40+ year	Baksh et al. (2023)	1.60	1.39-1.83
Aetiology	Down syndrome	Baksh et al. (2023)	1.67	1.35-2.06
Venous thrombosis	Total	Baksh et al. (2023)	0.82	0.71-0.93
		Hedgeman et al. (2017)	4.04-4.12**	1.01-16.17
Age	<40 year	Baksh et al. (2023)	0.41	0.28-0.58
	40+ year	Baksh et al. (2023)	1.17	0.99-1.37
Aetiology	Down syndrome	Baksh et al. (2023)	1.05	0.80-1.37
	Prader-Willi syndrome	Hedgeman et al. (2017)	4.04-4.12**	1.01-16.17
Source population	Primary care	Baksh et al. (2023)	0.82	0.71-0.93
	Hospital	Hedgeman et al. (2017)	4.04-4.12**	1.01-16.17

95%CI = 95% confidence interval; ID = intellectual disability; IR = incidence rate; py = person-years

*Age 20-29 year: IR 1.36 (95%CI 0.19-9.67); Age 30-39 year: IR 1.92 (95%CI 0.27-13.66)

** Age 20-29 year: IR 4.12 (95%CI 1.33-12.76); Age 30-39 year: IR 4.04 (95%CI 1.01-16.17)

Coronary artery disease: no subgroups to show for sex, level of ID, living circumstances, CVD risk factors, data collection method (all medical record data), and source population (all primary care).

Myocardial infarction: no subgroups to show for sex, level of ID, living circumstances, and CVD risk factors.

Heart failure: no subgroups to show for sex, level of ID, aetiology, living circumstances, CVD risk factors, data collection method (medical record data), and source population (specialist/residential ID care).

Table 3 Continued

Cerebrovascular disease: no subgroups to show for sex, level of ID, living circumstances, CVD risk factors, data collection method (medical record data), and source population (primary care).
Stroke: no subgroups to show for sex, level of ID, aetiology, living circumstances, and CVD risk factors.
Peripheral arterial disease: no subgroups to show for sex, level of ID, living circumstances, CVD risk factors, data collection method (all medical record data), and source population (all primary care).
Venous thrombosis: no subgroups to show for sex, level of ID, living circumstances, CVD risk factors, and data collection method (all medical record data).

Myocardial infarction

Twelve articles reported specific prevalence rates of myocardial infarction in adults with ID ranging from 0% to 7.9% (Figure 3) and between 0% to 6.7% in studies within the highest methodological quality tertile (n=5). Prevalence rates of subgroups are presented in Table 4. One study reported a twofold higher prevalence rate of myocardial infarction in adults aged 40 or older compared to those under 40 (3.0% versus 1.4%) [102].

Six articles reported specific incidence rates of myocardial infarction in adults with ID. Two of them did not use person-years to describe the incidence [119, 126]. The remaining four articles reported an incidence rate ranging from 0.3 to 2.8 per 1000py. The same range was observed in the studies within the highest methodological quality tertile (n=3). Incidence rates and subgroup data are presented in Table 3.

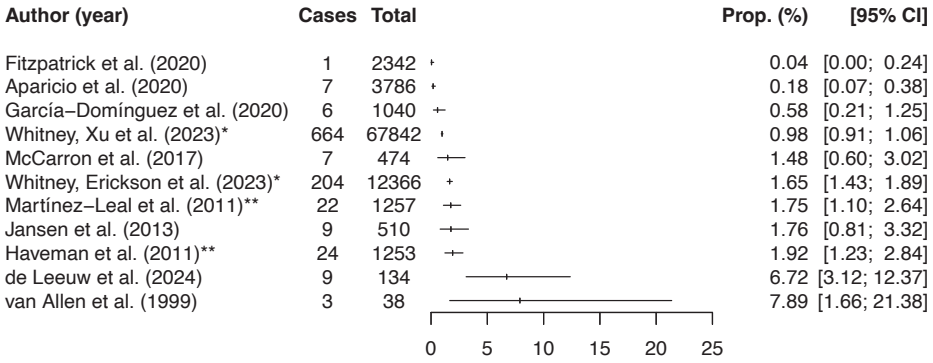

Figure 3 Prevalence myocardial infarction

Heterogeneity: I^2 = 93%
Hedgeman et al. (2017): 1-5 events out of n=66 (0.6-3.2%)
*Articles on the same study population described by Whitney et al. (2023)
**Articles from the POMONA-II project
Results were not pooled in a meta-analysis

Table 4 Prevalence subgroups myocardial infarction

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Age	<40 year	Haveman et al. (2011)[a]	6/436	1.4%	0.51-2.97
	40+ year	García-Domínguez et al. (2020)	6/1040	0.6%	0.21-1.25
		McCarron et al. (2017)	7/474	1.5%	0.60-3.02
		Jansen et al. (2013)	9/510	1.8%	0.81-3.32
		Haveman et al. (2011)[a]	9/301	3.0%	1.38-5.60
		de Leeuw et al. (2024)	9/134	6.7%	3.12-12.37
Sex	Females	Jansen et al. (2013)	3/226	1.3%	0.27-3.83
	Males	Jansen et al. (2013)	6/284	2.1%	0.78-4.54
Level of ID	Severe/ profound	van Allen et al. (1999)	3/38	7.9%	1.66-21.38
Aetiology	Down syndrome	Fitzpatrick et al. (2020)	1/2342	0.04%	0.00-0.24
		Aparicio et al. (2020)	7/3786	0.2%	0.07-0.38
		van Allen et al. (1999)	3/38	7.9%	1.66-21.38
	Prader-Willi syndrome	Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-

Table 4 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Data collection method	Medical record data	Fitzpatrick et al. (2020)	1/2342	0.04%	0.00-0.24
		Aparicio et al. (2020)	7/3786	0.2%	0.07-0.38
		Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-
		Jansen et al. (2013)	9/510	1.8%	0.81-3.32
		van Allen et al. (1999)	3/38	7.9%	1.66-21.38
	Health insurance data	Whitney et al. (2023)[126]b	664/67842	1.0%	0.91-1.06
		Whitney et al. (2023)[127]b	204/12366	1.7%	1.43-1.89
	Interviews	Martínez-Leal et al. (2011)a	22/1257	1.8%	1.10-2.64
	Surveys	García-Domínguez et al. (2020)	6/1040	0.6%	0.21-1.25
	Interviews/ surveys	McCarron et al. (2017)	7/474	1.5%	0.60-3.02
		Haveman et al. (2011)a	24/1253	1.9%	1.23-2.84
	Physical measurements	de Leeuw et al. (2024)	9/134	6.7%	3.12-12.37
Source population	Specialist/ residential ID care	García-Domínguez et al. (2020)	6/1040	0.6%	0.21-1.25
		Jansen et al. (2013)	9/510	1.8%	0.81-3.32
		de Leeuw et al. (2024)	9/134	6.7%	3.12-12.37
		van Allen et al. (1999)	3/38	7.9%	1.66-21.38
	Hospital	Fitzpatrick et al. (2020)	1/2342	0.04%	0.00-0.24
		Aparicio et al. (2020)	7/3786	0.2%	0.07-0.38
		Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-
	Insurance register	Whitney et al. (2023)[126]b	664/67842	1.0%	0.91-1.06
		Whitney et al. (2023)[127]b	204/12366	1.7%	1.43-1.89
	ID register	McCarron et al. (2017)	7/474	1.5%	0.60-3.02
	Other	Martínez-Leal et al. (2011)a	22/1257	1.8%	1.10-2.64
		Haveman et al. (2011)a	24/1253	1.9%	1.23-2.84

95%CI = 95% confidence interval; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

[a] Articles from the same study

[b] Articles from the same study

*No subgroups to show for living circumstances and CVD risk factors

Heart failure

Twenty articles reported prevalence rates of heart failure in adults with ID ranging from 0.8% to 18.6% (Figure 4) and between 1.4% to 14.0% in studies within the highest methodological quality tertile (n=10). Prevalence rates of subgroups are presented in Table 5. One article reported a higher prevalence rate of heart failure in adults aged 40 or older compared to those under 40 (10.7% versus 16.4%) [116]. One article only reported the prevalence of congestive heart failure exacerbation (6 out of 297 hospitalisations (2.0%) [120]).

Three articles reported the incidence of heart failure in adults with ID. Two of them did not use person-years to describe the incidence [110, 126]. The remaining article reported an incidence rate of 12.5 per 1000py (Table 3) and fell within the highest methodological quality tertile.

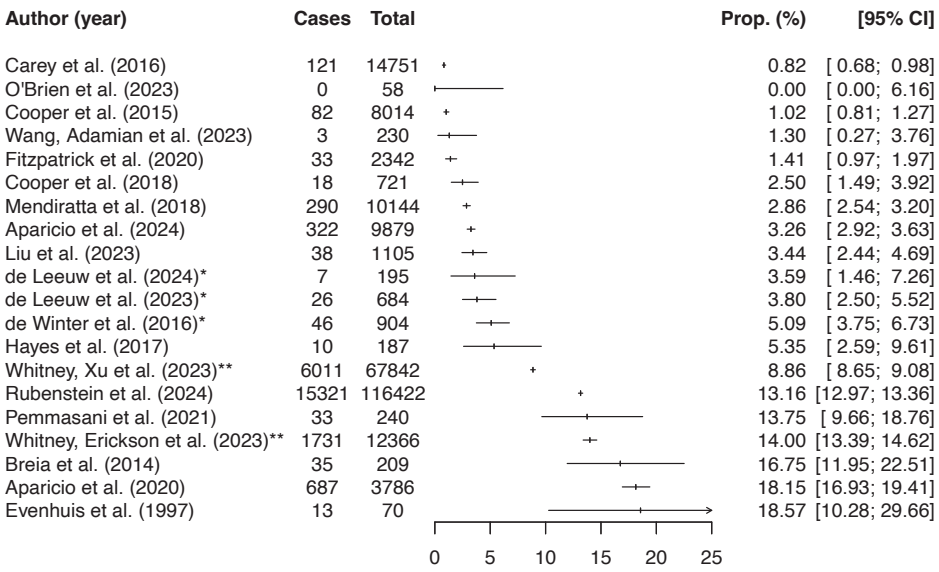

Figure 4 Prevalence heart failure

Heterogeneity: $I^2 = 100\%$

*Articles from the Healthy Ageing and Intellectual Disability (HA-ID) study

**Articles on the same study population described by Whitney et al. (2023)

Results were not pooled in a meta-analysis

Table 5 Prevalence subgroups heart failure

Subgroups		Author (year)	Cases/total	Prop. (%)	95%CI
Age	<40 year	Pemmasani et al. (2021)	12/112	10.7%	5.66-17.97
	40+ year	O'Brien et al. (2023)	0/58	0.0%	0.00-36.94
		Mendiratta et al. (2018)	290/10144	2.9%	2.54-3.20
		Liu et al. (2023)	38/1105	3.4%	2.44-4.69
		de Leeuw et al. (2024)[a]	7/195	3.6%	1.46-7.26
		de Leeuw et al. (2023)[a]	26/684	3.8%	2.50-5.52
		de Winter et al. (2016)[a]	46/904	5.1%	3.75-6.73
		Pemmasani et al. (2021)	21/128	16.4%	10.45-23.98
		Evenhuis et al. (1997)	13/70	18.6%	10.28-29.66
Aetiology	Down syndrome	Wang et al. (2023)	3/230	1.3%	0.27-3.76
		Fitzpatrick et al. (2020)	33/2342	1.4%	0.97-1.97
		Mendiratta et al. (2018)	290/10144	2.9%	2.54-3.20
		Aparicio et al. (2024)	322/9879	3.3%	2.92-3.63
		Hayes et al. (2017)	10/187	5.3%	2.59-9.61
		Rubenstein et al. (2024)	15321/116422	13.2%	12.97-13.36
		Breia et al. (2014)	35/209	16.7%	11.95-22.51
		Aparicio et al. (2020)	687/3786	18.1%	16.93-19.41
	Prader-Willi syndrome	Pemmasani et al. (2021)	33/240	13.8%	9.66-18.76
Data collection method	Medical record data	Carey et al. (2016)	121/14751	0.8%	0.68-0.98
		Cooper et al. (2015)	82/8014	1.0%	0.81-1.27
		Wang et al. (2023)	3/230	1.3%	0.27-3.76
		Fitzpatrick et al. (2020)	33/2342	1.4%	0.97-1.97
		Cooper et al. (2018)	18/721	2.5%	1.49-3.92
		Aparicio et al. (2024)	322/9879	3.3%	2.92-3.63
		Liu et al. (2023)	38/1105	3.4%	2.44-4.69
		de Leeuw et al. (2024)[a]	7/195	3.6%	1.46-7.26
		de Leeuw et al. (2023)[a]	26/684	3.8%	2.50-5.52
		de Winter et al. (2016)[a]	46/904	5.1%	3.75-6.73
		Hayes et al. (2017)	10/187	5.3%	2.59-9.61
		Pemmasani et al. (2021)	33/240	13.8%	9.66-18.76

Table 5 Continued

Subgroups		Author (year)	Cases/total	Prop. (%)	95%CI
		Breia et al. (2014)	35/209	16.7%	11.95-22.51
		Aparicio et al. (2020)	687/3786	18.1%	16.93-19.41
		Evenhuis et al. (1997)	13/70	18.6%	10.28-29.66
	Health insurance data	Whitney et al. (2023)[126]b	6011/67842	8.9%	8.65-9.08
		Rubenstein et al. (2024)	15321/116422	13.2%	12.97-13.36
		Whitney et al. (2023)[127]b	1731/12366	14.0%	13.39-14.62
	Interviews	O'Brien et al. (2023)	0/58	0.0%	0.00-36.94
	Surveys/ medical record data	Mendiratta et al. (2018)	290/10144	2.9%	2.54-3.20
Source population	Specialist/ residential ID care	de Leeuw et al. (2024)[a]	7/195	3.6%	1.46-7.26
		de Leeuw et al. (2023)[a]	26/684	3.8%	2.50-5.52
		de Winter et al. (2016)[a]	46/904	5.1%	3.75-6.73
		Breia et al. (2014)	35/209	16.7%	11.95-22.51
		Evenhuis et al. (1997)	13/70	18.6%	10.28-29.66
	Primary care	Carey et al. (2016)	121/14751	0.8%	0.68-0.98
		Cooper et al. (2015)	82/8014	1.0%	0.81-1.27
		Cooper et al. (2018)	18/721	2.5%	1.49-3.92
	Hospital	Fitzpatrick et al. (2020)	33/2342	1.4%	0.97-1.97
		Mendiratta et al. (2018)	290/10144	2.9%	2.54-3.20
		Aparicio et al. (2024)	322/9879	3.3%	2.92-3.63
		Hayes et al. (2017)	10/187	5.3%	2.59-9.61
		Pemmasani et al. (2021)	33/240	13.8%	9.66-18.76
		Aparicio et al. (2020)	687/3786	18.1%	16.93-19.41
	Outpatient clinic	Wang et al. (2023)	3/230	1.3%	0.27-3.76
	Insurance register	Whitney et al. (2023)[126]b	6011/67842	8.9%	8.65-9.08
		Rubenstein et al. (2024)	15321/116422	13.2%	12.97-13.36
		Whitney et al. (2023)[127]b	1731/12366	14.0%	13.39-14.62
	ID register	O'Brien et al. (2023)	0/58	0.0%	0.00-36.94
	National register	Liu et al. (2023)	38/1105	3.4%	2.44-4.69

Table 5 Continued

95%CI = 95% confidence interval; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

[a] Articles from the same study

[b] Articles from the same study

*No subgroups to show for sex, level of ID, living circumstances, and CVD risk factors

Cerebrovascular disease

Sixteen articles reported overall prevalence rates of cerebrovascular disease in adults with ID ranging from 0.7% to 15.0% (Figure 5). The same range was observed in the studies within the highest methodological quality tertile (n=8). Articles exclusively focusing on the prevalence and incidence of stroke are summarised in the 'Stroke' section below. Prevalence rates of subgroups are presented in Table 6. Higher prevalence rates were reported in adults aged 40 or older compared to those under 40 [123, 128]. Except for one study [96], higher prevalence rates were reported in studies using health insurance data/insurance registers [100, 126, 127] compared to those in studies employing other data collection methods/source populations.

Four articles reported overall incidence rates of cerebrovascular disease in adults with ID. Three of them did not use person-years to describe the incidence [110, 119, 126]. The remaining article reported an incidence rate of 2.55 per 1000py and fell within the highest methodological quality tertile. The incidence rate and subgroup data are presented in Table 3.

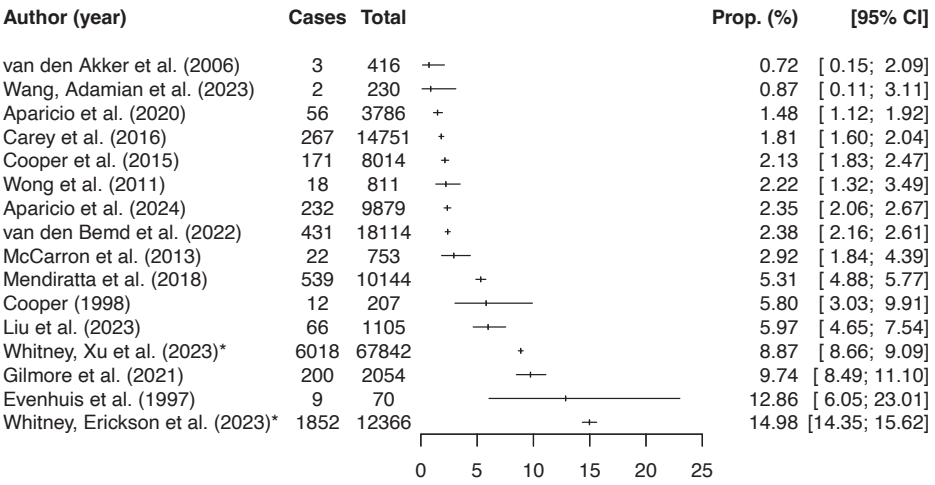

Figure 5 Prevalence cerebrovascular disease

Heterogeneity: $I^2 = 100\%$
*Articles on the same study population described by Whitney et al. (2023)
Results were not pooled in a meta-analysis

Table 6 Prevalence subgroups cerebrovascular disease

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Age	<40 year	Wong et al. (2011)	1/324	0.3%	0.01-1.71
		van den Bemd et al. (2022)	53/1737	3.1%	2.29-3.97
	40+ year	Wong et al. (2011)	13/486	2.7%	1.43-4.53
		McCarron et al. (2013)	22/753	2.9%	1.84-4.39
		Mendiratta et al. (2018)	539/10144	5.3%	4.88-5.77
		Liu et al. (2023)	66/1105	6.0%	4.65-7.54
		Cooper et al. (1998)	12/134	9.0%	4.71-15.12
		Gilmore et al. (2021)	200/2054	9.7%	8.49-11.10
		van den Bemd et al. (2022)	378/3878	9.7%	8.83-10.72
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
Sex	Females	Wong et al. (2011)	10/379	2.6%	1.27-4.80
	Males	Wong et al. (2011)	8/432	1.9%	0.80-3.62

Table 6 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Aetiology	Down syndrome	Wong et al. (2011)	0/107	0.0%	0.00-3.39
		Wang et al. (2023)	2/230	0.9%	0.11-3.11
		Aparicio et al. (2020)	56/3786	1.5%	1.12-1.92
		Aparicio et al. (2024)	232/9879	2.4%	2.06-2.67
		Mendiratta et al. (2018)	539/10144	5.3%	4.88-5.77
Data collection method	Medical record data	van den Akker et al. (2006)	3/416	0.7%	0.15-2.09
		Wang et al. (2023)	2/230	0.9%	0.11-3.11
		Aparicio et al. (2020)	56/3786	1.5%	1.12-1.92
		Carey et al. (2016)	267/14751	1.8%	1.60-2.04
		Cooper et al. (2015)	171/8014	2.1%	1.83-2.47
		van den Bemd et al. (2022)	431/18114	2.4%	2.16-2.61
		Aparicio et al. (2024)	232/9879	2.4%	2.06-2.67
		Liu et al. (2023)	66/1105	6.0%	4.65-7.54
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
	Health insurance data	Whitney et al. (2023)[126]a	6018/67842	8.9%	8.66-9.09
		Gilmore et al. (2021)	200/2054	9.7%	8.49-11.10
		Whitney et al. (2023)[127]a	1852/12366	15.0%	14.35-15.62
	Interviews	McCarron et al. (2013)	22/753	2.9%	1.84-4.39
	Surveys	Wong et al. (2011)	18/811	2.2%	1.32-3.49
	Interviews/ medical record data	Cooper et al. (1998)	12/207	5.8%	3.03-9.91
	Surveys/medical record data	Mendiratta et al. (2018)	539/10144	5.3%	4.88-5.77
Source population	Specialist/ residential ID care	van den Akker et al. (2006)	3/416	0.7%	0.15-2.09
		Wong et al. (2011)	18/811	2.2%	1.32-3.49
		Evenhuis et al. (1997)	9/70	12.9%	6.05-23.01
	Primary care	Carey et al. (2016)	267/14751	1.8%	1.60-2.04
		Cooper et al. (2015)	171/8014	2.1%	1.83-2.47
		van den Bemd et al. (2022)	431/18114	2.4%	2.16-2.61

Table 6 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
	Hospital	Aparicio et al. (2020)	56/3786	1.5%	1.12-1.92
		Aparicio et al. (2024)	232/9879	2.4%	2.06-2.67
		Mendiratta et al. (2018)	539/10144	5.3%	4.88-5.77
	Outpatient clinic	Wang et al. (2023)	2/230	0.9%	0.11-3.11
	Insurance register	Whitney et al. (2023)[126]a	6018/67842	8.9%	8.66-9.09
		Gilmore et al. (2021)	200/2054	9.7%	8.49-11.10
		Whitney et al. (2023)[127]a	1852/12366	15.0%	14.35-15.62
	ID register	McCarron et al. (2013)	22/753	2.9%	1.84-4.39
		Cooper et al. (1998)	12/207	5.8%	3.03-9.91
	National register	Liu et al. (2023)	66/1105	6.0%	4.65-7.54

95%CI = 95% confidence interval; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

[a] Articles from the same study

*No subgroups to show for level of ID, living circumstances, and CVD risk factors

Stroke

Twenty-one articles reported specific prevalence rates of stroke between 1.3% and 17.2% in adults with ID (Figure 6) and between 1.8% to 7.8% in studies within the highest methodological quality tertile (n=6). Prevalence rates of subgroups are presented in Table 7. Generally, higher prevalence rates were reported in adults aged 40 or older compared to those under 40 [98, 102, 118]. One article reported only on the prevalence rate of fatal spontaneous haemorrhagic stroke (2 cases in 187 individuals (1.1%) [103]) and did not address the prevalence of non-fatal spontaneous haemorrhagic stroke.

Three articles reported specific incidence rates of stroke in adults with ID. One of them did not use person-years to describe the incidence [119]. The remaining two articles reported an incidence rate ranging from 2.7 to 3.2 per 1000py, both fell within the highest methodological quality tertile. Incidence rates and subgroup data are presented in Table 3.

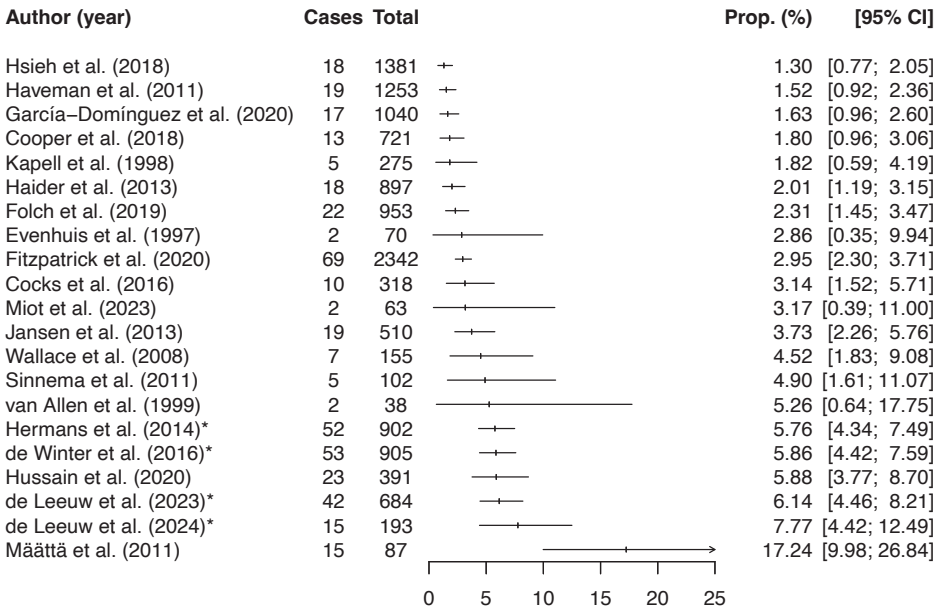

Figure 6 Prevalence stroke

Heterogeneity: I^2 = 87%
*Articles from the Healthy Ageing and Intellectual Disability (HA-ID) study
Results were not pooled in a meta-analysis

Table 7 Prevalence subgroups stroke

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Age	<40 year	Folch et al. (2019)	0/244	0.0%	0.00-1.50
		Haveman et al. (2011)	5/436	1.2%	0.37-2.66
		Sinnema et al. (2011)	1/50	2.0%	0.05-10.65
	40+ year	García-Domínguez et al. (2020)	17/1040	1.6%	0.96-2.60
		Kapell et al. (1998)	5/275	1.8%	0.59-4.19
		Haveman et al. (2011)	6/301	2.0%	0.74-4.29
		Evenhuis et al. (1997)	2/70	2.9%	0.35-9.94
		Jansen et al. (2013)	19/510	3.7%	2.26-5.76
		Wallace et al. (2008)	7/155	4.5%	1.83-9.08
		Cocks et al. (2016)	5/98	5.1%	1.68-11.51
		Hermans et al. (2014)[a]	52/902	5.8%	4.34-7.49

Table 7 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
		de Winter et al. (2016)[a]	53/905	5.9%	4.42-7.59
		Hussain et al. (2020)	23/391	5.9%	3.77-8.70
		de Leeuw et al. (2023)[a]	42/684	6.1%	4.46-8.21
		Miot et al. (2023)	2/30	6.7%	0.82-22.07
		de Leeuw et al. (2024)[a]	15/193	7.8%	4.42-12.49
		Folch et al. (2019)	17/406	4.2%	2.45-6.60
		van Allen et al. (1999)	2/20	10.0%	1.24-31.70
		Sinnema et al. (2011)	3/26	11.5%	2.45-30.15
Sex	Females	Jansen et al. (2013)	9/226	4.0%	1.84-7.42
		Hussain et al. (2020)	7/146	4.8%	1.95-9.63
	Males	Jansen et al. (2013)	10/284	3.5%	1.70-6.38
		Hussain et al. (2020)	16/245	6.5%	3.78-10.39
Level of ID	Mild/moderate	Folch et al. (2019)	11/553	2.0%	1.00-3.53
		Hussain et al. (2020)	23/391	5.9%	3.77-8.70
	Severe/profound	Folch et al. (2019)	11/400	2.8%	1.38-4.87
		van Allen et al. (1999)	2/38	5.3%	0.64-17.75
Aetiology	Down syndrome	Kapell et al. (1998)	3/128	2.3%	0.49-6.70
		Fitzpatrick et al. (2020)	69/2342	2.9%	2.30-3.71
		van Allen et al. (1999)	2/38	5.3%	0.64-17.75
		Määttä et al. (2011)	15/87	17.2%	9.98-26.84
	Prader-Willi syndrome	Sinnema et al. (2011)	5/102	4.9%	1.61-11.07
CVD risk factors	BMI <25	Sinnema et al. (2011)	3/18	16.7%	3.58-41.42
	BMI 25-30	Sinnema et al. (2011)	1/27	3.7%	0.09-18.97
	BMI >30	Sinnema et al. (2011)	1/57	1.8%	0.04-9.39
Data collection method	Medical record data	Cooper et al. (2018)	13/721	1.8%	0.96-3.06
		Evenhuis et al. (1997)	2/70	2.9%	0.35-9.94
		Fitzpatrick et al. (2020)	69/2342	2.9%	2.30-3.71
		Jansen et al. (2013)	19/510	3.7%	2.26-5.76
		Wallace et al. (2008)	7/155	4.5%	1.83-9.08
		van Allen et al. (1999)	2/38	5.3%	0.64-17.75

Table 7 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
		Hermans et al. (2014)[a]	52/902	5.8%	4.34-7.49
		de Winter et al. (2016)[a]	53/905	5.9%	4.42-7.59
		de Leeuw et al. (2023)[a]	42/684	6.1%	4.46-8.21
		de Leeuw et al. (2024)[a]	15/193	7.8%	4.42-12.49
		Määttä et al. (2011)	15/87	17.2%	9.98-26.84
	Interviews	Haider et al. (2013)	18/897	2.0%	1.19-3.15
		Hussain et al. (2020)	23/391	5.9%	3.77-8.70
	Surveys	Hsieh et al. (2018)	18/1381	1.3%	0.77-2.05
		García-Domínguez et al. (2020)	17/1040	1.6%	0.96-2.60
	Interviews/surveys	Haveman et al. (2011)	19/1253	1.5%	0.92-2.36
		Cocks et al. (2016)	10/318	3.1%	1.52-5.71
	Interviews/medical record data	Kapell et al. (1998)	5/275	1.8%	0.59-4.19
		Folch et al. (2019)	22/953	2.3%	1.45-3.47
		Sinnema et al. (2011)	5/102	4.9%	1.61-11.07
	Surveys/medical record data	Miot et al. (2023)	2/63	3.2%	0.39-11.00
Source population	Specialist/residential ID care	García-Domínguez et al. (2020)	17/1040	1.6%	0.96-2.60
		Folch et al. (2019)	22/953	2.3%	1.45-3.47
		Evenhuis et al. (1997)	2/70	2.9%	0.35-9.94
		Miot et al. (2023)	2/63	3.2%	0.39-11.00
		Jansen et al. (2013)	19/510	3.7%	2.26-5.76
		Wallace et al. (2008)	7/155	4.5%	1.83-9.08
		van Allen et al. (1999)	2/38	5.3%	0.64-17.75
		Hermans et al. (2014)[a]	52/902	5.8%	4.34-7.49
		de Winter et al. (2016)[a]	53/905	5.9%	4.42-7.59
		Hussain et al. (2020)	23/391	5.9%	3.77-8.70
		de Leeuw et al. (2023)[a]	42/684	6.1%	4.46-8.21
		de Leeuw et al. (2024)[a]	15/193	7.8%	4.42-12.49
	Primary care	Cooper et al. (2018)	13/721	1.8%	0.96-3.06
	Hospital	Fitzpatrick et al. (2020)	69/2342	2.9%	2.30-3.71

Table 7 Continued

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
	Outpatient clinic	Haider et al. (2013)	18/897	2.0%	1.19-3.15
		Sinnema et al. (2011)	5/102	4.9%	1.61-11.07
	ID register	Kapell et al. (1998)	5/275	1.8%	0.59-4.19
		Määttä et al. (2011)	15/87	17.2%	9.98-26.84
	Other	Hsieh et al. (2018)	18/1381	1.3%	0.77-2.05
		Haveman et al. (2011)	19/1253	1.5%	0.92-2.36
		Cocks et al. (2016)	10/318	3.1%	1.52-5.71

BMI = Body Mass Index; 95%CI = 95% confidence interval; CVD = cardiovascular disease; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

[a] Articles from the same study

*No subgroups to show for living circumstances

Peripheral arterial disease

Six articles reported prevalence rates of peripheral arterial disease between 0.4% and 20.7% in adults with ID (Figure 7). The only study within the highest methodological quality tertile reported a prevalence of 20.7%. Prevalence rates of subgroups are presented in Table 8. Two studies reported higher prevalence rates among participants residing in a central setting compared to those living independently or in community-based settings [70, 129]. Higher prevalence rates were reported for the following CVD risk factors: current smoking [70, 129], physical inactivity [70], and the use of atypical antipsychotics [70]. Additionally, higher prevalence rates were reported in studies using physical measurements in a specialist/residential ID care population [70, 129] compared to those in studies using medical record data from primary care [90, 93] or a national register [110]. One article only reported a prevalence rate of (intermittent) claudication (2 cases in 70 individuals (2.9%) [96]).

Two articles reported the incidence of peripheral arterial disease in adults with ID. One of them did not use person-years to describe the incidence [110]. The remaining article reported an incidence rate of 1.1 per 1000py and fell within the highest methodological quality tertile. The incidence rate and subgroup data are presented in Table 3.

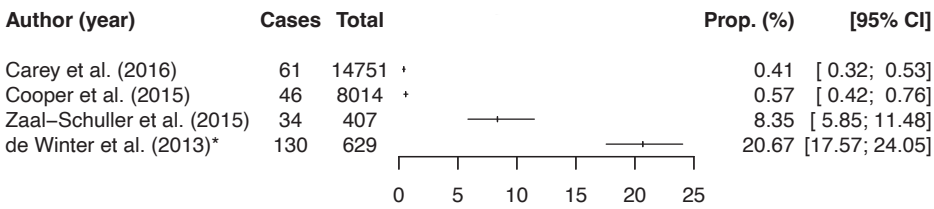

Figure 7 Prevalence peripheral arterial disease

Heterogeneity: I^2 = 100%
Liu et al. (2023): <5 events out of n=1105
*Hermans et al. (2014) report the exact same data from the same study population of the Healthy Ageing and Intellectual Disability (HA-ID) study
Results were not pooled in a meta-analysis

Table 8 Prevalence subgroups peripheral arterial disease

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Age	40+ year	Liu et al. (2023)	<5/1105	0.0-0.4%	-
		Zaal-Schuller et al. (2015)	34/407	8.4%	5.85-11.48
		de Winter et al. (2013)	130/629	20.7%	17.57-24.05
Sex	Females	Zaal-Schuller et al. (2015)	15/171	8.8%	4.99-14.06
		de Winter et al. (2013)	59/292	20.2%	15.75-25.28
	Males	Zaal-Schuller et al. (2015)	19/236	8.1%	4.92-12.29
		de Winter et al. (2013)	71/337	21.1%	16.84-25.82
Level of ID	Mild/moderate	Zaal-Schuller et al. (2015)	12/208	5.8%	3.02-9.86
		de Winter et al. (2013)	97/475	20.4%	16.88-24.33
	Severe/profound	Zaal-Schuller et al. (2015)	22/199	11.1%	7.06-16.26
		de Winter et al. (2013)	23/110	20.9%	13.74-29.70
Aetiology	Down syndrome	Zaal-Schuller et al. (2015)	7/68	10.3%	4.24-20.07
		de Winter et al. (2013)	13/69	18.8%	10.43-30.06
Living circum-stances	Central setting	Zaal-Schuller et al. (2015)	24/252	9.5%	6.20-13.84
		de Winter et al. (2013)	70/283	24.7%	19.82-30.19
	Community based	Zaal-Schuller et al. (2015)	10/136	7.4%	3.58-13.11
		de Winter et al. (2013)	53/305	17.4%	13.30-22.11
	Independent (with support or with relatives)	Zaal-Schuller et al. (2015)	0/19	0.0%	0.00-17.65
		de Winter et al. (2013)	7/41	17.1%	7.15-32.06

Table 8 Prevalence subgroups peripheral arterial disease

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
CVD risk factors	Smoking current	Zaal-Schuller et al. (2015)	4/15	26.7%	7.79-55.10
		de Winter et al. (2013)	43/151	28.5%	21.44-36.38
	Smoking previous	Zaal-Schuller et al. (2015)	1/28	3.6%	0.09-18.35
	Smoking never	Zaal-Schuller et al. (2015)	29/328	8.8%	6.00-12.45
	Physical inactivity	de Winter et al. (2013)	49/219	22.4%	17.04-28.48
	(Atypical) antipsychotics	Zaal-Schuller et al. (2015)	11/164	6.7%	3.40-11.68
		de Winter et al. (2013)	12/34	35.3%	19.75-53.51
Data collection method	Medical record data	Liu et al. (2023)	<5/1105	0.0-0.4%	-
		Carey et al. (2016)	61/14751	0.4%	0.32-0.53
		Cooper et al. (2015)	46/8014	0.6%	0.42-0.76
	Physical measurements	Zaal-Schuller et al. (2015)	34/407	8.4%	5.85-11.48
		de Winter et al. (2013)	130/629	20.7%	17.57-24.05
Source population	Specialist/ residential ID care	Zaal-Schuller et al. (2015)	34/407	8.4%	5.85-11.48
		de Winter et al. (2013)	130/629	20.7%	17.57-24.05
	Primary care	Carey et al. (2016)	61/14751	0.4%	0.32-0.53
		Cooper et al. (2015)	46/8014	0.6%	0.42-0.76
	National register	Liu et al. (2023)	<5/1105	0.0-0.4%	-

95%CI = 95% confidence interval; CVD = cardiovascular disease; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

Venous thrombosis

Three articles reported prevalence rates of venous thrombosis (deep venous thrombosis + pulmonary embolism) in adults with ID ranging from 7.2% to 12.4% (Figure 8). All three included articles fell within the highest methodological quality tertile. Prevalence rates of subgroups are presented in Table 9. One article also reported a prevalence of arterial thrombosis (65 cases in 1093 individuals (5.9%) [89]).

Two articles reported the incidence of venous thrombosis in adults with ID. Both articles reported incidence rates ranging from 0.8 to 4.1 per 1000py. One of them fell within the highest methodological quality tertile and reported an incidence of 0.8 per 1000py. Incidence rates and subgroup data are presented in Table 3.

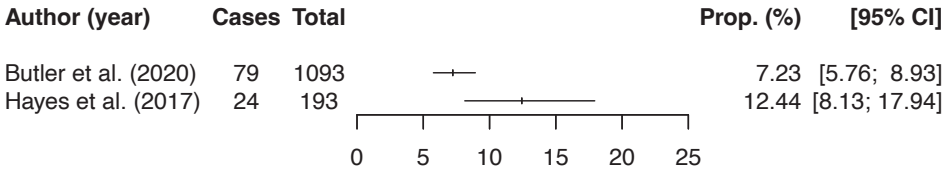

Figure 8 Prevalence venous thrombosis

Heterogeneity: I^2 = 83%
Hedgeman et al. (2017): 1-5 events out of n=66 (0.6-3.2%)
Results were not pooled in a meta-analysis

Table 9 Prevalence subgroups venous thrombosis

Subgroups		Author (year)	Cases/ total	Prop. (%)	95%CI
Aetiology	Down syndrome	Hayes et al. (2017)	24/193	12.4%	8.13-17.94
	Prader-Willi syndrome	Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-
		Butler et al. (2020)	79/1093	7.2%	5.76-8.93
Data collection method	Medical record data	Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-
		Hayes et al. (2017)	24/193	12.4%	8.13-17.94
	Health insurance data	Butler et al. (2020)	79/1093	7.2%	5.76-8.93
Source population	Hospital	Hedgeman et al. (2017)	1-5/66	0.6-3.2%	-
		Hayes et al. (2017)	24/193	12.4%	8.13-17.94
	Insurance register	Butler et al. (2020)	79/1093	7.2%	5.76-8.93

95%CI = 95% confidence interval; Prop. (%) = proportion expressed as a percentage
*No subgroups to show for age, sex, level of ID, living circumstances, and CVD risk factors

Atrial fibrillation

Six articles reported prevalence rates of atrial fibrillation between 0.8% and 6.3% in adults with ID (Figure 9) and between 1.0% to 6.3% in studies within the highest methodological quality tertile (n=3). Prevalence rates of subgroups are presented in Table 10. A higher prevalence rate was reported in a study using health insurance data/insurance registers [117] compared to studies employing other data collection

methods/source populations. Four articles only reported prevalence rates of cardiac arrhythmias (13313 cases in 74025 individuals (18.0%) [126], 4662 cases in 18549 individuals (25.1%) [127], 488 cases in 9879 individuals (4.9%) [18], and 60 cases in 1706 individuals (3.5%) [119]), one article only reported a prevalence rate of atrial fibrillation/other cardiac arrhythmias (31 cases in 1105 individuals (2.8%) [110]), one article only reported a prevalence rate of atrial fibrillation/flutter (17 cases in 122 individuals (13.9%) [103]), and one article only reported a prevalence of abnormal heart rhythm (0 cases in 58 individuals (0%) [115]).

One article reported the incidence of atrial fibrillation and other cardiac arrhythmias in adults with ID [110], but did not use person-years to describe the incidence.

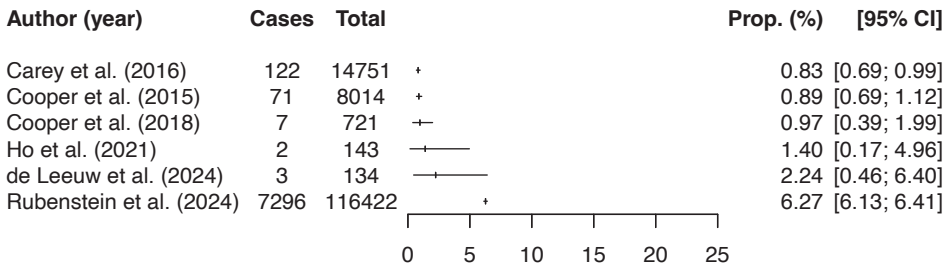

Figure 9 Prevalence atrial fibrillation

Heterogeneity: $I^2 = 99\%$

Results were not pooled in a meta-analysis

Table 10 Prevalence subgroups atrial fibrillation

Subgroups		Author (year)	Cases/total	Prop. (%)	95%CI
Age	40+ year	de Leeuw et al. (2024)	3/134	2.2%	0.46-6.40
Aetiology	Down syndrome	Rubenstein et al. (2024)	7296/116422	6.3%	6.13-6.41
Data collection method	Medical record data	Carey et al. (2016)	122/14751	0.8%	0.69-0.99
		Cooper et al. (2015)	71/8014	0.9%	0.69-1.12
		Cooper et al. (2018)	7/721	1.0%	0.39-1.99
		Ho et al. (2021)	2/143	1.4%	0.17-4.96
	Health insurance data	Rubenstein et al. (2024)	7296/116422	6.3%	6.13-6.41
	Physical measurements	de Leeuw et al. (2024)	3/134	2.2%	0.46-6.40
Source population	Specialist/ residential ID care	Ho et al. (2021)	2/143	1.4%	0.17-4.96
		de Leeuw et al. (2024)	3/134	2.2%	0.46-6.40
	Primary care	Carey et al. (2016)	122/14751	0.8%	0.69-0.99
		Cooper et al. (2015)	71/8014	0.9%	0.69-1.12
		Cooper et al. (2018)	7/721	1.0%	0.39-1.99
	Insurance register	Rubenstein et al. (2024)	7296/116422	6.3%	6.13-6.41

95%CI = 95% confidence interval; ID = intellectual disability; Prop. (%) = proportion expressed as a percentage

*No subgroups to show for sex, level of ID, living circumstances, and CVD risk factors

Other

Additionally, the literature search identified prevalence rates for some other CVD diagnoses: atherosclerosis (24 cases in 70 individuals (34.3%) [96]), venous insufficiency (11 cases in 209 individuals (5.3%) [88]; 12 cases in 28 individuals (42.9%) [109]), varicose veins (7 cases in 811 individuals (0.9%) [128]), syncope (myocardial infarction and arrhythmia) hospitalisations (10 cases in 297 hospitalisations (3.4%) [120]), rheumatic heart disease (1 case in 38 individuals (2.6%) [121]), and acute rheumatic fever and chronic rheumatic heart diseases (1 case in 416 individuals (0.2%) [122]).

DISCUSSION

The aim of this systematic review was to provide a comprehensive synthesis of literature focusing on the prevalence and incidence of CVD in adults with ID. This systematic review, including 55 articles, reported a broad range of prevalence and incidence rates for various CVD diagnoses, such as for heart failure, a prevalence rate ranging from 0.8% to 18.6% was found. Only a limited number of longitudinal studies (n=6) were identified that reported or allowed the calculation of CVD incidence rates per 1000py, including stroke incidence rates ranging from 2.7 to 3.2 per 1000py. Due to variability in methodological quality, clinical characteristics and high statistical heterogeneity, it is challenging to draw conclusions about the overall population of adults with ID, highlighting the importance of the presented subgroup data, allowing for the identification of prevalence and incidence rates within specific subgroups. Overall, higher prevalence and incidence rates were reported in older adults compared to younger adults, and in studies that used physical measurements rather than medical record data for diagnosis.

We observed a broad range in methodological quality across the included articles (quality score 1 to 8). About half of the articles scored zero points on criterion 4; the same applied to criterion 6 and 7, which pertain to the description of the study subjects and the validity and reliability of the data collection methods for identifying the CVD diagnoses. It is important to take this into account when interpreting the results, given the impact on the generalisability, validity, and reliability of the findings in these articles. The methodological quality checklist we used does not provide a clear cutoff, making it difficult to reliably distinguish between high and low methodological quality. In this paper, we categorised methodological quality scores into tertiles solely to illustrate relative differences. While these categories are not validated cutoffs, nor do we intend to suggest otherwise, they provided a practical means of differentiation. Most of the 22 studies with the highest methodological quality (score: 7-9) utilised medical record data or health insurance data but showed diversity in terms of source population and sample size. These studies focused on specific source populations, including those from specialists/residential ID care [51, 69, 95, 122, 128], primary care [43, 87, 123], health insurance registers [19, 89, 100, 106, 117, 126, 127], hospitals [18, 25, 97, 103, 119], and ID/national registers [108, 110], as well as specific groups such as individuals with Down syndrome [18, 97, 103, 117, 119] and Prader-Willi syndrome [25, 89]. In addition, the sample sizes of these studies varied widely, ranging from 66 to 116422 participants. This diversity is also evident in the other included articles and, along with the variation in methodological quality scores, may contribute to the high heterogeneity and wide ranges of prevalence and incidence rates found in this review.

Other reviews on CVD prevalence and incidence in adults with ID also report wide ranges across various CVD diagnoses [48], although some show narrower ranges due to stricter inclusion and exclusion criteria [49, 50]. This pattern of broad ranges is also evident in de general population. For instance, a recent systematic review on the global prevalence of myocardial infarction reported rates ranging from 0.4% to 41.1% [130]. Similarly, the reported prevalence of atrial fibrillation in the general population varies from 0.5% to 15% [131].

Despite the potential for underdiagnosis in adults with ID [51, 65, 67, 69], most articles relied on medical record data for data collection. Diagnostic work-up for CVD in adults with ID is challenging as they may exhibit atypical presentation of symptoms, may experience limitations articulating health problems, and may exhibit limited cooperation and capacity during physical examination [67]. Referral policies for this vulnerable group are made with the greatest possible care in close consultation with physicians, representatives, healthcare staff, and other stakeholders. Careful consideration is given to the potential impact of diagnostic processes on the individual's quality of life, which may sometimes result in the decision to refrain from further diagnosis [68]. As a result, this increases the likelihood of underdiagnosis in older adults with ID and underscores the need for objective measurements to establish the diagnosis. Only three articles employed objective measurements: electrocardiography (ECG) [95] and the ankle-brachial index [70, 129]. Except for one study, the ECG study reported a significantly higher prevalence of myocardial infarction (6.7%) compared to the other studies (0% to 1.9%). This study compared ECG-based prevalence with medical records, revealing an 88.9% underdiagnosis of myocardial infarction in older adults with ID [95]. Also the ankle-brachial index studies reported significantly higher prevalence rates of peripheral arterial disease (8.4% to 20.7%) compared to those relying on medical record data (0% to 0.6%), further supporting the claim of underdiagnosis in this specific population.

In this systematic review, we also reported CVD prevalence and incidence rates for subgroups based on age, sex, level of ID, aetiology of ID, living circumstances, CVD risk factors, data collection methods, and source populations. Although some studies provided subgroup data, most did not. Where available, subgroup information was presented in separate tables. However, even when subgroups were reported, significant differences were not always evident. Overall, higher prevalence and incidence rates were reported in older compared to younger adults. For example, one study reported a twofold higher prevalence of myocardial infarction in adults aged 40 or older compared to those under 40 (3.0% versus 1.4%) [102]. This finding aligns with the fact that the CVD diagnoses discussed in

this systematic review are age-related [132]. For peripheral arterial disease, we identified two articles that reported prevalence data across different subgroups [70, 129]. Alongside the previously noted differences in prevalence rates related to data collection methods, these articles also reported higher prevalence rates for subgroups characterised by current smoking, physical inactivity, and atypical antipsychotic use, which is expected given that these are well-known CVD risk factors [21, 33]. These studies also reported higher prevalence rates among participants residing in centralised settings compared to those living independently or in community-based settings. Historically, CVD was thought to be less common in individuals with Down syndrome [133]. However, this review found that the prevalence rates of CVD in individuals with Down syndrome fall within the same range as those observed in the broader population of individuals with ID, across various diagnoses of CVD. The exception to this is the study by Rubenstein et al. (2024) [117], which reported a higher prevalence of atrial fibrillation in a large cohort of individuals with Down syndrome (n=116422) compared to the prevalence rates observed in the general ID population (6.3% versus 0.8%-2.2%). It is important to emphasise that the presented subgroup data provide descriptive comparisons between subgroups within or across studies. Other factors may also contribute to observed differences. Therefore, these tables should be considered primarily as exploratory analyses of subgroup variations and are particularly useful for those interested in the literature regarding CVD prevalence or incidence within specific subgroups.

Strengths of this systematic review include independent, duplicate study selection, data extraction, and quality assessment to maximise reliability. Additionally, this review conducted a broad search for the prevalence and incidence of CVD in adults with ID, without pre-specifying specific diagnoses, subgroups, source populations, or data collection methods. This resulted in a large number and wide variety of included articles, providing a comprehensive overview of the available literature. However, due to variability in clinical characteristics and high statistical heterogeneity, we were unable to perform meta-analyses for CVD diagnoses. This underscores the importance of the presented subgroup tables, allowing for the identification of prevalence and incidence rates within specific subgroups.

To gain more insight into the prevalence and incidence of CVD in (subgroups of) adults with ID, we would like to make several recommendations for future research. First, to ensure methodological quality, studies should clearly define the study sample and use valid, reliable methods for data collection. Ideally, objective measurements should be applied, or, when using medical record reviews,

standardised diagnostic criteria such as ICD classifications should be employed. The application of these data collection methods varied substantially across the included studies, both in terms of ID diagnosis ascertainment and CVD outcome measurements, potentially leading to variations in the estimates of prevalence and incidence rates. Aligning the methodology with longitudinal cohort studies of representative groups from the general population also enables comparisons between adults with ID and their peers in the general population. Second, the relatively small number of studies reporting CVD incidence rates highlights the need for more longitudinal studies in adults with ID, with clear reporting of person-years to enable comparison of incidence rates across studies. Third, during the article selection process, we identified numerous studies reporting prevalence or incidence rates for combined or non-specific CVD categories, such as general heart conditions or cardiovascular disorders. Since these studies did not provide prevalence and incidence rates for specific CVD diagnoses, they have been excluded from the current review. Considering that these articles likely contain valuable additional data, we would like to emphasise the importance of precise documentation of the prevalence and incidence rates for individual CVD diagnoses. Finally, due to the heterogeneity of this population, we emphasise that reporting prevalence and incidence data for specific subgroups will offer valuable additional insights in future research.

This systematic review highlights significant variability in methodological quality, clinical characteristics, and statistical heterogeneity across studies, making it challenging to draw broad conclusions about CVD prevalence and incidence in adults with ID. While the subgroup data presented are valuable for identifying rates within specific subgroups, these findings highlight the need for further research. Given the importance of this information in ensuring optimal care and resource allocation, future research should prioritise longitudinal data collection and use valid and reliable data collection methods (preferably objective measurements) that are ideally aligned with longitudinal cohort studies in the general population. Additionally, researchers should clearly report individual CVD diagnoses and perform comprehensive subgroup analyses to provide more definitive insights.

CHAPTER 3

Healthy Ageing and Intellectual Disability study: summary of findings and the protocol for the 10-year follow-up study

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ABSTRACT

Introduction

The Healthy Ageing and Intellectual Disability (HA-ID) study is a prospective multicentre cohort study in the Netherlands that started in 2008, including 1050 older adults (aged ≥50) with intellectual disabilities. The study is designed to learn more about the health and health risks of this group as they age. Compared to the amount of research in the general population, epidemiological research into the health of older adults with intellectual disabilities is still in its infancy. Longitudinal data about the health of this vulnerable and relatively unhealthy group are needed so that policy and care can be prioritised and for guiding clinical decision making about screening, prevention and treatment to improve healthy ageing.

Methods and analysis

This article presents a summary of the previous findings of the HA-ID study and describes the design of the 10-year follow-up in which a wide range of health data will be collected within five research themes: 1) cardiovascular disease; 2) physical activity, fitness and musculoskeletal disorders; 3) psychological problems and psychiatric disorders; 4) nutrition and nutritional state; and 5) frailty.

Ethics and dissemination

Ethical approval for the 10-year follow-up measurements of the HA-ID study has been obtained from the Medical Ethics Review Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2019-0562). This cohort study is registered in the Dutch Trial Register (NTR number NL8564) and has been conducted according to the principles of the Declaration of Helsinki.

INTRODUCTION

The Healthy Ageing and Intellectual Disability (HA-ID) study is a prospective multicentre cohort study including older adults with intellectual disabilities (ID) in the Netherlands. The study was designed in response to the increasing longevity of people with ID and the lack of epidemiological data about their health and health risks at older ages. The absence of this knowledge raised questions about how to organise care and support for this vulnerable and relatively unhealthy group [12]. Based on this need for knowledge, a consortium was established in 2006 consisting of three ID care organisations (Ipse de Bruggen, Amarant and Abrona) and the research group of Intellectual Disability Medicine of the Erasmus MC, University Medical Centre Rotterdam. The HA-ID consortium aims to 1) increase knowledge on healthy ageing in people with ID through scientific research; 2) strengthen the scientific attitude of care professionals through participation in research and continuous education; and 3) innovate care by implementing research outcomes. In 2008, the HA-ID study started with a focus on physical activity and fitness, nutrition and nutritional state, and mood and anxiety. A detailed description of the rationale and design of the baseline measurements can be found elsewhere [12]. After three and five years, follow-up measurements consisting of medical file research and questionnaires about the health of the participants were completed. New topics were included during this follow-up period: cardiovascular disease, frailty, mortality, and causes of death [134].

The baseline results of the HA-ID study showed that older adults with ID had more health problems than their peers in the general population and that these problems occurred at younger ages [65, 135]. Older adults with ID became frail earlier and became more severely frail than their peers in the general population [136]. High prevalences of polypharmacy [137], multi-morbidity [137], sleep problems [138], major depressive disorders [139], dysphagia [140], obesity [36], suboptimal nutritional intake [141], and low physical activity and fitness levels were found [39, 61, 62, 142].

Based on data from the 3 and 5-year follow-ups, frailty at baseline was predictive for the development of comorbidity [143], a decline in daily functioning and mobility [144], increased medication use [143], increased care intensity [145], and a higher mortality risk [146]. Also poor physical fitness was predictive for a decline in mobility [147], daily functioning [147, 148], and for a higher mortality risk [149]. Use of atypical antipsychotics, chronic kidney disease, abdominal obesity, and histories of stroke and heart failure were predictive for developing cardiovascular

disease (CVD) over a 3-year period [51]. These first results from the longitudinal data of the HA-ID study provided important insights for policy and care about how to contribute to a better health of older adults with ID. The results of the HA-ID study have been used in developing of diagnostic instruments and guidelines [135, 150, 151] and to illustrate the vulnerability and poor health situation of people with ID, resulting in changes to the Dutch legislation on long-term financing of support, care and treatment for people with ID.

Following the start of the HA-ID study, other research groups initiated longitudinal studies focusing on various aspects of health in adults with ID, such as the IDS-TILDA study in Ireland [22], the SAge-ID study in Australia [23], and a longitudinal cohort study about dementia and mortality in people with Down syndrome in the Netherlands [152]. Despite these initiatives, epidemiological research into the health of adults with ID is still extremely limited. Too little is known about the health of this group as they age, or about changes in health status over time and early indicators for health problems. However, this knowledge is important for providing the evidence base for improving care and support of older adults with ID and guiding care providers in preparing for this growing group of elderly with ID. Longitudinal research makes it possible to make statements about causality, which contributes to e.g. identifying group-specific risk factors, groups at risk of specific diseases and other negative outcomes such as declining in independence. This knowledge can be used to reduce the occurrence of specific risk factors and identify, monitor and treating high-risk groups in good time. More longitudinal studies focusing on the health of this specific group are therefore urgently needed.

This article describes the design for the 10-year follow-up measurements of the HA-ID cohort. To learn more about changes in health status and indicators for health problems over time, a wide range of health data will be collected. Based on previous measurements and results, the focus will be on five research themes: 1) cardiovascular disease; 2) physical activity, fitness and musculoskeletal disorders; 3) psychological problems and psychiatric disorders (including sleep problems); 4) nutrition and nutritional state (including dysphagia); and 5) frailty. This article presents the design of the HA-ID cohort study and a summary of the main findings up to now, and provides an update of the planned measurements of the 10-year follow-up research themes.

METHODS AND ANALYSIS

Study cohort

The HA-ID cohort consists of older adults with borderline to profound ID. All participants receive care or support from one of the care organisations of the HA-ID consortium. These organisations provide care to a wide spectrum of individuals with ID (in terms of the level of ID, residential status, and mobility) in various settings (central residential settings, community-based homes, day activity centres, and supported living) in both urban and rural areas in various regions in the Netherlands. At baseline, the care organisations provided care to approximately 10% of the total Dutch ID population receiving care or support from an ID care organisation [153]. At the start of the study, 10% of the individuals receiving care from the HA-ID care organisations was 50 or older, comparable to the total Dutch ID population receiving care or support from ID care organisations [153]. Based on these numbers, we concluded that the base population was representative for the total population of older adults with ID receiving care or support from ID care organisations in the Netherlands [12]. All individuals with ID within the consortium aged 50 or older by September 2008 were eligible to participate and received an invitation. Ultimately, 1050 of the 2322 (45.2%) invited individuals with ID participated in the baseline measurements. Table 1 presents the baseline characteristics of the participants, which were largely comparable to the overall group of invited individuals with ID and formed a near-representative study population for the total Dutch population of older adults with ID receiving formal support or care, with an underrepresentation of 80-to 84-year -olds, a slight overrepresentation of women, and an underrepresentation of the more independent group. A more detailed description of the representativeness of the sample has been published elsewhere [12].

Figure 1 summarises the number of participants in the cohort over time. At baseline, measurements consisted of reviewing medical files, administering questionnaires, physical examinations with portable measuring equipment, fitness tests, observations, interviews, laboratory assessments, and diaries [12]. At the 3-year follow-up, medical files were reviewed and professional caregivers completed questionnaires about the participant's health. Five years after the baseline measurements, causes of death were examined in the files of the deceased participants. The participants themselves were not actively involved in the data collection for these follow-up measurements. At the 3-year and 5-year follow-ups, the cohort consisted of 873 and 787 participants respectively.

Table 1 Baseline characteristics of the HA-ID cohort (n=1050) [12]

Characteristics		***n* (%)**
Sex	Male	539 (51)
	Female	511 (49)
Age		60 (11, 50-93)*
Level of ID	Borderline	31 (3.0)
	Mild	223 (21.2)
	Moderate	506 (48.2)
	Severe	172 (16.4)
	Profound	91 (8.7)
	Unknown	27 (2.6)
Residential status	Central setting	557 (53.0)
	Community-based	432 (41.1)
	Independent with ambulatory support	43 (4.1)
	With relatives	7 (0.7)
	Unknown	11 (1.1)
Level of care (ZZP-scores)	Only day care indication	6 (0.6)
	Only indication ambulant care	37 (3.5)
	Residence with minimal support (1 VG)	12 (1.1)
	Residence with support (2 VG)	39 (3.7)
	Residence with support and care (3 VG)	138 (13.1)
	Residence with support and intensive care (4 VG)	207 (19.7)
	Residence with intensive support and intensive care (5 VG)	325 (31.0)
	Residence with intensive support, care and regulation of behaviour (6 VG)	93 (8.9)
	(Enclosed) residence with very intensive support, care and regulation of behaviour (7 VG)	142 (13.5)
	Mental Health Care ZZP scores	2 (0.2)
	Unknown	49 (4.7)

ID = intellectual disability; VG = Dutch abbreviation for intellectual disability; ZZP = the Dutch classification of levels of support, care and/or treatment as a basis for long-term financing (Zorgzwaartepakket) [154];
*Median (interquartile range, range)

All individuals with ID who participated in the baseline measurements and still receive care or support from one of the participating care organisations will be invited to participate in the 10-year follow-up measurements. There is one exclusion criterion: individuals are excluded from physical measurements if they are so seriously ill that participating in the study is not desirable. This decision is made based on shared decision making with caregivers and professionals. Based on previous mortality rates and historical loss to follow-up, it is estimated that 424 participants from the HA-ID cohort could be invited to participate in the 10-year follow-up measurements. With a conservative inclusion rate estimate of 50%, approximately 212 participants are expected to actually participate in these measurements.

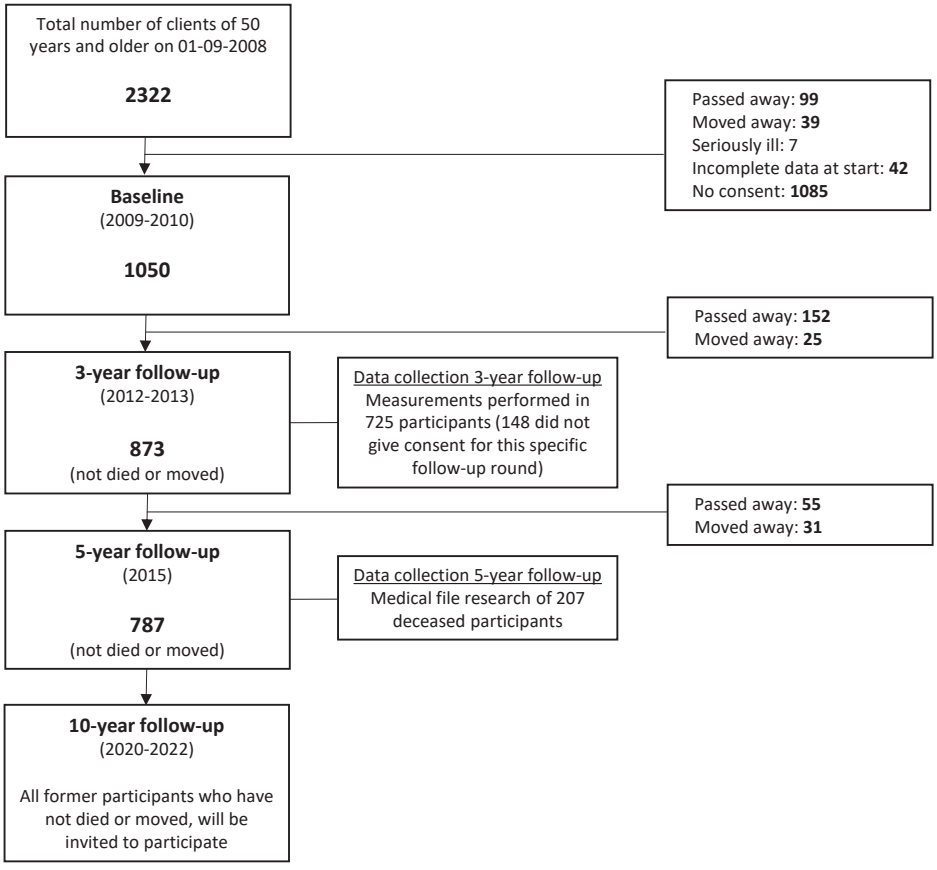

Figure 1 Flow chart that shows the number of participants in the HA-ID cohort over time

Figure presents 1) the number of participants eligible for participation in the HA-ID cohort, 2) the number of participants who participated in measurements, 3) and the numbers of participants who dropped out the cohort

Informed consent procedure

Because not all individuals with ID are mentally capable of giving informed consent, two separate consent procedures are followed. A behavioural scientist evaluates whether the individual is able to understand the specifically designed study information to let them make an informed decision about participation. If an individual is capable of making an informed decision, an easy-to-read information letter with supporting pictures and a consent form will be sent to this individual. If the behavioural scientist assesses the individual as being unable to make an informed decision about participation, an information letter and consent form will be sent to the legal representative of this individual. The professional caregiver of the individual with ID is informed about the study and the informed consent procedure to support the individual or legal representative in making their decision for participation.

Inclusion of the participants started in July 2020 and the data collection in October 2020. Both the inclusion and the data collection are still ongoing.

Ethics and dissemination

As for the previous parts of the HA-ID study (MEC-2008-234 and MEC-2011-309), ethical approval for the 10-year follow-up has been obtained from the Medical Ethics Review Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2019-0562). This cohort study is registered in the Dutch Trial Register (NTR number NL8564) and follows the guidelines of the Declaration of Helsinki [155]. Local ethical committees and boards of individuals with ID and their representatives of the three involved care organisations were informed. Inclusion of the participants started in July 2020 and is ongoing.

Research themes

An outline is presented of the published results for each research theme, followed by a description of the data collection for the 10-year follow-up, with a specific focus on newly added measurements. In the 10-year follow-up, we also omitted measurements that turned out to be unfeasible, invalid, or unreliable, based on the baseline measurements. For clarity, these measurements are not listed separately below. An overview of all measurements at baseline and the 3, 5, and 10-year follow-ups can be found in Table 2.

Cardiovascular disease

The HA-ID study provided many insights into the prevalence of CVD risk factors and the incidence of CVD in older adults with ID. The prevalences of hypertension (53.0%), diabetes (13.7%), metabolic syndrome (44.7%), and chronic kidney disease (15.3%) were similarly to those in the general population [40, 198]. However, the prevalence of peripheral arterial disease (20.7%) and obesity in women (25.6%) as measured by the Body Mass Index (BMI) was significantly higher than in the general population [36, 70]. The incidence of newly diagnosed CVD during a 3-year follow-up period was also examined. Incidence rates for myocardial infarction (2.8 per 1000 person-years (py)), stroke (3.2 per 1000py), and heart failure (12.8 per 1000py) were similar to the general population [51]. The use of atypical antipsychotics, chronic kidney disease, abdominal obesity, and histories of stroke and heart failure turned out to be predictive for developing CVD during the 3-year follow-up period [51].

The baseline measurements revealed underdiagnosis of CVD risk factors in the HA-ID cohort. For example, 54% of the participants with diabetes had not been previously diagnosed with this condition. This was the case in 46% of the participants for hypercholesterolaemia, in 50% for hypertension and in 94% for metabolic syndrome [40]. Atypical presentation of symptoms, limitations in communication, and limited cooperation and resilience make diagnostics in people with ID more challenging [67]. This makes underdiagnosis a common problem in people with ID [65, 199]. The incidence of CVD described above is therefore also probably underestimated [51].

With increasing longevity and increased prevalence of some CVD risk factors, people with ID may be at higher risk of developing CVD. The 10-year follow-up of the HA-ID cohort provides opportunities to learn more about CVD risk factors and the development of CVD over time in older adults with ID. The planned measurements for the 10-year follow-up are summarised in Table 2. The presence of CVD risk factors, CVD and CVD treatments/interventions over the past ten years will be assessed by reviewing the medical files of all participants who participated in the baseline measurements, including the medical files of deceased participants. Blood will be collected through venepuncture. Blood will be stored for 15 years at -80°C, allowing analyses of relevant biochemical markers now and in the future (Table 2).

Table 2 Measurements within the HA-ID study: baseline, 3, 5 and 10-year follow-up per research theme*

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Demographics						
Medical file	Age	-	X	X	X	X
	Sex	-	X			
	Residential status	Central setting (with or without 24-hour support), community based (with or without 24-hour support), independent with ambulatory support (by appointment), with relatives, with partner, independent.	X			X
	Level of care	Care Intensity Packages (Dutch ZZP-scores) [154].	X	X		X
1. Cardiovascular disease						
Physical assessment	Brachial blood pressure*	Omron M7 (OMRON Healthcare, the Netherlands).	X			
	Central blood pressure and arterial stiffness	Mobil-O-Graph 24h PWA Monitor (IEM GmbH, Germany) including pulse wave velocity.				X
	Ankle-Arm-Index*	Omron M7 (OMRON Healthcare, the Netherlands) (arm). Boso classico and 8-MHz Doppler probe (Huntleigh MD II, United Kingdom) (ankle). Ankle-arm-index calculated: systolic blood pressure ankle divided by systolic blood pressure arm.	X			X
	Heart rate variability	Polar Vantage V HR H10 (Polar Electro Oy, Finland).				X
	Electrical activity of the heart	Electrocardiogram (ECG).				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Fat percentage	Formulas Durnin and Womersly [156] for calculating fat percentage from the sum of four skinfolds: triceps, biceps, subscapular and suprailiacal. Thickness of skinfolds measured with skinfold calliper (Harpenden, Baty International, United Kingdom).	X			X
		Tanita Body Composition Analyser DC-430 MA (Tanita, the Netherlands).				X
	Body composition	Tanita Body Composition Analyser DC-430 MA (Tanita, the Netherlands).				X
Venipuncture	Biochemical markers*	Fasting plasma levels: glucose, cholesterol (total/HDL*/LDL), haemoglobin (HB)*, haemoglobin A1c (HbA1c), triglyceride, C-reactive protein (CRP), interleukin 6 (IL-6), Tumour Necrosis Factor alpha (TNF alpha), albumin, vitamin D, calcium, creatinine, cystatin C, troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP) etc. The participants' blood is stored for 15 years at -80 degrees Celsius, in order to perform additional analyses afterwards.	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Medical file	Cardiovascular disease*	Presence of CVD (heart failure, myocardial infarction, stroke, transient ischemic attack (TIA), cardiac arrhythmias, angina pectoris, aortic aneurysm, peripheral arterial disease (PAD), hypertension etc.), CVD risk factors (diabetes mellitus, central obesity, metabolic syndrome, rheumatoid arthritis, incriminating family history etc.) and treatments/ interventions (revascularisation of the coronary artery, pacemaker and implantable cardioverter-defibrillator (ICD)).	X	X		X
	Endocrine disorders*	Presence of endocrine disorders (such as diabetes mellitus*, hypercholesterolemia and metabolic syndrome).	X			X
2. Physical activity, fitness and musculoskeletal disorders						
Fitness assessment	Manual dexterity*	Box and block test [157].	X			X
	Reaction time	Auditive and visual reaction time test [158, 159].	X			
	Balance*	Berg Balance Scale [160].	X			
		Comfortable and maximum walking speed (5m) [150]*.	X			X
		Static balance test (for stances) [150].				X
	Grip strength*	Jamar Hand Dynamometer (#5030J1, Sammons Preston Rolyan, USA) [150].	X			X
	Muscle endurance	30s chair stand [150].	X			X
		5 times chair stand [150].				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Cardiorespiratory endurance	10m Incremental shuttle walking test [161]. Results of this test recalculated to VO2max [162].	X			
		2 minute step test [163], with heart rate monitor (Polar RS400, Polar Electro Oy, Finland).				X
	Flexibility	Extended version of Modified back saver sit and reach test [164, 165].	X			
Measurement at home	Physical activity	Pedometer NL-1000 (New Lifestyles, USA).	X			
		ActiGraph wGT3X-BT Accelerometer (ActiGraph, USA).				X
Questionnaires professional caregiver		Self-assembled questionnaire about the participants' habitual physical activity.	X			
		International Physical Activity Questionnaire – short version (IPAQ-s) [166].				X
	Activities of daily life/mobility	Animated Activity Questionnaire (AAQ) [167].				X
	Mobility*	Self-assembled questionnaire based on the Hauser Ambulation Index [168] and the characteristics of the Gross Motor Function Classification Scale [169].	X	X		X
	Falling	Self-assembled questionnaire about the number of falls in the last three months.		X		X
	Symptoms/ limitations related to (hip/knee) OA	Hip disability and OA Outcome Score (HOOS) [170, 171].				X
		Knee injury and OA Outcome Score (KOOS) [172].				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Use of lower extremity aids	Self-assembled questions about the presence/use of aids for extra support of the lower extremity (such as orthopaedic footwear, splints and braces).	X			X
Physical assessment	Clinical/ symptomatic OA	Physical examination to examine the ACR criteria for clinical osteoarthritis of the hip and the knee [173, 174]. The following tests will be performed [175]: palpable warmth of the knee joint, joint crepitus of the knee, bony enlargement of the knee joint, quadriceps wasting, bone margin tenderness, patellofemoral joint tenderness, anserine tenderness, tibiofemoral joint tenderness, bulge sign of the knee, range of motion flexion and extension of the knee, range of motion flexion and extension of the hip, range of motion endorotation and exorotation of the hip. In addition, the laxity of the joints will be tested [176] and the gait and the postural alignment will be observed [177].				X
Interview	Self-report pain	The participants undergo a comprehension test to test whether their self-reported pain on a face-scale is a valid measurement [178]. When they succeed they will be asked to grade their pain during examination of the joint tenderness, flexion of the joints and hip internal rotation on a face-scale.				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Observation	Observed pain	The health care professional will perform the Rotterdam Elderly Pain Observation Scale (REPOS) to observe pain behaviour during the physical examination for OA. A NRS-obs will be asked from the professional caregiver as part of the REPOS observation [179].				X
Medical imaging	Radiographic hip/ knee OA	X-rays of the hip and knee: anterior posterior (AP) view of both knees (if possible weight-bearing), lateral view of right and left knee, skyline view of the patellofemoral joint of right and left knee, AP view of pelvis, faux profile view of right and left hip (only made by participants who are able to stand up (with support)).				X
Medical file	Musculoskeletal disorders*	Presence of musculoskeletal disorders in the medical file (such as OA, scoliosis*, spasticity and bone fractures).	X			X
3. Psychological problems and psychiatric disorders						
Measurement at home	Sleep-wake & circadian rhythm	Actiwatch AW7 (Cambridge Technology Ltd, United Kingdom).	X			
		GENEActiv Original (Activinsights Ltd, United Kingdom).				X
Interview	Self-report depression	Inventory of Depressive Symptomatology Self Report (IDS-SR) [180]. Phrasing of the questions adapted to people with ID.	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Self-report anxiety	Glasgow Anxiety Scale for people with an Intellectual Disability (GAS-ID) [181].	X			X
		Hospital Anxiety and Depression Scale (HADS) – anxiety subscale [182]. Phrasing of the questions adapted to people with ID.	X			
	Quality of life	Intellectual Disability Quality of Life (IDQOL-16) [183].	X			
	Diagnostic interview depression and/or anxiety	Participants with scores above the preset cut-off scores on one of the depression or anxiety questionnaires are further examined using the Psychiatric Assessment Schedule for Adults with Developmental Disability ICD-10 version (PAS-ADD-10). Interviews are conducted with the participant or his/her caregiver [184].	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Questionnaires professional caregiver	Informant-report depression and anxiety*	Anxiety, Depression and Mood Scale (ADAMS) [185]*.	X			X
		Signaallijst Depressie Zwakzinnigen (SDZ) [186]*.	X			X
	Somatic complaints	Somatic complaints subscale of the Symptom Checklist-90 (SCL-90) [187].	X			
	Life-events	Self-assembled checklist about life events based on other checklists, earlier life event-studies and experience from professionals working with people with ID.	X			X
	Social outcome	Self-assembled checklist about number of contacts with family, friends and peers and visiting leisure-clubs.	X			
	Cognitive functioning*	Dementia questionnaire for people with intellectual disabilities (DMR) [188].	X			X
	Aberrant behaviour	Aberrant Behaviour Checklist (ABC) [189].				X
	Sleep problems	Self-assembled questions about sleep problems, including problems with falling asleep and waking up early.	X			X
	Sleep hygiene	Self-assembled questions about sleep hygiene (such as sleeping conditions, bedtimes, sleeping rituals, eating habits and use of TV, smartphone or tablet before going to bed and provided professional support).				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Psychological file	Psychological problems and psychiatric disorders	Baseline: level of intellectual disability, autism, depression, anxiety, dementia, psychoses, other psychiatric disorders and serious behavioural problems. 10-year follow-up: baseline variables + mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, attachment disorders, personality disorders, psychotic disorders, post-traumatic stress disorder, cognitive disorders (including dementia), traumatising and support or treatment received by the participant.	X			X
Medical file	Sleep disorders/ sleep problems	Presence of sleep disorders/ problems in the medical file (such as problems with falling asleep and waking up early).	X			X
Physical assessment	Cortisol concentration last month	A small hair sample of at least 1cm (length) will be taken from the posterior vertex close to the scalp [190].				X
4. Nutritional intake and nutritional state						
Physical assessment	Height*	-	X			X
	Weight*	-	X			X
	Body circumferences	Measuring tape for hip, calf* and upper arm circumference.	X			X
	Bone Quality*	Ultrasonometer (Lunar Achilles Insight, GE Healthcare, United States) for measuring bone stiffness calcaneus.	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Diary	Food intake	Self-assembled 3-day food intake diary.	X			X
Meal time observation	Dysphagia*	Dysphagia Disorder Survey [191].	X			X
Questionnaires professional caregiver	Malnutrition*	Mini Nutritional Assessment (MNA) [192]*.	X			X
		Short Nutritional Assessment Questionnaire for Residential Care (SNAQRC) [193].				X
	Eating disorders*	Screening Tool of fEeding Problems (STEP) [194].	X			X
	Gastro-oesophageal reflux disease	GORD Questionnaire: self-assembled questionnaire consisting of 50 items involving risk factors and symptoms of gastro-oesophageal reflux disease.	X			
Dental file	Dental condition	Baseline: dental condition, premedication/sedation during check-up or treatment, dental prosthesis and enamel wear. 10-year follow-up: baseline variables + number of dentist/ dental hygienist visits, number of elements in the upper/lower jaw, dental wear, dental caries, plastic restorations, crowns and bridges, implants, gingivitis/periodontitis, mobile elements and loss of dental elements due to trauma.	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
Medical file	Gastrointestinal diseases*	Presence of gastrointestinal disease in the medical file (such as gastroesophageal reflux disease*, gastric ulcer, constipation* and dysphagia*).	X			X
5. Frailty						
All outcomes / measurements with an asterisk* in this table are part of the overarching research theme 'Frailty'.						
General health data						
Medical file	Aetiology of intellectual disability	Presence of the aetiology of the intellectual disability in the medical file (such as a specific genetic syndrome).	X			X
	Malignancies*	Presence of malignancies in the medical file.	X			X
	Pulmonary diseases*	Presence of pulmonary disease in the medical file (such as asthma*, chronic obstructive pulmonary disease* and sleep apnoea syndrome).	X			X
	Neurological disorders	Presence of neurological disorders in the medical file (such as dementia, epilepsy and Parkinson's disease).	X			X
	Diseases of the genitourinary system	Presence of diseases of the genitourinary system in the medical file (such as urinary tract infections, incontinence and renal failure).	X			X
	Visual and hearing impairments*	Presence of visual and hearing impairments in the medical file.	X			X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Medication use*	Medication use (medicament and dosage) as stated in the medical file.	X			X
	Hospitalisation*	Number of hospitalisations in the past period.		X		X
	Mortality	Date of death, as stated in the medical file.		X	X	X
	Cause of death	Cause of death, as stated in the medical file.		X	X	X
Questionnaires professional caregiver	Activities of daily life*	Barthel Index [195]*.	X	X		X
	Instrumental activities of daily life*	Questionnaire based on the Instrumental Activities of Daily Living of Lawton and Brody [196] and the Groningen Activities Restriction Scale [197].	X	X		X
	Daytime activities*	Self-assembled questions about daytime activities and/or work of the participant.	X			X
	Smoking	Self-assembled questions about the smoking habits of the participant (how many cigars, cigarettes and/or pipe per day + past smoking habits).	X			X
	Alcohol use	Self-assembled questions about the participant's alcohol consumption (alcohol use per day + alcohol use in the past).	X			X
	Drug use	Self-assembled questions about the drug use of the participant (use of cannabis and hard drugs per day + drug use in the past).				X

Table 2 Continued

Type	Outcome	Details	Moment of data collection			
			Baseline (2009-2010)	**3-year follow-up (2012-2013)**	**5-year follow- up (2015)**	**10-year follow-up (2020-2022)**
	Use of caffeinated drinks	Self-assembled questions about the use of caffeinated drinks (coffee, tea, Coke, energy drink and chocolate milk) by the participant.				X

The following measurements were added to the physical examination to gain more insight into the presence of CVD and its risk factors. Body composition will be studied with Bioelectrical Impedance Analysis (BIA) using the Tanita Body Composition Analyser (Tanita DC-430 MA, Tanita, Netherlands). An electrocardiogram will be performed to examine heart conditions. In addition, heart rate variability will be measured as a marker for the autonomic nervous system by wearing a heart rate monitor (Polar Vantage V HR H10, Polar Electro Oy, Finland) at rest for 5 minutes. Finally, various haemodynamic measurements (mean arterial pressure (mmHg), pulse pressure (mmHg), resting heart rate (bpm), stroke volume (mL), cardiac output (l/min), cardiac index (l/m*1/m), augmentation index (%), peripheral vascular resistance (s*mmHg/mL) and pulse wave velocity (m/s)) will be obtained with a non-invasive electronic blood pressure oscillometric monitoring system (Mobil-O-Graph 24h PWA Monitor, I.E.M. GmbH, Germany) [200]. Adding the Mobil-O-Graph provides a clearer picture of the presence of arterial stiffness and central systolic blood pressure, two important risk factors for CVD and morbidity [201].

Physical activity, fitness and musculoskeletal disorders

The HA-ID study yielded important results about physical activity and fitness. Older adults with ID had very low physical activity and fitness levels [39, 61]. In short, most participants were categorised as 'low active' (5000-7449 steps/day; 25.3%) or 'sedentary' (<5000 steps/day; 38.5%). Only 36.2% of the participants walked ≥7500 steps/day [39]. These results are likely to underestimate the problem because physical activity levels were only measured in participants who were physically able to walk at a sufficiently high speed for the pedometers to provide reliable measurements. In addition to these low physical activity levels, people with ID

aged 50 and over had physical fitness levels comparable to or worse than people in the general population aged 70 and over [61, 62]. Data from the 3 and 5-year follow-ups showed that these low physical fitness levels at baseline were indicative of a decline in daily functioning and mobility over the 3-year follow-up period and a higher mortality risk over the 5-year follow-up period [147-149, 202]. Additionally, it was found that being fit is more important for survival than obesity. People who were unfit had a mortality risk four times higher than people who were fit, regardless of obesity [202]. Because of the importance of physical fitness, suitable fitness tests for this population are essential. Based on our previous research examining the reliability and feasibility of eight physical fitness tests in older adults with ID [203, 204] we developed the ID-fitscan to assess the physical fitness levels of adults with ID [150].

In the 10-year follow-up measurements, physical activity and fitness levels will be assessed again (see Table 2). Based on previous results and experiences, some changes were made to the measurements. Physical activity will be measured using the ActiGraph (wGT3X-BT Accelerometer, ActiGraph, USA), an instrument that can make measurements at very low walking speeds and provides more detailed information about the physical activity levels of the participant. Complementary to this, we will use the International Physical Activity Questionnaire – Short Form (IPAQ-SF) to collect physical activity data [166]. The ID-fitscan [150], supplemented with the two-minute step test [163], will be used to assess physical fitness. Physical fitness tests that turned out to be less suitable at the baseline measurements are excluded [150].

The 10-year follow-up will also focus on musculoskeletal disorders, in particular osteoarthritis. Osteoarthritis is common in older people in the general population, leading to pain, joint instability, limitations in daily activities, and decreased quality of life [205, 206]. Little is known about the prevalence of knee and hip osteoarthritis in people with ID. High prevalence is expected because many factors that have been associated with osteoarthritis (such as obesity, poor physical fitness levels, poor motor skills, gait abnormalities, musculoskeletal complications, and developmental problems) are commoner in adults with ID than in the general population [61, 207-211].

Osteoarthritis of the hip and the knee will be assessed by applying the American College of Rheumatology (ACR) criteria for the diagnosis of osteoarthritis. These criteria cover clinical symptoms, consisting of pain and functional limitations of the joint and include radiological characteristics from X-rays as well [174]. The 10-

year follow-up includes several tests to identify the presence of the ACR criteria, including physical examinations with pain observations (Rotterdam Elderly Pain Observation Scale (REPOS) filled out by the health professional performing the physical examination, supplemented by a Numeric Rating Scale observation filled out by the professional caregiver during the physical examination and a face-scale for self-report of pain [178]). The REPOS will also be used to assess pain during rest and daily activities that may provoke osteoarthritis complaints. Also, the Animated Activity Questionnaire (AAQ) will be used to identify whether the participants have complaints due to osteoarthritis during daily living activities, filled out by the professional caregivers of the participants [167]. Additional, data about gait characteristics that may be related to osteoarthritis will be collected through a structured observation. To signal pain, stiffness and range of motion the standardised questionnaires (the Hip disability and Osteoarthritis Outcome Score (HOOS) [170, 171] and the Knee disability and Osteoarthritis Outcome Score (KOOS) [172]) will be used.

Psychological problems and psychiatric disorders

At baseline, data were collected on the prevalence of depression and anxiety disorders. The prevalence of major depressive disorder was 7.6% [139], which is higher than in the general population (1.8% to 4.0%) [212]. Only 4.4% of the participants met the criteria for one of the anxiety disorders [139]. This was lower than expected and lower than the prevalence in the general population (10.2% to 11.6%) [213]. This may be explained by the fact that proxy reports had to be used in 78% of the participants. It is difficult for respondents such as professional caregivers to recognise symptoms of anxiety (e.g. pounding heart, worrying). This may have led to underestimation of the prevalence of anxiety disorders.

In the general population there is a strong association between sleep problems and anxiety- and mood disorders [214]. Data on sleep and sleep-wake rhythm were therefore also collected at baseline based on wrist-worn accelerometry (Actiwatch AW7, Cambridge Technology Ltd, Cambridge, United Kingdom [49, 50]). It was found that 23.9% of the participants lay awake for more than one hour before falling asleep. In addition, 63.1% lay awake for more than 90 minutes after sleep onset and before final morning awakening, 20.9% slept less than 6 hours and 9.3% were already awake for more than 60 minutes before getting out of bed [215]. In total 72.1% of the participants were classified as having at least one of these sleep problems [215].

During the 10-year follow-up, data about anxiety disorders, depression and sleep will be collected again, with some changes and additions to the baseline data collection (see Table 2). The 10-year follow-up has been extended with data retrieval from the psychological files about the presence of mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, attachment disorders, personality disorders, psychotic disorders, post-traumatic stress disorder and cognitive disorders (including dementia). In older people with ID, there is an association between the presence of a mental health diagnosis and problem behaviour [216]. Data about problem behaviour will therefore also be collected within the 10-year follow-up using the Aberrant Behaviour Checklist (ABC) [189]. The ABC is a widely used behaviour rating scale and measures problem behaviour using five subscales: irritability, lethargy, stereotypy, hyperactivity, and excessive speech. In addition, a potential objective biomarker for long-term stress in people with ID will be evaluated, which may help to future diagnostic assessment. Long-term stress over the recent months will be retrospectively examined with a hair cortisol measurement. Recently published studies in the general population indicate that there is a strong association between the level of hair cortisol, life events, and symptoms of anxiety and depression [217-220]. Data on sleep and sleep-wake rhythm will still be collected with accelerometry; however, we will now use the GENEActiv (Original, Activinsights Ltd, UK). Data from the GENEActiv are comparable to data collected by the Actiwatch that was used at baseline [221]. Extra questions about sleep hygiene and sleep circumstances have been added to learn more about the influence of these factors on sleep in older adults with ID.

Nutritional intake and nutritional state

The baseline measurements of the HA-ID study yielded insights into the dietary intake and nutritional state of older adults with ID. Three-day dietary records completed by professional caregivers revealed inadequate dietary intake, with none of the participants meeting all Dutch recommendations for a healthy dietary intake. The food intake was too low in calories in 68.6% of the participants, too low in protein in 30.2%, too low in dietary fibre in 98.2%, and too high in saturated fat in 89.5% of the participants [141]. Forty-two percent of the participants had vitamin D deficiency, of which 9% had severe vitamin D deficiency [222]. Vitamin D supplement were routinely provided to 45% of the participants and this group had significantly higher mean vitamin D serum levels than those without supplement. This calls for more attention for prescribing vitamin D in older adults with ID [222]. These results also indicate that there is plenty of room for improvement in healthy nutrition. Mealtime observations using the Dysphagia Disorder Survey (DDS) [191] showed moderate to severe dysphagia in 51.7% of the participants, which is

comparable to the prevalence in nursing homes [140]. In 89.5% of the participants with dysphagia, this had not been previously diagnosed. The high degree of underdiagnosis illustrates the importance of screening and diagnosing dysphagia to prevent complications in clinical practice. Greater age, Down syndrome, mobility impairment, needing help with feeding, and use of benzodiazepines were positively and independently associated with dysphagia [140].

The prevalence of sarcopenia was also studied. Fourteen percent of the participants were classified as having sarcopenia, which developed at a relatively young age compared to the general population. At a prevalence of 12.7%, sarcopenia was already significantly present in participants aged 50 to 64 [223]. Additionally, the bone quality was low in 43.9% of participants. Being female, greater age, more severe ID, mobility impairment, and anticonvulsant drug use were positively associated with low bone quality [224]. Higher BMI was negatively associated with low bone quality [224]. These results suggest an approach for periodic screening of high-risk groups for low bone quality and target groups for prevention in clinical practice [224].

In the 10-year follow-up, the baseline measurements will be repeated (see Table 2). To gain a better picture of the degree of malnutrition among older adults with ID, the Short Nutritional Assessment Questionnaire for Residential Care (SNAQRC) will be added to the data collection. The SNAQRC is a screening instrument for early detection of undernutrition in nursing or residential home settings using a traffic light system in which BMI and four questions related to involuntary weight loss, loss of appetite, and eating with help are combined [193]. The SNAQRC will be completed by professional caregivers.

At baseline, a short dental file examination provided some data on the dental condition of the participants. To get a fuller picture of the dental condition and dental hygiene of older adults with ID, the dental file review will be extended. Data will be collected about dental condition, premedication and sedation during check-up and treatment, dental prosthesis, enamel wear, the number of dentist and dental hygienist visits, the number of elements in the upper and lower jaw, dental wear, dental caries, plastic restorations, crowns and bridges, implants, gingivitis and periodontitis, mobile elements, and loss of dental elements due to trauma.

Frailty

Frailty is a clinically recognisable state of increased vulnerability resulting from age-associated decline in reserves and functions across multiple physiological systems [225]. Frailty leads to deterioration of daily functioning and mobility,

increased disability, development of comorbidity, and increased care intensity [144, 226, 227]. As a result, signalling frailty could play a valuable role in care planning, potentially improving quality of life and increasing the life expectancy of frail people with ID. In the general population, frailty is usually measured by tools such as the frailty phenotype [228]. However, we theorised that the ID population might require a more specific approach than the available tools allow. Based on the baseline data, an ID-Frailty Index was created consisting of 51 items [135]. The ID-Frailty Index focuses on multiple aspects of daily functioning, opposed to a broader focus on physical frailty and mobility impairment [229]. As a result, the ID-Frailty Index could be applied to a larger proportion of the study population than the frailty phenotype and was deemed more suitable for measuring frailty in older adults with ID [229]. Furthermore, the ID-Frailty index showed a stronger relationship with mortality than the frailty phenotype [229]. The 3-year follow-up data showed that higher scores on the ID-Frailty Index resulted in a greater risk of death [146]. Finally, the ID-Frailty Index was predictive for a decline in mobility and increases in disability, polypharmacy, and care intensity [143-145].

In the 10-year follow-up all previous measurements that were used to create the ID-Frailty index will be repeated (see Table 2). This lets us investigate the characteristics of frailty over time. In an attempt to further increase the practical and clinical usability of the ID-Frailty Index, a shortened version was developed. During the 10-year follow-up, the utility of this short form of the ID-Frailty Index will be further investigated.

General health data

In addition to these five research themes, data on other health variables will also be collected such as data on other diseases, medication use, hospitalisation, mortality, activities of daily life, smoking, and alcohol/drug use (Table 2, under the heading 'General health data').

Procedure

To limit the burden and impact on participants and their professional caregivers, all measurements will be done in settings close to where the participants live. All measurements will be carried out by test administrators consisting of professionals working in the care organisations. All test administrators will be trained to ensure accurate administration and correct scoring of the measurements. All measurements for a specific participant will be scheduled within one week. This test week consists of a physical examination performed by medical staff, fitness tests supervised by movement therapists or physiotherapists, observations

to assess pain during activities of daily life performed by trained healthcare professionals, a mealtime observation to screen for dysphagia performed by speech and language therapists, and a maximum of two interviews by trained and qualified professionals aimed at screening and diagnosing anxiety and depression. The participant will wear portable measuring equipment on the wrist and hip for seven days to monitor physical activity and sleep-wake rhythm. If separate consent is provided, blood samples and a tuft of scalp hair will be collected. For logistical reasons, the hip and knee X-rays take place outside this test week. All measurements together require a maximum time investment of four hours for each participant. However, the time investment per participant will probably vary because not every participant can undergo all measurements. The study will not interfere with routine medical practice. In addition to measurements for which active involvement of the participants is needed, the professional caregiver will be asked to complete questionnaires about the participant's health and data will be collected from the medical, psychological, and dental files. The medical file review is performed using the records of all participants who participated in the baseline measurements, including the medical files of deceased participants. A complete overview of all measurements within the HA-ID study can be found in Table 2. After the test week, the participant's physician and behavioural scientist receive a report with a summary of the results of the measurements.

Statistical analysis

In line with the previous measurements, the 10-year follow-up will provide cross-sectional and longitudinal data. Various statistical analyses will be applied. Descriptive statistics are used to answer questions about the prevalence and incidence of health conditions and possible risk factors. Multivariable regression analyses are used to answer questions about differences between subgroups and associations between variables, considering possible confounders and to adjust for these covariates. Survival analysis with Cox proportional hazard models will be used to investigate relationships between various factors (including age, sex, level of ID, and comorbidity) and several health conditions and mortality over time. For repeated measurements, the dependency of measurements for the same participant will be adjusted by using generalised linear mixed-effects models (GLME).

IMPLICATIONS FOR PRACTICE

The HA-ID study so far has yielded knowledge of various health problems that are prevalent in older adults with ID, and how these compare to the general population. This knowledge suggested approaches for improving care for adults with ID. The 10-year follow-up will provide a deeper understanding of the course of health over time and risk factors for health problems in older adults with ID. Research into CVD risk factors in this population, for example, is still very limited. More knowledge about CVD risk factors and possible group-specific risk factors will give a better estimate of the cardiovascular risk profile of older adults with ID. The 10-year follow-up will also give a clearer picture of how frailty develops over time and whether there are certain groups of people with ID who are at higher risk for adverse outcomes.

What characterises the HA-ID study is that it is a prospective multicentre cohort study in which, compared to other ID studies, a relatively large (n=1050) and heterogeneous group of older adults with ID is followed over time. The extensive measurements let us evaluate the health of older adults with ID from a broad perspective and investigate the interrelationships between medical domains such as cardiovascular disease, physical fitness, psychological problems and psychiatric disorders, nutrition, and frailty. Looking across research themes is especially important because multi-morbidity is common in people with ID [65].

We know from experience that conducting epidemiological research into this field can be difficult and involves challenges in selecting suitable measuring instruments; some require certain levels of cognitive, physical, or verbal ability that may not be compatible with those of the participants. To allow for optimal comparison between the general population and our cohort, we have aligned the measurements of the 10-year follow-up as much as possible to existing cohort studies of (specifically older) adults in the general population. However, feasibility, validity and reliability in older adults with ID were the leading criteria when selecting measuring instruments, using previously acquired knowledge and experience from the HA-ID study. How invasive and time-consuming instruments are was also considered, as were the feasibility for a large proportion of our population, the extent to which it is possible to do the measurement at the care organisations, and the extent to which the instruments can be used by a large group of professionals without making concessions in terms of inter-rater reliability. In addition, the costs of the measuring instruments were examined, considering use in clinical practice. The HA-ID study is continuously searching for innovative and feasible measuring instruments that can be implemented for data collection.

A limitation of our study is that financial and feasibility reasons mean it has not been possible to perform follow-up measurements more regularly. Fortunately, the presence of routine registrations performed by the care organisations in medical, psychological and dental files lets us retrospectively collect data on the health of the participants over the past 10 years. Given the age of our study population and the length of follow-up, selection bias caused by the survival of healthier participants may distort our results. We are aware of this healthy survivor effect and address this when analysing and interpreting our results. It should be noted, that we do have access to the medical files of participants who have passed away. This lets us retrospectively collect data on the health of this group.

Results from the 10-year follow-up measurements are important for prioritising policy and care and underpinning clinical decision making about screening, prevention and treatment to improve healthy ageing of adults with ID. Longitudinal data collected in the 10-year follow-up of the HA-ID cohort therefore has high added value.

CHAPTER 4

Feasibility and findings of electrocardiogram recording in older adults with intellectual disabilities: results of the Healthy Ageing and Intellectual Disabilities study

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ABSTRACT

Background

Older adults with intellectual disabilities (ID) have a high risk of cardiovascular diseases (CVD). At the same time, challenging diagnostic work-up increases the likelihood of underdiagnosis of CVD in this population. To limit this underdiagnosis, it would be beneficial to use objective measures such as the electrocardiogram (ECG). However, little is known about the feasibility of ECG recording and the prevalence of ECG abnormalities in this population. Therefore, the aims of this study were to investigate the feasibility of resting ECG recording, to study the prevalence of ECG abnormalities, and to compare the frequency of ECG abnormalities with medical records in older adults with ID.

Method

A cross-sectional study was performed within a cohort of older adults (≥60 years) with ID as part of the Healthy Ageing and Intellectual Disabilities (HA-ID) study. A resting 12-lead ECG was attempted and the ECG recording was considered feasible if the recording could be made and if the ECG could be interpreted by a cardiologist and the Modular ECG Analysis System (MEANS). ECGs were assessed for the presence of ECG abnormalities and medical record review was performed. If the cardiologist or MEANS concluded that there was evidence of myocardial infarction, atrial fibrillation, or QTc prolongation on the ECG in the absence of this ECG diagnosis in the participant's medical record, this was classified as a previously undiagnosed ECG diagnosis.

Results

ECG recording was feasible in 134 of the 200 participants (67.0%). Of these 134 participants (70.6 ± 5.8 years; 52.2% female), 103 (76.9%) had one or more ECG abnormality, with the most prevalent being prolonged P-wave duration (27.6%), QTc prolongation (18.7%), minor T-wave abnormalities (17.9%), first degree atrioventricular block (12.7%), and myocardial infarction (6.7%). Eight out of 9 (88.9%) myocardial infarctions and all cases of (significant) QTc prolongation (100%) were previously undiagnosed.

Conclusions

This study showed that ECG recording is feasible in the majority of older adults with ID and revealed a substantial underdiagnosis of ECG abnormalities. These results stress the importance of ECG recording and warrant further research into the yield of opportunistic ECG screening in older adults with ID.

INTRODUCTION

Older adults with intellectual disabilities (ID) are at high risk of cardiovascular diseases (CVD) [51]. They have increased CVD risk due to syndrome-specific risk factors, such as Prader–Willi syndrome [24, 118] and cerebral palsy [230]. Furthermore, the high prevalence of psychotropic drug use, such as antipsychotics, increases the CVD risk of older adults with ID [27, 33]. In addition, compared to the general population, several CVD risk factors are more common in older adults with ID, such as hypertension [34], type 2 diabetes [34], obesity [34, 36], metabolic syndrome [37], and physical inactivity [39]. Finally, as the life expectancy of older adults with ID increases [9, 10] the burden of age-related CVD is growing.

Despite the high prevalence of CVD risk factors, research suggests that the prevalence of CVD in older adults with ID is equal to that in the general population [51, 69]. These studies were based on prevalence rates from retrospective medical records. However, it is known that diagnostic work-up for CVD in older adults with ID is challenging as they may exhibit atypical presentation of symptoms, may experience limitations articulating health problems, and may exhibit limited cooperation and capacity during physical examination [67]. Referral policies for this vulnerable group are made with the greatest possible care and in consultation with physicians, representatives, healthcare staff, and others involved, which can sometimes lead to, for example, the choice to refrain from further diagnosis in the interest of the individual's quality of life [68]. As a result, this increases the likelihood of underdiagnosis in older adults with ID [51, 65, 67, 69]. This is also supported by previous research on peripheral arterial disease (PAD), which showed a higher prevalence of PAD in older adults with ID compared to the general population (17.4% versus 8.1%; respectively) and a high degree of underdiagnosis in older adults with ID (97% had not been previously diagnosed with PAD) [70].

To limit underdiagnosis of CVD in older adults with ID, it would be beneficial to use objective measures such as the electrocardiogram (ECG). An ECG allows to detect a wide range of cardiac abnormalities, including myocardial infarction, left ventricular hypertrophy, arrhythmias, and conduction abnormalities [71]. An ECG is easily made, low cost, and widely applicable in the general population [72]. The feasibility of ECG recording in older adults with ID, however, may not be self-evident and has not been previously studied in this specific group. Lying still may be challenging due to tics, restlessness, anxiety, or limited ability to follow instructions. This may have consequences for the feasibility and interpretability of the ECG. In addition, the prevalence of ECG abnormalities in older adults with

ID has been sparsely studied. Most available studies enrolled children or adults, but not older adults, and specifically targeted on certain syndromes such as Down syndrome [74, 75], Prader-Willi syndrome [76], and Williams Syndrome [77, 78], or on specific groups such as those with severe motor and intellectual disabilities [79]. Nevertheless, to our knowledge, such studies are lacking in older adults with ID.

More insight into the feasibility of ECG recording and the prevalence of ECG abnormalities in older adults with ID may contribute to screening, diagnostic protocols and (preventive) therapy to improve cardiovascular health in this specific group. Therefore, the aims of this study were to 1) investigate the feasibility of resting ECG recording, 2) study the prevalence of ECG abnormalities, and 3) compare the frequency of ECG abnormalities with medical records in older adults with ID.

METHODS

Study design and participants

This study is part of the Healthy Ageing and Intellectual Disabilities (HA-ID) study. The HA-ID study is a prospective multicentre cohort study on physical and mental health of older adults with ID who use formal ID care and support. A detailed description of the design and recruitment of the HA-ID study has been published previously [12, 231]. The data collection of the HA-ID study was conducted in the three participating ID care organisations (Abrona, Amarant, and Ipse de Bruggen), which provide support to a wide spectrum of people with borderline to profound ID in different care settings across the Netherlands. All older adults with ID who received care or support from one of these care organisations, and who were 50 years or older on September 1, 2008, were invited to participate. Ultimately, 1050 out of 2322 (45.2%) invitees agreed to participate in the baseline measurements in 2008-2009. All 429 participants who still received care from one of the three participating care organisations on July 1, 2020 and consented to be contacted for participation were invited for the follow-up measurements. Data were collected between October 2020 and July 2023.

A behavioural scientist evaluated whether eligible participants were capable of understanding the study information and able to provide informed consent to participate. If participants were incapable of providing informed consent, informed consent was obtained from their legal representative. Efforts were made to inform the older adults with ID who were incapable of providing consent

themselves, using easy to read information letters and oral information provided by the participant's professional caregiver. Participants or their legal representatives could give consent for all measurements including the physical examination or only for questionnaire and medical record review. Ethical approval was obtained from the Medical Ethics Review Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2019-0562). The study is registered in the Dutch Trial Register (NTR number: NL8564, https://onderzoekmetmensen.nl/nl/trial/28611) and follows the guidelines of the Declaration of Helsinki [155].

Data collection

Participant characteristics

Demographics

Data on age and sex were collected from the administrative electronic systems of the care organisations. Information about the level of ID was collected from behavioural records and categorised as borderline, mild, moderate, severe, or profound based on the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) [2]. Information on the presence of Down syndrome (yes/no) was retrieved from the participant's medical record. Data on residential status (central setting, community based, independent with ambulatory support, with relatives), and mobility (independent, with walking aid, wheelchair) were collected through a questionnaire completed by the participant's professional caregiver.

Medical record data

At the time of the ECG recording, a review of the participants' available medical records was conducted by research assistants to check for a history of angina pectoris, myocardial infarction, heart failure, atrial fibrillation, QTc prolongation, coronary revascularisation, cardiac pacemaker, congenital heart disease, valvular heart disease, stroke, and medication use.

Cardiovascular disease risk factors

Blood pressure was measured three times after at least 2 min of rest in seated position using the Mobil-O-Graph (I.E.M. GmbH, Stolberg, Germany); if this was unsuccessful, blood pressure was measured manually or electrically with another available blood pressure monitor. Hypertension was defined as a mean systolic blood pressure ≥140 mm/Hg or a mean diastolic blood pressure ≥90 mm/Hg [232] or the use of blood pressure lowering drugs. Measuring tape was used to measure waist and hip circumference. 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 diametre around the buttocks. Females with a waist-to-hip ratio of ≥0.85 and males with a waist-to-hip ratio of ≥0.90 were classified as obese [233]. Vena puncture was performed after an overnight fast and samples were analysed to determine hypercholesterolemia (total cholesterol >4 mmol/L and low-density lipoprotein (LDL-C) ≥ 2.6 mmol/L [234] or the use of lipid lowering drugs) and diabetes mellitus (fasting glucose ≥7 mmol/L, and/or HbA1c ≥48 mmol/mol [235] or the use of glucose lowering drugs). Data on current daily smoking were collected through a questionnaire completed by the participant's professional caregiver.

ECG recording

According to the standard method used in clinical practice, recording of a 10-second 12-lead resting ECG was attempted in all participants using a Welch Allyn CardioPerfect or a Bionet Cardio 7 electrocardiograph. ECGs were recorded with a sampling rate of at least 500 Hz and digitally stored. Trained professionals, working in the care organisations and experienced in performing ECG recordings and working with older adults with ID, performed the ECGs. All ECGs were performed within the care organisations in a setting close to where the participants live. If a participant showed any kind of resistance, recording was stopped.

ECG analysis

The ECG analysis mainly focused on abnormalities with direct clinical consequences and abnormalities associated in the literature with increased risk of CVD morbidity and mortality. All ECGs were reviewed by a cardiologist (M.J.G.L) for the presence of the following ECG abnormalities: atrial fibrillation or flutter, atrioventricular blocks, bundle branch blocks, Wolff-Parkinson-White syndrome, suspected prior myocardial infarction, left ventricular hypertrophy, and right ventricular hypertrophy. In case of an actionable ECG finding, the participant's treating physician was informed.

Additionally, ECGs were analysed using the Modular ECG Analysis System (MEANS) [236]. MEANS provides automatic ECG measurement and diagnostic interpretation and coding, and has extensively been validated previously [237-239]. In this study, MEANS was used to determine premature ventricular complexes, premature atrial complexes, heart rate (HR) in beats per minute (bpm), bradycardia (HR <60 bpm) [240], tachycardia (HR >100 bpm) [240], left axis deviation (frontal QRS axis -30° to -90°) [241], right axis deviation (frontal QRS axis 90° to 180°) [241], extreme axis deviation (frontal QRS axis -90° to -180°) [241], prolonged P-wave duration (>120 milliseconds (ms)) [242], short PR interval (<120 ms) [240], prolonged QRS duration (>120 ms) [240], abnormal frontal P-wave axis (<0° or >75°) [243], QTc prolongation

(based on Bazett's formula [244]; women >470 ms, men >450 ms) [245], significant QTc prolongation (>500 ms) [246], abnormal frontal T-wave axis (<15° or >75°) [247], and abnormal spatial QRS-T angle (>135°) [248]. ECGs were also coded according to the Minnesota Code (MC) [249] to examine major Q-wave abnormalities (MC 1-1, 1-2), minor Q-wave abnormalities (MC 1-3), major ST-segment depression (MC 4-1, 4-2), minor ST-segment depression (MC 4-3), major T-wave abnormalities (MC 5-1, 5-2), and minor T-wave abnormalities (MC 5-3). Outliers of MEANS results were verified by a cardiologist (M.J.G.L.).

If there was ECG evidence of prior myocardial infarction, atrial fibrillation or (significant) QTc prolongation in the absence of this ECG diagnosis in the participant's medical record, this was classified as a previously undiagnosed ECG diagnosis.

Feasibility ECG recording

In order to assess the feasibility of the ECG recordings, the number of participants who took part in the physical examination was taken as the baseline population. In this baseline population, an ECG was attempted with all participants. Feasibility of the ECG recording was assessed in two steps. First, if an ECG could not be recorded, reasons for dropout of the ECG recording were systematically recorded as follows: 1) physical disability, 2) fear of the ECG recording, 3) incapable of understanding the instructions, 4) not wanting to participate, and 5) other reasons (essay question). Second, for all ECGs obtained, the quality of the recordings was examined. Lying still during the recording may be challenging for individuals with ID. For this reason, we specifically looked at the number of ECGs that were deemed of insufficient quality due to motion artifacts. The quality of the ECG recordings was expressed separately for the assessment through the independent cardiologist and through MEANS using three categories: 1) interpretable, 2) partially interpretable, and 3) not interpretable. Finally, we classified a participant's ECG recording as feasible if the ECG recording could be made (no dropout of the ECG recording) and if the ECG was partially or in whole deemed interpretable by both the cardiologist and MEANS. A feasibility percentage was calculated, which expresses the percentage of the baseline population for whom ECG recording was feasible.

Statistical analysis

We provide descriptive statistics for the total study population that took part in the physical examination, and separately for participants with and without feasible ECG recordings. Differences in participant characteristics between participants with and without feasible ECG recordings were analysed with independent t-tests

for continuous variables, fisher's exact tests (2-sided) for binary variables and chi-square tests for categorical variables. Statistical significance was set at $p<0.05$. Descriptive statistics were used to describe the prevalence of ECG abnormalities among participants with an interpretable ECG and medical record review. We present previously undiagnosed ECG abnormalities as differences between prevalence figures from ECG recording and prevalence figures from medical record review. Analyses were performed using IBM SPSS statistics version 28.0 (IBM Corporation, New York).

RESULTS

Feasibility ECG recording

Of the 429 invited older adults with ID, 278 provided consent to participate in the HA-ID study. Of these, 222 gave permission to participate in the physical examination and 200 participants actually underwent the physical examination. Of these 200 participants, 136 (68.0%) successfully underwent ECG recording and 64 (32.0%) did not have an ECG recording due to a physical disability (n=14; 7.0%), resistance to the ECG recording (n=7; 3.5%), fear of the ECG recording (n=4; 2.0%), incapability to understand the instructions (n=3; 1.5%), or other reasons including restlessness, technical issues, and problems with staffing (n=8; 4.0%). The reason for not participating was unknown for 28 participants (14.0%).

A total of 121 (89.0%) of the ECGs reviewed by the cardiologist were categorised as interpretable, 14 (10.3%) were categorised as partially interpretable, and 1 (0.7%) as not interpretable. MEANS categorised 120 (88.2%) ECGs as interpretable, 15 (11.0%) as partially interpretable, and 1 (0.7%) as not interpretable. The cardiologist and MEANS both categorised one, but not the same, ECG recording as not interpretable, resulting in a total of two uninterpretable ECGs. When both the success rate of the ECG recording and the quality of the ECGs were considered, ECG recording appeared to be feasible in 134 of the 200 participants (67.0%) (Figure 1).

Participant characteristics

Table 1 shows the characteristics of the 200 participants who took part in the physical examination, together and separately for participants with (n=134) and without (n=66) feasible ECG recordings. Participants for whom ECG recording was feasible had significantly more often mild ID (20.9% versus 10.6%) and less often severe ID (11.9% versus 33.3%) compared to participants without a feasible ECG (p=0.01). They used more often a walking aid (34.0% versus 13.2%) and less often

a wheelchair (5.5% versus 31.6%) compared to participants without a feasible ECG recording (p<0.001). Participants for which ECG recording was feasible had significantly less often a history of stroke (7.1% versus 13.5%; p=0.04) and less often congenital heart disease (1.6% versus 7.6%; p=0.046) compared to participants for which ECG recording was not feasible. No significant differences were found between participants with and without a feasible ECG recording for the other characteristics.

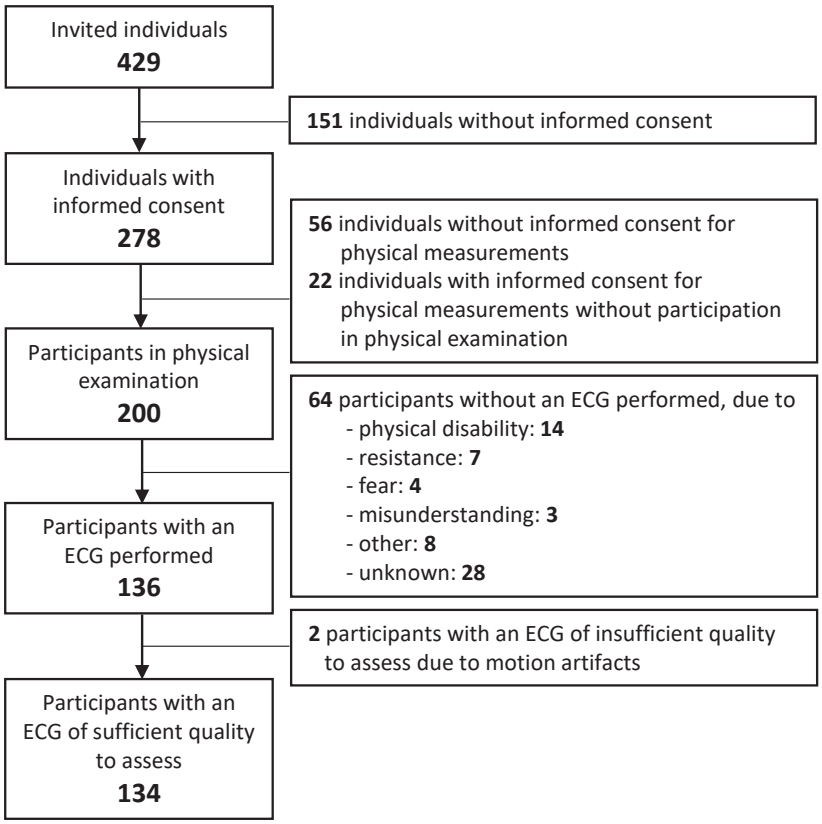

Figure 1 Feasibility of ECG recording among older adults with intellectual disabilities

The mean age of the 134 participants with a (partially) interpretable ECG recording was 70.6 years (standard deviation (SD) 5.7; range 62-91 years) and 52.2% were women. Down syndrome was diagnosed in 4.5% of these participants. In this group the following prevalence of CVD risk factors were found: hypertension (48.5%), obesity (59.7%), and hypercholesterolemia (62.7%).

Table 1 Participant characteristics of the study sample of older adults with intellectual disabilities

	Total study sample (n=200)	**Feasible ECG** (n=134)	**Not feasible ECG** (n=66)	***p*-value**
Age, mean (SD) (n=200; 134; 66)	70.7 (5.7)	70.6 (5.7)	70.8 (5.7)	0.81
Women, *n* (%) (n=200; 134; 66)	99 (49.5%)	70 (52.2%)	29 (43.9%)	0.30
Level of ID, *n* (%) (n=197; 131; 66)				**0.01**
Borderline	11 (5.6%)	7 (5.3%)	4 (6.1%)	
Mild	35 (17.8%)	28 (21.4%)	7 (10.6%)	
Moderate	97 (49.2%)	69 (52.7%)	28 (42.4%)	
Severe	38 (19.3%)	16 (12.2%)	22 (33.3%)	
Profound	16 (8.1%)	11 (8.4%)	5 (7.6%)	
Residential status, *n* (%) (n=196; 130; 66)				0.22
Central setting	106 (54.1%)	65 (50.0%)	41 (62.1%)	
Community based	89 (45.4%)	64 (49.2%)	25 (37.9%)	
Independent with ambulatory support	1 (0.5%)	1 (0.8%)	0 (0%)	
With relatives	0 (0%)	0 (0%)	0 (0%)	
Down syndrome, *n* (%) (n=194; 129; 65)	12 (6.2%)	6 (4.7%)	6 (9.2%)	0.22
Mobility, *n* (%) (n=129; 91; 38)				**<0.001**
Independent	76 (59.0%)	55 (60.4%)	21 (55.3%)	
With walking aid	36 (27.9%)	31 (34.0%)	5 (13.2%)	
Wheelchair	17 (13.2%)	5 (5.5%)	12 (31.6%)	
Waist to hip ratio, mean (SD) (n=158; 116; 42)	0.9 (0.1)	0.9 (0.2)	0.9 (0.1)	0.28
Obesity, *n* (%) (n=158; 116; 42)	113 (71.5%)	80 (69.0%)	33 (78.6%)	0.33
Current smoking, *n* (%) (n=153; 113; 40)	21 (13.7%)	16 (14.2%)	5 (12.5%)	1.00
Hypertension, *n* (%) (n=199; 133; 66)	92 (46.2%)	65 (48.9%)	27 (40.9%)	0.30
Hypercholesterolemia, *n* (%) (n=197; 131; 66)	120 (60.9%)	84 (64.1%)	36 (54.5%)	0.22
Diabetes mellitus, *n* (%) (n=198; 132; 66)	25 (12.6%)	19 (14.4%)	6 (9.1%)	0.37

Table 1 Continued

	Total study sample (n=200)	Feasible ECG (n=134)	Not feasible ECG (n=66)	*p*-value
Angina pectoris, *n* (%) (n=190; 127; 63)	3 (1.6%)	2 (1.6%)	1 (1.6%)	1.00
History of myocardial infarction, *n* (%) (n=193; 127; 66)	4 (2.1%)	3 (2.4%)	1 (1.5%)	0.25
History of heart failure, *n* (%) (n=195; 129; 66)	7 (3.6%)	4 (3.1%)	3 (4.5%)	0.69
History of coronary revascularisation, *n* (%), (n=192; 127; 65)	3 (1.6%)	3 (2.6%)	0 (0%)	0.55
Cardiac pacemaker, *n* (%) (n=195; 129; 66)	1 (0.5%)	1 (0.8%)	0 (0%)	1.00
Congenital heart disease, *n* (%) (n=195; 129; 66)	7 (3.6%)	2 (1.6%)	5 (7.6%)	**0.046**
Valvular heart disease, *n* (%) (n=195; 129; 66)	9 (4.6%)	3 (2.3%)	6 (9.1%)	0.06
History of stroke, *n* (%) (n=193; 127; 66)	15 (7.8%)	6 (7.1%)	9 (13.5%)	**0.04**
Use of antipsychotics, *n* (%) (n=182; 123; 59)	32 (17.6%)	20 (16.3%)	12 (20.3%)	0.54
Use of antidepressants, *n* (%) (n=182; 123; 59)	18 (9.9%)	11 (8.9%)	7 (11.9%)	0.60
Use of beta blockers, *n* (%) (n=182; 123; 59)	14 (7.7%)	12 (9.8%)	2 (3.4%)	0.23

ECG = electrocardiogram; ID = intellectual disability; n = number of participants; *p*-value = $p<0.05$ is statistically significant; SD = standard deviation

ECG abnormalities

Of the 134 participants with a feasible ECG, 103 (76.9%) had one or more ECG abnormalities. The most prevalent ECG abnormalities identified by the cardiologist were first degree atrioventricular block (12.7%; 95%CI 7.6-19.5%), prior myocardial infarction (6.7%; 95%CI 3.1-12.4%), left bundle branch block (3.7%; 95%CI 1.2-8.5%), right bundle branch block (3.7%; 95%CI 1.2-8.5%), and incomplete right bundle branch block (3.7%; 95%CI 1.2-8.5%) (Table 2). The most prevalent ECG abnormalities identified by MEANS were prolonged P-wave duration (27.6%; 95%CI 20.3-36.0%), (significant) QTc prolongation (18.7%; 95%CI 12.5-26.3%), and minor T-wave abnormalities (17.9%; 95%CI 11.8-25.5%) (Table 2). In five participants one or more premature ventricular complexes were observed: three participants had a single premature ventricular complex and two participants had three premature ventricular complexes. At least one premature atrial complex was found in two participants: one participant had one premature atrial complex, the other two. The mean resting heart rate of the participants was 74 bpm (SD 14, range 46-118). In one participant, an ectopic atrial rhythm was found.

Table 2 Prevalence ECG abnormalities among older adults with intellectual disabilities

	n=134, *n* (%; 95%CI)
Assessed by cardiologist	
Arrhythmias	
Atrial fibrillation	3 (2.2%; 0.5-6.4%)
Conduction abnormalities	
First degree atrioventricular block	17 (12.7%; 7.6-19.5%)
Second or third degree atrioventricular block	0 (0%)
Left bundle branch block	5 (3.7%; 1.2-8.5%)
Right bundle branch block	5 (3.7%; 1.2-8.5%)
Incomplete right bundle branch block	5 (3.7%; 1.2-8.5%)
Bifascicular block	2 (1.5%; 0.2-5.3%)
Trifascicular block	1 (0.7%; 0.02-4.1%)
Wolff-Parkinson-White syndrome	0 (0%)
QRS abnormalities	
Myocardial infarction	9 (6.7%; 3.1-12.4%)
Left ventricular hypertrophy	2 (1.5%; 0.2-5.3%)
Right ventricular hypertrophy	0 (0%)
Assessed by MEANS	
Arrhythmias	
Premature ventricular complexes	5 (3.7%; 1.2-8.5%)
Premature atrial complexes	2 (1.5%; 0.2-5.3%)
Frequency abnormalities	
Bradycardia	19 (14.2%; 8.8-21.3%)
Tachycardia	4 (3.0%; 0.8-7.5%)
QRS axis deviation	
Left	14 (10.5%; 5.8-16.9%)
Right	1 (0.7%; 0.02-4.1%)
Extreme	8 (6.0%; 2.6-11.4%)
Conduction abnormalities	
Prolonged P-wave duration	37 (27.6%; 20.3-36.0%)
Short PR interval	0 (0.0%)
Prolonged QRS duration	14 (10.4%; 5.8-16.9%)

Table 2 Continued

	n=134, *n* (%; 95%CI)
Depolarisation abnormalities	
Abnormal frontal P-wave axis	4 (3.0%; 0.8-7.5%)
Major Q-wave abnormalities	18 (13.4%; 8.2-20.4%)
Minor Q-wave abnormalities	10 (7.5%; 3.6-13.3%)
Repolarisation abnormalities	
QTc prolongation	23 (17.2%; 11.2-24.6%)
Significant QTc prolongation	2 (1.5%; 0.2-5.3%)
Abnormal frontal T-wave axis	20 (14.9%; 9.4-22.1%)
Abnormal spatial QRS-T angle	13 (9.7%; 5.3-16.0%)
Major ST-segment depression	10 (7.5%; 3.6-13.3%)
Minor ST-segment depression	9 (6.7%; 3.1-12.4%)
Major T-wave abnormalities	13 (9.7%; 5.3-16.0%)
Minor T-wave abnormalities	24 (17.9%; 11.8-25.5%)

ECG = electrocardiogram; n = number of participants; 95%CI = 95% confidence interval

All 3 participants with atrial fibrillation during ECG recording already had a clinical history thereof. Another participant had a history of atrial fibrillation but displayed sinus rhythm during ECG recording. In nine participants, prior myocardial infarction was suspected based on the ECG recording. Eight of these participants did not have diagnosis history thereof in their medical records. In two participants a diagnosis of myocardial infarction was reported in the medical record, but not visible in the ECG recording. In 25 participants, QTc prolongation was noted. Two participants had a significantly prolonged QTc interval >500 ms. None of these participants had this diagnosis in their medical records.

DISCUSSION

We studied the feasibility of resting ECG recording, the prevalence of ECG abnormalities, and the prevalence of undiagnosed ECG abnormalities when compared to medical records in older adults with ID. ECG recording was feasible in 67.0% of the older adults with ID. Feasibility was lower with increasing severity of ID and for wheelchair users. Among participants with a feasible ECG recording, 76.9% had one or more ECG abnormalities, with the most prevalent being prolonged

P-wave duration (27.6%), (significant) QTc prolongation (18.7%), minor T-wave abnormalities (17.9%), first degree atrioventricular block (12.7%), and suspected prior myocardial infarction (6.7%). Eight out of nine (88.9%) myocardial infarctions and all cases of (significant) QTc prolongation (100%) were previously undiagnosed.

The present study shows that ECG recording is feasible in the majority of older adults with ID. In some subgroups we found lower feasibility, such as participants with a severe level of ID and participants who are dependent on a wheelchair. We also found several reasons that negatively affect the feasibility of ECG recording, such as the presence of a physical disability, resistance, fear, difficulty understanding the instructions, and restlessness. Therefore, to increase the likelihood of a successful ECG recording in this specific population, training and experience with people with ID is important (such as for providing a suitable explanation of the measurement and handling any fear or restlessness), which might not be available in every clinical setting. During the day of the ECG recording, the participants took part in several (physical) measurements in different rooms and by different professionals. This data collection method was demanding for some participants, which may have contributed to the feasibility of the ECG recording. Besides, some ECGs were not performed because of technical issues, problems with staffing or because the correct raising aid was not available to match the participant's physical limitations. In addition, if a participant showed any kind of resistance, recording was immediately stopped. Contrary to daily clinical practice, a second attempt of making an ECG was not tried in case of for example resistance. In short, in the current study clear predefined protocols were followed, whereas in clinical practice additional efforts may be made to ensure the success of the recording. For these reasons, the actual feasibility of ECG recording in older adults with ID in clinical practice might be even higher than the 67% found in this study.

There has been limited research on the prevalence of ECG abnormalities in older adults with ID, which complicates comparing our results with other studies in this specific group. The existing studies enrolled children or adults, but not older adults, and specifically targeted on certain syndromes such as Down syndrome [74, 75], Prader–Willi syndrome [76] and Williams Syndrome [77, 78], or on specific groups such as those with severe motor and intellectual disabilities [79]. These studies yielded high prevalence rates of various ECG abnormalities compared to the general population, such as QTc prolongation.

To study whether certain ECG abnormalities occur less or more often in older adults with ID, we compared the results of our study with the general elderly population. The prevalence rate of prior myocardial infarction found in our study (6.7%) does

not appear to deviate remarkably from the diverse prevalence rates observed in the older general population, which range from 3.0% [250] to 11.6% [130, 251]. Since the literature describes that certain CVD risk factors are more common among older adults with ID [34], we had anticipated a higher prevalence of prior myocardial infarction in our cohort. A potential explanation for the absence of this finding is the similar prevalence of CVD risk factors such as hypertension and diabetes in our study sample compared to the general older population [40], which may have arisen due to survival bias in our follow-up study. Compared to the prevalence rate of atrial fibrillation in our cohort (2.2%), we found several studies describing comparable prevalence rates of this condition in the general older population [131, 250, 252-259]. Based on these findings, the prevalence of prior myocardial infarction and atrial fibrillation in our cohort of older adults with ID appears to be similar to that in the general elderly population.

The prevalence of QTc prolongation we found (18.7%) is high compared to studies in older adults in the general population, where prevalence figures of 5.7% [250] and 6.7% [260] are described. Only few participants had significantly prolonged QTc (>500 ms; n=2, 1.5%). A possible explanation is the high prevalence of QTc-prolonging psychotropic drug use in older adults with ID [27, 33]. Many psychotropic drugs, such as antidepressants and antipsychotics, can delay cardiac repolarisation as measured by the QT interval [30]. Of the 25 participants with QTc prolongation in our study, more than one third used antidepressants and/or antipsychotics, including one of the two participants with significant QTc prolongation.

Contrary to being a rare ECG abnormality in the general population [261], we found a prevalence of 6.0% for extreme axis deviation in our cohort of older adults with ID. Of the eight participants with extreme axis deviation, one participant had a pacemaker and one participant had misplaced limb electrodes which can both explain the extreme axis deviation. Some congenital heart defects are also associated with extreme axis deviation. Although many congenital heart defects are more prevalent in people with ID [122], of the remaining six participants, only one had a congenital heart defect (dextrocardia) listed in the medical record.

We found an underdiagnosis of prior myocardial infarction of 88.9%, a twice as high percentage compared to cohort studies in the general population, in which values of undiagnosed myocardial infarctions are reported up to 44% [262, 263]. People with a history of myocardial infarction are at increased risk of recurrent cardiovascular complications [263], with similar prognoses for people with diagnosed and undiagnosed myocardial infarctions [262, 264, 265].

For QTc prolongation we found an even higher underdiagnosis rate of 100%. QTc prolongation predisposes to life-threatening ventricular arrhythmia [31] and may result from psychotropic drug use [30]. For this reason, the Dutch Multidisciplinary Guideline on Problem Behaviour in adults with ID recommends ECG monitoring for psychotropic drug prescriptions that are associated with QTc prolongation in combination with the presence of other risk factors [73]. The high degree of underdiagnosis of both myocardial infarction and QTc prolongation found in this study underlines the importance of performing ECGs in older adults with ID, which may aid to prevent further cardiovascular complications. The European Society of Cardiology already recommends opportunistic screening through ECG recording for atrial fibrillation for people aged 65 years and over [266].

To our knowledge this is the first study that investigated the feasibility of resting ECG recording and the prevalence and underdiagnosis of ECG abnormalities in older adults with ID. Strengths of this study are the unselected sample of asymptomatic older adults with ID who use formal ID care and support, the data collection in a setting familiar and close to where the participants live within the participating care organisations, and the use of ECG recording as an objective assessment in addition to medical record review. However, some limitations should be noted.

Due to the sample size, we found wide confidence intervals around the prevalence rates, and we were unable to examine differences between subgroups, such as differences between men and women, level of ID, comorbidities, and specific medication use. Besides, we were not able to make a comparison between the total invited group of older adults and the group that participated in the ECG recording. In addition, due to limited data availability from the medical record review, the present study focused solely on the possible underdiagnosis of atrial fibrillation, myocardial infarction, and QTc prolongation. Finally, dropout during the ECG recording resulted in an overrepresentation of participants with mild ID and participants who used a walking aid and consequently an underrepresentation of participants with severe ID and participants who were wheelchair dependent. When interpreting the findings of this study, it is important to take these points into account.

In future research, it would be advantageous to use larger sample sizes, allowing more accurate estimates of the prevalence of ECG abnormalities, and potentially looking into subgroups. Regarding (research into) the feasibility of ECG recording in older adults with ID, it would be beneficial to consider specific factors. These include conducting the ECG recording in a quiet and familiar environment for the

participant, selecting a time of day comfortable for the participant, performing the recording with patience by someone experienced in working with older adults with ID, ensuring the presence of a trusted person, providing suitable raising aids, and undertaking additional attempts or follow-up research as deemed necessary.

This study showed that ECG recording is feasible in the majority of older adults with ID and revealed a substantial underdiagnosis of ECG abnormalities in clinical practice. Given that early detection of ECG abnormalities may increase the opportunity of taking appropriate preventive measures, we would like to emphasise the feasibility and importance of ECG recording in this group, and warrant further research into the yield of opportunistic ECG screening in older adults with ID.

CHAPTER 5

Associations between physical fitness and cardiovascular disease in older adults with intellectual disabilities: Results of the Healthy Ageing and Intellectual Disability study

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ABSTRACT

Background

Reduced physical fitness is a cardiovascular disease (CVD) risk factor in the general population. However, generalising these results to older adults with intellectual disabilities (ID) may be inappropriate given their pre-existing low physical fitness levels and high prevalence of comorbidities. Therefore, the aim of this study is to investigate the difference in physical fitness between older adults with ID with and without CVD.

Method

Baseline data of a cohort of older adults with borderline to profound ID (HA-ID study) were used (n=684; 61.6 ± 8.2yr; 51.3% male). CVD status (coronary artery disease, heart failure, stroke) was obtained from medical files. Cardiorespiratory fitness (10-m incremental shuttle walking test), comfortable and fast gait speed (over 5 m distance), and grip strength (hand dynamometer) were measured. Multivariable linear regression models were used to investigate the association between these physical fitness components and the presence of CVD, adjusted for participant characteristics.

Results

Of the 684 participants 78 (11.4%) had CVD. Participants with CVD scored lower on cardiorespiratory fitness (-81.4m; p=0.002), comfortable gait speed (-0.3km/h; p=0.04), and fast gait speed (-1.1km/h; p=0.04). No significant differences were found for grip strength (-0.2kg; p=0.89).

Conclusions

Older adults with CVD had significantly lower physical fitness levels than those without CVD, except for grip strength. Longitudinal research is needed to investigate causality.

INTRODUCTION

Cardiovascular diseases (CVD), including coronary artery disease, heart failure, and stroke, account for almost one-third of all deaths worldwide [13]. These diseases are not only an important health issue for the population at large; they are also associated with high morbidity and mortality in people with intellectual disabilities (ID) [122, 267]. Several studies, mainly based on retrospective medical file research, suggest that the prevalence and incidence of CVD in older people with ID are equal to that in the general population [51, 69].

Risk factors for CVD include hypertension, hypercholesterolemia, diabetes, smoking, obesity, and family history of premature CVD [234]. Compared to the general population, hypertension [34], diabetes [34], and obesity [34, 36] are more often present in people with ID. CVD risk factors are especially common in people with a mild level of ID, who live more independently, and make their own lifestyle decisions [40]. Furthermore, some people with ID have increased CVD risk due to syndrome-specific risk factors, such as people with Prader–Willi syndrome [24, 118] and cerebral palsy [230].

Research in the general population showed that physical fitness [52, 53], especially cardiorespiratory fitness [54-56], is an important factor in the risk of CVD. Also, slow gait speed [57, 58] and low grip strength [59, 60] are predictive for a higher risk of CVD and cardiovascular mortality. These results may not be generalisable to people with ID in whom very low physical fitness levels have been found [61-63]. The physical fitness levels of older adults with ID, aged 50 years and over, were comparable to, or even worse than, those of adults in the general population who were 20 years older [61]. Given these overall low physical fitness levels, combined with the high prevalence of comorbidities at a younger age [64], physical fitness might be less discriminative between people with ID with and without CVD.

Therefore, this study investigated the difference in physical fitness levels between older adults with ID with and without CVD. We hypothesised that adults with CVD had significantly lower physical fitness levels than those without CVD for the physical fitness components cardiorespiratory fitness, gait speed, and grip strength.

METHODS

Study design and participants

Baseline data from the Healthy Ageing and Intellectual Disability (HA-ID) study were used. The HA-ID study is a prospective multicentre cohort study on the physical and mental health of older adults with ID who use formal ID support. A detailed description of the design and recruitment of the HA-ID study has been published elsewhere [12]. Currently the 10-year follow-up of the HA-ID study is being performed [231]. However, in the present study we will focus on the baseline data only. The data collection of the HA-ID study was conducted in three participating ID care organisations (Abrona, Amarant and Ipse de Bruggen) that provide support to a wide spectrum of individuals with ID in different care settings in the Netherlands. All individuals with ID who received care or support from one of these three care organisations, and who were 50 years or older on September 1, 2008, were eligible to participate and received an invitation. All data were collected between February 2009 and July 2010.

Two separate consent procedures were followed. A behavioural scientist evaluated whether potential participants were able to understand the study information and to make an informed decision about participation. If yes, they were sent an easy-to-read information letter with supporting pictures and consent form, and signed the consent form themselves. For individuals who were unable to give informed consent, informed consent was requested from their legal representative. Efforts were made to inform the individuals who could not provide consent themselves. At all times, resistance by the participant to parts of the measurements were leading in deciding to perform the measurements.

To assure safe participation to the physical fitness test, the Revised Physical Activity Readiness Questionnaire (PAR-Q) was administered by professional caregivers prior to the data collection [268].

If any of the questions were answered with 'yes' or 'unknown' the physician of the participant was consulted to determine whether the participant could safely take part in the physical fitness measurements.

Ethical approval was obtained from the Medical Ethics Review Committee of the Erasmus MC, University Medical Center Rotterdam (MEC-2008-234). This study follows the guidelines of the Declaration of Helsinki [155].

Measurements

Participant characteristics

Data on age and sex were collected from the administrative electronic systems of the care organisations. Data about residential status (central setting, community based, independent with ambulatory support, with relatives) were collected through a questionnaire completed by the participant's professional caregiver. Information about the level of ID was collected from psychologists' and behavioural therapists' files and categorised as borderline (intelligence quotient (IQ)=70-80), mild (IQ=55-70), moderate (IQ=35-55), severe (IQ=25-35), or profound (IQ<25) based on the International Classification of Diseases (ICD-10) criteria [269]. Information on the presence of Down syndrome (yes, no, unknown) was retrieved from the participant's medical file.

Cardiovascular disease and CVD risk factors

The participant's personal physician was asked to provide information about whether the participant had ever been diagnosed with coronary artery disease, heart failure, or stroke. The diagnoses were based on events or episodes in the participant's medical file. Participants with at least one of these three CVD diagnoses in their medical file were classified as having 'CVD'. Participants without one of these diagnoses in their medical file were classified as having 'no CVD'.

The following CVD risk factors were measured (exact procedures are described elsewhere [36, 40, 198]): hypertension (mean systolic blood pressure ≥140 mmHg, or a mean diastolic blood pressure ≥90 mmHg, or the use of blood pressure lowering drugs) [40], hypercholesterolemia (fasting serum total cholesterol >6.5 mmol/l or the use of lipid lowering drugs) [40], diabetes mellitus (fasting serum glucose >6.1 mmol/l or the use of glucose lowering drugs) [40], body mass index (BMI) [36], waist circumference [36], waist to hip ratio [36], metabolic syndrome (according to the criteria of the joint interim statement 2009) [37, 270], inflammation (elevated C-reactive protein >10 mg/L) [198], and chronic kidney disease (glomerular filtration rate according to the CKD-creatinine-cystatin-C equation <60 ml/min/1.73 m^2) [198, 271]. Data about smoking at least 1 cigarette/day (yes, no) were collected through a questionnaire completed by the participant's professional caregiver. Information on the use of antipsychotics was retrieved from the participant's medical file.

Physical fitness

Cardiorespiratory fitness was measured with the 10-m incremental shuttle walking test [161]. Participants walked back and forth on a 10-m course at increasing speed. They started at 0.50 m/s and the walking speed increased every minute by 0.17 m/s. The test ended when the participant failed to complete a 10-m shuttle within the allowed

time. The test was performed twice, and the test with the best effort (during which the participant attained the highest peak heart rate) was regarded as the best test and used in the analyses. The test score was the distance (m) covered by the participant during the test.

Gait speed was evaluated by measuring the time it took to cover 5m, after 3m for acceleration, with an additional 3m at the end for deceleration. Participants walked at comfortable gait speed and at fast gait speed [272]. Participants walked three times for each condition. For comfortable gait speed the three trials were averaged. For fast gait speed the fastest trial was the result. Gait speed was measured in m/s and converted into km/h.

Grip strength was measured with the Jamar Hand Dynamometer (#5030J1, Sammons Preston Rolyan, USA) [273]. Participants squeezed the dynamometer with maximum force in a seated position according to the recommendations of the American Society of Hand Therapists [273]. Three attempts were performed for both hands with one-minute rest in between. The test result was the maximal produced force in either one of the hands (in kg). A more detailed description of the tests and the execution can be found elsewhere [147]. The feasibility and reliability of these instruments is good in older adults with ID [203, 204], and validity and reliability have also been confirmed in the general population [161, 162, 274-277].

Physiotherapists, occupational therapists, and physical activity instructors with experience in working with people with ID conducted the physical fitness tests. Prior to data collection, all test instructors received an instruction manual and training for the execution of the tests. The test instructors were trained in the standardised instruction and execution of all the tests, and if a participant was not able to understand the test instructions or not able to execute the test according to the test description, the test was deemed invalid. All assessors were blinded for the participant's cardiovascular disease status. Participants had the opportunity to practice each test to make sure they understood the test.

Statistical analysis

Only participants with available medical file information about their CVD status who participated in the physical fitness tests were included in the statistical analysis. Descriptive statistics were used to describe the participant characteristics, presence of CVD risk factors and CVD, and the physical fitness levels. Differences in characteristics and physical fitness levels between participants with CVD and participants without CVD were analysed with independent t-tests for continuous variables and chi-square tests for categorical variables.

After assumptions were checked, multivariable linear regression models were used to investigate the association between the physical fitness components (dependent variables) and the presence of CVD (independent variable), adjusted for participant characteristics (age, sex, residential status, level of ID, and Down syndrome). For each of the four physical fitness components one multivariable linear regression model was build. All independent variables were entered into the multivariable regression model simultaneously. Multicollinearity was checked with the variance inflation factor (which had to be below 10) and tolerance values (which had to be higher than 0.1) [278]. Statistical significance was set at $p<0.05$. Analyses were performed using IBM SPSS statistics version 25.0 (IBM Corporation, New York).

RESULTS

Participant characteristics

Of the 2322 invited individuals, 1050 (45.2%) consented to participate and were included in the HA-ID cohort. Of the total cohort, 684 participants (65.1%) had complete data and were included in the analysis. Reasons for exclusion were the unavailability of medical file information (n=151; 14.4%) and non-participation in the physical fitness tests (n=233; 22.2%). Reasons for no participation in the physical fitness tests were not being able to walk and a lack of understanding of instructions or test execution, primarily by participants with a profound or severe level of ID.

Table 1 summarises the characteristics of the participants with and without a diagnosis of CVD in their medical file. The mean age of the study sample was 61.6 years (standard deviation 8.2), and 51.3% of the participants was male. Most of the participants lived in a central setting (54.2%) or in the community (41.1%) and had a mild (22.1%), moderate (52.8%), or severe (15.9%) level of ID. Down syndrome was diagnosed in 14.9% of the participants. Participants with CVD were significantly older than participants without CVD (mean difference 8.3 years; $p<0.001$) and had less often Down syndrome (3.8% versus 16.3% respectively; $p=0.01$).

Table 1 Baseline characteristics of the study sample

		CVD in medical file n=78 (11.4%)	**No CVD in medical file** n=606 (88.6%)	***p*-value**
Participant characteristics				
Age	Mean (SD)	69.1 (9.9)	60.8 (7.4)	**<0.001**
	50-59 years *n* (%)	12 (15.4%)	307 (50.7%)	
	60-69 years *n* (%)	30 (38.5%)	204 (33.7%)	
	70-79 years *n* (%)	27 (34.6%)	88 (14.5%)	
	80 + years *n* (%)	9 (11.5%)	7 (1.2%)	
Sex *n* (%)	Male	39 (50%)	312 (51.5%)	0.81
	Female	39 (50%)	294 (48.5%)	
Residential status *n* (%)	Central setting	42 (53.8%)	329 (54.3%)	0.90
	Community based	33 (42.3%)	248 (40.9%)	
	Independent with ambulatory support	2 (2.6%)	21 (3.5%)	
	With relatives	1 (1.3%)	4 (0.7%)	
	Unknown	0 (0%)	4 (0.7%)	
Level of ID *n* (%)	Borderline	3 (3.8%)	17 (2.8%)	0.87
	Mild	17 (21.8%)	134 (22.1%)	
	Moderate	43 (55.1%)	318 (52.5%)	
	Severe	11 (14.1%)	98 (16.2%)	
	Profound	2 (2.6%)	30 (5%)	
	Unknown	2 (2.6%)	9 (1.5%)	
Down syndrome *n* (%)	No	71 (91%)	484 (79.9%)	**0.01**
	Yes	3 (3.8%)	99 (16.3%)	
	Unknown	4 (5.1%)	23 (3.8%)	
CVD risk factors				
Hypertension *n* (%)	No	25 (32.1%)	307 (50.7%)	**0.002**
	Yes	53 (67.9%)	298 (49.2%)	
	Unknown	0 (0%)	1 (0.2%)	
Hypercholesterolemia *n* (%)	No	28 (35.9%)	351 (57.9%)	**<0.001**
	Yes	29 (37.2%)	102 (16.8%)	

Table 1 Continued

		CVD in medical file	**No CVD in medical file**	***p*-value**
		n=78 (11.4%)	n=606 (88.6%)	
	Unknown	21 (26.9%)	153 (25.2%)	
Diabetes mellitus *n* (%)	No	47 (60.3%)	396 (65.3%)	0.30
	Yes	10 (12.8%)	57 (9.4%)	
	Unknown	21 (26.9%)	153 (25.2%)	
BMI in kg/m^2	Mean (SD)	28.7 (5.0)	27.3 (5.2)	**0.03**
Waist circumference in cm	Mean (SD)	98.8 (11.4)	94.2 (13.4)	**0.005**
Waist to hip ratio	Mean (SD)	0.9 (0.1)	0.9 (0.1)	0.47
Smoking *n* (%)	No	49 (62.8%)	460 (75.9%)	**0.01**
	Yes	29 (37.2%)	146 (24.1%)	
	Unknown	0 (0%)	0 (0%)	
Use of antipsychotics *n* (%)	No	60 (76.9%)	446 (73.6%)	0.50
	Yes	17 (21.8%)	154 (25.4%)	
	Unknown	1 (1.3%)	6 (1%)	
Chronic kidney disease *n* (%)	No	33 (42.3%)	341 (56.3%)	**<0.001**
	Yes	17 (21.8%)	52 (8.6%)	
	Unknown	28 (35.9%)	213 (35.1%)	
Metabolic syndrome *n* (%)	No	14 (17.9%)	219 (36.1%)	**0.001**
	Yes	34 (43.6%)	184 (30.4%)	
	Unknown	30 (38.5%)	203 (33.5%)	
C-reactive protein (> 10 mg/L) *n* (%)	No	48 (61.5%)	397 (65.5%)	0.68
	Yes	8 (10.3%)	56 (9.2%)	
	Unknown	22 (28.2%)	153 (25.2%)	

CVD = cardiovascular disease (coronary artery disease, heart failure or stroke); n = number of participants; *p*-value = $p<0.05$ is statistically significant, SD = standard deviation; ID = intellectual disability; BMI = body mass index; kg/m^2 = kilogram per square metre; cm = centimetre.

Cardiovascular disease and CVD risk factors

Seventy-eight participants (11.4%) had at least one diagnosis of CVD in their medical file at the time of the physical fitness tests. In the medical files of these participants, a total of 18 diagnoses of coronary artery disease (2.6%), 26 diagnoses of heart

failure (3.8%), and 42 diagnoses of stroke (6.1%) were found. Four participants were diagnosed with heart failure and coronary artery disease, three participants with heart failure and stroke, and one participant with coronary artery disease and stroke.

Table 1 shows the presence of CVD risk factors of participants with and without CVD. Compared to participants without CVD, participants with CVD smoked significantly more often (37.2% versus 24.1% respectively; p=0.01), had a significantly higher BMI (28.7 versus 27.3 kg/m^2 respectively; p=0.03) and waist circumference (98.8 versus 94.2 cm respectively; p=0.005) and significantly more often had hypertension (67.9% versus 49.2% respectively; p=0.002), hypercholesterolemia (37.2% versus 16.8% respectively; p<0.001), chronic kidney disease (21.8% versus 8.6% respectively; p<0.001), and metabolic syndrome (43.6% versus 30.4% respectively; p=0.001).

Physical fitness and cardiovascular disease

The unadjusted physical fitness scores of the participants with and without CVD are presented in Table 2. Participants with CVD had significantly lower scores on cardiorespiratory fitness (136.9 m versus 244.1 m respectively; p<0.001), comfortable gait speed (2.8 km/h versus 3.5 km/h respectively; p<0.001), and fast gait speed (4.7 km/h versus 6.5 km/h respectively; p=0.002) compared to participants without CVD. No significant difference was found between the two groups for the physical fitness component grip strength (22.7 kg versus 24.0 kg respectively; p=0.29).

Table 2 Physical fitness results of the CVD and no CVD group

Physical fitness	**CVD in medical file** mean (SD) n=78 (11.4%)	**No CVD in medical file** mean (SD) n=606 (88.6%)	**B (95%CI)**	***p*-value**
Cardiorespiratory fitness in m[a]	136.9 (93.3)	244.1 (170.5)	-107.2 (-164.5 to -49.9)	**<0.001**
Comfortable gait speed in km/h[a]	2.8 (1.2)	3.5 (1.2)	-0.7 (-1.0 to -0.3)	**<0.001**
Fast gait speed in km/h[a]	4.7 (2.3)	6.5 (3.1)	-1.8 (-3.0 to -0.7)	**0.002**
Grip strength in kg[a]	22.7 (10.1)	24.0 (10.0)	-1.3 (-3.8 to 1.1)	0.29

CVD = cardiovascular disease (coronary artery disease, heart failure or stroke); SD = standard deviation; n = number of participants; B = beta; CI = confidence interval; p-value = p<0.05 is statistically significant; m = metre; km/h = kilometres per hour; kg = kilogram

[a] A higher score represents a better performance

Table 3 presents the results of the multivariable linear regression models we performed to investigate the difference in physical fitness levels between older adults with ID with and without CVD. Table 3 presents the regression coefficients and associated 95% confidence interval and p-value for the presence of CVD in relation to each of the four physical fitness components. After adjusting for age, sex, residential status, level of ID, and Down syndrome, participants with CVD scored significantly lower on cardiorespiratory fitness, comfortable gait speed, and fast gait speed. Participants with CVD walked an average of 81.4 metres less on the cardiorespiratory fitness test (p=0.002), walked on average 0.3 km/h slower during the comfortable gait speed test (p=0.04), and walked on average 1.1 km/h slower during the fast gait speed test (p=0.04) compared to participants without CVD. In accordance with the unadjusted results, no significant differences between both groups were found for physical fitness component grip strength (p=0.89). All participant characteristics showed a significant relationship with physical fitness in most of the models. In general, participants who were younger, who were male, who had borderline or mild ID, who did not have Down syndrome, and who lived more independently had better physical fitness levels.

Table 3 Cross-sectional associations between four physical fitness components and CVD, adjusted for participant characteristics (multivariable linear regression analyses)

		Cardiorespiratory fitness (walked distance m)[a]		
		B	**95%CI**	***p*-value**
Constant		661.2	537.6 to 784.8	**<0.001**
CVD	No	0 (ref)		
	Yes	-81.4	-134.1 to -28.8	**0.002**
Age	In years	-6.1	-8.0 to -4.2	**<0.001**
Sex	Male	0 (ref)		
	Female	-63.1	-89.7 to -36.5	**<0.001**
Residential status	Central setting	0 (ref)		
	Community based	80.2	50.6 to 109.8	**<0.001**
	Independent with ambulatory support	85.0	10.8 to 159.2	**0.03**
	With relatives	-54.5	-200.9 to 91.8	0.47
Level of ID	Borderline - Mild	0 (ref)		
	Moderate	-55.5	-88.2 to -22.8	**<0.001**
	Severe - Profound	-79.1	-122.5 to -35.7	**<0.001**
Down syndrome	No	0 (ref)		
	Yes	-70.5	-109.4 to -31.6	**<0.001**

m = metre; km/h = kilometres per hour; kg = kilogram; B = beta; CI = confidence interval; *p*-value = $p<0.05$ is statistically significant; CVD = cardiovascular disease (coronary artery disease, heart failure or stroke); ID = intellectual disability

[a]A higher score represents a better performance

DISCUSSION

In this study we investigated the difference in physical fitness levels between older adults with ID with and without CVD. Participants with CVD had significantly lower physical fitness levels than those without CVD for the physical fitness components cardiorespiratory fitness, comfortable gait speed, and fast gait speed. We found no statistically significant difference between the two groups for grip strength.

Our study specifically looked at the physical fitness levels of participants who have CVD compared to those who have no CVD. Despite the already very low physical fitness levels of older adults with ID [61], the physical fitness scores of participants

Comfortable gait speed (km/h)[a]			Fast gait speed (km/h)[a]			Grip strength (kg)[a]		
B	**95%CI**	***p*-value**	**B**	**95%CI**	***p*-value**	**B**	**95%CI**	***p*-value**
6.7	5.9 to 7.5	**<0.001**	15.8	13.4 to 18.1	**<0.001**	42.1	36.4 to 47.9	**<0.001**
0 (ref)			0 (ref)			0 (ref)		
-0.3	-0.7 to -0.02	**0.04**	-1.1	-2.2 to -0.1	**0.04**	-0.2	-2.3 to 1.9	0.89
-0.04	-0.1 to -0.04	**<0.001**	-0.1	-0.2 to -0.1	**<0.001**	-0.2	-0.3 to -0.1	**<0.001**
0 (ref)			0 (ref)			0 (ref)		
-0.5	-0.6 to -0.3	**<0.001**	-1.8	-2.4 to -1.4	**<0.001**	-9.2	-10.5 to -7.8	**<0.001**
0 (ref)			0 (ref)			0 (ref)		
0.5	0.3 to 0.7	**<0.001**	1.1	0.6 to 1.6	**<0.001**	2.8	1.4 to 4.2	**<0.001**
0.8	0.3 to 1.3	**0.001**	1.2	-0.1 to 2.6	0.08	3.1	-0.5 to 6.7	0.09
-0.2	-1.1 to 0.8	0.73	1.7	-1.3 to 4.7	0.27	1.6	-6.5 to 9.6	0.70
0 (ref)			0 (ref)			0 (ref)		
-0.3	-0.5 to -0.04	**0.02**	-0.5	-1.1 to 0.1	0.09	-3.8	-5.4 to -2.2	**<0.001**
-0.7	-1.0 to -0.4	**<0.001**	-1.7	-2.6 to -0.9	**<0.001**	-8.5	-10.9 to -6.1	**<0.001**
0 (ref)			0 (ref)			0 (ref)		
-0.4	-0.7 to -0.2	**0.002**	-0.4	-1.1 to 0.4	0.32	-4.7	-6.7 to -2.7	**<0.001**

with CVD were even worse. Participants with CVD scored significantly lower on most physical fitness tests: they walked fewer metres on the cardiorespiratory fitness test and had a lower comfortable and fast gait speed compared to participants without CVD. Hilgenkamp et al. [61] previously reported very low physical fitness levels in the HA-ID cohort. The participants (aged 50 years and over) performed comparable or even worse than people in the general population who were 20 years older [61]. This implicates that physical fitness might be a target for improvement of cardiovascular health in older adults with ID and those with CVD in particular. Oppewal et al. (2020) hypothesised that even among very unfit people with ID, small improvements in physical fitness may lead to major improvements in health [279]. This may also be the case for cardiovascular health. Therefore,

health promotion focussing on improving physical fitness and reducing CVD risk is important. However, existing health promotion and prevention programmes to reduce CVD risk are often not fully suited for older adults with ID and should be adjusted for this population.

From research in the general population, it is known that several physical fitness components are predictive for CVD morbidity and mortality, with the strongest evidence for cardiorespiratory fitness [54-56], gait speed [57, 58], and grip strength [59, 60]. Our results are in line with those seen in the general population, showing that the presence of CVD is associated with cardiorespiratory fitness and gait speed in older adults with ID. In general, participants who were younger, who were male, who had borderline or mild ID, who did not have Down syndrome, and who lived more independently had better physical fitness levels. We did not find a relationship between the presence of CVD and grip strength. This is in line with results of previous studies of the HA-ID cohort in which we also found no relationship between grip strength and other outcome measures known from research in the general population, such as (instrumental) activities or daily living [147, 148].

In this study we found a prevalence of coronary artery disease of 2.6%, a prevalence of heart failure of 3.8%, and a prevalence of stroke of 6.1% in older adults with ID. The overall prevalence of CVD (coronary artery disease, heart failure, or stroke) found in our cohort was 11.4%. These prevalence rates are largely in line with results of previous studies in (older) adults with ID [43, 69], although wide variations in CVD prevalence rates are reported [48, 50]. Overall the prevalence of CVD we found in older adults with ID seems to fall in the range of the prevalence in the general Dutch population [280], which is in agreement with findings from previous studies [51, 69]. However, at the same time the literature describes a higher prevalence of several CVD risk factors in adults with ID [34, 36]. This discrepancy in prevalence rates suggests that CVD may be underdiagnosed in this group. This is also supported by previous research on peripheral arterial disease (PAD), which showed a higher prevalence of PAD in older adults with ID compared to the general population (17.4% versus 8.1% respectively) and a high degree of underdiagnosis in older adults with ID (97% of the participants with PAD had not been previously diagnosed with this condition) [70]. This may be explained by the fact that diagnostics in people with ID are more challenging because of atypical presentation of symptoms, limitations in articulating health problems, and limited cooperation and resilience during physical examination [67, 199]. Referral policies for this vulnerable group are made with the greatest possible care

and in consultation with physicians, representatives, healthcare staff, and others involved, which can sometimes lead to, for example, the choice to refrain from further diagnosis in the interest of the individual's quality of life [281]. As a result, the actual prevalence of CVD in people with ID might be higher than reported in our study and in previous publications [51, 69].

Strengths of this study are the extensive physical fitness tests at baseline and the large sample size. To our knowledge this is the first study that investigated the cross-sectional associations between the presence of CVD and various physical fitness components in older adults with ID. However, some limitations of this study should be noted. The HA-ID cohort consists of adults who receive any form of registered formal ID care or support. The HA-ID cohort is near-representative for this population [12], but our results are not generalisable for all adults with ID because we did not include adults without formal ID care. In addition, drop out during the physical fitness tests resulted in underrepresentation of people who were not able to walk, or had severe or profound ID, and an overrepresentation of adults of 50-59 years, who walked independently, and who had borderline or mild ID [61]. When interpreting the findings of this study, it is important to take these points into account. It should also be noted that due to a lack of statistical power we had to use the physical fitness components as dependent variables in the multivariable linear regression models instead of the presence of CVD. For this reason, we were unable to adjust for CVD risk factors in the multivariable analysis. Also, it is important to point out that the CVD status of the participants was only based on medical file research. For this reason, we must acknowledge that we cannot rule out underdiagnosis of CVD in our study. Finally, due to the cross-sectional data collection, it is not possible to make statements about causality based on the results of this study. It is possible that people with lower physical fitness levels are more likely to get CVD, but it could also be that people with CVD are less physically fit because of their condition. For this reason, this study should be seen as a first exploration of the relationship between physical fitness and CVD in older adults with ID.

Based on the findings in this study, our recommendations for future research are the following. First, in addition to the participant characteristics in this study, other (population-specific) factors may influence both physical fitness and cardiovascular health in older adults with ID. Therefore, it would be interesting to include additional factors, such as other genetic syndromes, medication use, specific physical and psychiatric co-morbidities, and CVD risk factors, in the analyses of future research. Second, to overcome possible underdiagnosis of

CVD in future research, it would be of great value to use more objective measures for diagnosing CVD in people with intellectual disabilities. For example, by using electrocardiogram (ECG) or cardiac ultrasound measurements. Finally, we assessed the association between physical fitness and CVD at a single time point. Longitudinal follow-up research will provide a deeper understanding of the course of physical fitness and CVD over time and allows to make causality statements about the impact of physical fitness on developing CVD in older adults with ID. This knowledge is needed to get insight into the dose-response relationship between changes in physical fitness and the resulting decrease or increase in risk for developing CVD in older adults with ID. Some studies show that exercise interventions increase physical fitness and decrease CVD risk factors in people with ID [282]. However, the available evidence is still limited, which impairs the provision of clear training prescriptions [279]. For this reason, we strongly recommend longitudinal and intervention research into this topic. We are currently working on the 10-year follow-up of the HA-ID cohort [231], which will allow us to explore such longitudinal questions in the future.

In conclusion, this study shows that older adults with ID who have CVD had significantly lower physical fitness levels (cardiorespiratory fitness, comfortable gait speed, and fast gait speed) than those without CVD. Grip strength was not significantly associated with the presence of CVD. Longitudinal follow-up research in adults with ID is needed to study the relationship between physical fitness and CVD over time, to make statements about the direction of the relationship, and causality. It will also help to gain more insight into what extent physical fitness is an important target area for prevention and interventions to improve cardiovascular health of adults with ID.

CHAPTER 6

Cardiovascular disease incidence and risk factors in older adults with intellectual disabilities: Results of the Healthy Ageing and Intellectual Disabilities study

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ABSTRACT

Background

Previous research has shown that older adults with intellectual disabilities (ID) are at increased risk of cardiovascular diseases (CVD). However, longitudinal studies investigating the actual incidence of CVD and its associated risk factors in this population are limited. Such research is essential for optimising healthcare delivery and informing effective resource allocation. Therefore, this study aimed to examine CVD incidence in older adults with ID and explore its associations with participant characteristics and risk factors.

Method

A prospective longitudinal study was conducted in older adults (≥50 years) with ID as part of the Healthy Ageing and Intellectual Disabilities study. Baseline measurements were performed in 2009-2010, with follow-up assessments, including medical record reviews, in 2020-2023. Incidence rates for myocardial infarction, heart failure, and stroke were calculated by sex and 10-year age categories. Competing risk analysis was performed to examine the associations between CVD diagnoses during follow-up and baseline participant characteristics/CVD risk factors, accounting for mortality as a competing risk.

Results

Among 598 participants (62.0 ± 8.5yr; 49.3% female), with a mean follow-up of 8.6 years, incidence rates were 2.3 per 1000 person-years for myocardial infarction, 7.2 for heart failure, and 5.3 for stroke. Hypertension (HR 3.17; $p<0.001$), Down syndrome (HR 2.66; $p<0.01$), and antipsychotic use (HR 1.98; $p=0.04$) were associated with an increased CVD risk during follow-up.

Conclusions

A lower incidence of myocardial infarction and a similar to higher incidence of heart failure and stroke were found in older adults with ID than in the general population. Further research, including a focus on the association of CVD incidence with Down syndrome, is needed. Meanwhile, proactive assessment and management of CVD risk factors, such as hypertension and antipsychotic use, are important for improving cardiovascular health in older adults with ID.

INTRODUCTION

Cardiovascular diseases (CVD), including myocardial infarction, heart failure, and stroke are a major health concern for the general population [13], and also lead to high rates of morbidity and mortality in individuals with intellectual disabilities (ID) [122, 267]. Several risk factors, such as hypertension [34], type 2 diabetes [34], obesity [34, 36], metabolic syndrome [37], and physical inactivity [39], are more prevalent in adults with ID than in the general population. This is particularly the case for individuals with mild ID, who live more independently and make their own lifestyle choices [40]. The high prevalence of psychotropic drug use, including antipsychotics, in this population compounds this risk [27, 33]. These medications can delay cardiac repolarisation, leading to QTc prolongation [30], which increases the risk of ventricular arrhythmias and CVD [31]. Antipsychotics further elevate CVD risk through side effects like weight gain and metabolic syndrome [32, 33]. Finally, the increasing life expectancy of individuals with ID [9, 10] leads to a growing burden of age-related CVD in this population, making it increasingly important to understand and address their heightened CVD risk.

However, longitudinal studies on CVD and its risk factors in adults with ID remain scarce. Only a limited number of studies have reported incidence rates for myocardial infarction (0.3-2.8 per 1000 person years (py)), heart failure (12.5 per 1000py), and stroke (2.7-3.2 per 1000py) [283]. Data on the predictive value of risk factors for CVD morbidity in this group also remains limited. One study [51] identified obesity, atypical antipsychotic use, chronic kidney disease, and history of heart failure or stroke as associated risk factors over a 3-year follow-up period. However, this study noted limited statistical power due to the limited amount of events with the relative short follow-up time, emphasising the need for larger study populations or longer follow-up periods. Understanding the predictive value of CVD risk factors is essential to determine if risk profiles of the general population are suitable for individuals with ID and if existing CVD prevention guidelines need adaptation for this specific group. Longitudinal data on CVD incidence and its risk factors is crucial for ID and primary care providers, public health planners, and policy makers [43, 44], as they are essential for optimising healthcare delivery [45] and ensuring effective allocation of healthcare resources [46]. The current limited research underscores the need for more longitudinal studies in adults with ID.

Therefore, the aims of this longitudinal study were to 1) examine the incidence of CVD (myocardial infarction, heart failure, and stroke) in older adults with ID and to 2) explore its associations with participant characteristics and CVD risk factors.

METHODS

Study design and participants

This study is part of the Healthy Ageing and Intellectual Disabilities (HA-ID) study. The HA-ID study is a prospective multicentre cohort study on physical and mental health of older adults with ID who use formal ID care and support. A detailed description of the design and recruitment has been published previously [12, 231]. The data collection of the HA-ID study was conducted in three participating ID care organisations (Abrona, Amarant, and Ipse de Bruggen), which provide support to a wide spectrum of individuals with borderline to profound ID in different care settings across the Netherlands. All adults with ID who received care or support from one of these care organisations, and who were 50 years or older on September 1, 2008, were invited to participate. Out of 2322 invitees, 1050 (45.2%) agreed to participate in the baseline measurements in 2009-2010. All 429 participants who still received care from one of the three participating care organisations on July 1, 2020 and consented to be contacted for participation were invited for the follow-up measurements. Data were collected between October 2020 and July 2023.

Ethics and consent

A behavioural scientist evaluated whether eligible participants were capable of understanding the study information and able to provide informed consent to participate. If participants were incapable of providing informed consent, this was obtained from their legal representative. Efforts were made to inform the older adults with ID who were incapable of providing consent themselves, using easy to read information letters and oral information provided by the participant's professional caregiver. For participants involved in the baseline measurements who had passed away by July 1, 2020, available medical record data were collected unless the participants had previously objected. Ethical approval was obtained from the Medical Ethics Review Committee of the Erasmus MC, University Medical Center Rotterdam (MEC 2008-234, MEC-2019-0562). The study is registered in the Dutch Trial Register (NTR number: NL8564, https://onderzoekmetmensen.nl/nl/trial/28611) and follows the guidelines of the Declaration of Helsinki [155].

Data collection

Participant characteristics

At baseline, data on age and sex were collected from the administrative electronic systems of the care organisations. Information about the level of ID was collected from behavioural records and categorised as borderline, mild, moderate, severe, or profound. Information on the presence of genetic syndromes (yes/no) was extracted

from participants' medical records. Only Down syndrome had a sufficient number of participants to be presented as a subgroup. Data on residential status (central setting, community based, independent with ambulatory support, with relatives), number of day activity programme sessions per week, and mobility (independent, with walking aid, wheelchair) were collected through a questionnaire completed by the participant's professional caregiver.

Cardiovascular disease risk factors

The following CVD risk factors were measured at baseline (exact procedures are described elsewhere [36, 39, 40, 147, 198]): hypertension (mean systolic blood pressure ≥140 mmHg or a mean diastolic blood pressure ≥90 mmHg or the use of blood pressure lowering drugs) [40], hypercholesterolemia (fasting serum total cholesterol >6.5 mmol/l or the use of lipid lowering drugs) [40], diabetes mellitus (fasting serum glucose >6.1 mmol/l or the use of glucose lowering drugs) [40], waist to hip ratio [36] (females with a waist-to-hip ratio of ≥0.85 and males with a waist-to-hip ratio of ≥0.90 were classified as obese [233]), metabolic syndrome (according to the criteria of the joint interim statement 2009) [37, 270], inflammation (elevated C-reactive protein >10 mg/L) [51], and chronic kidney disease (glomerular filtration rate according to the CKD-creatinine-cystatin-C equation <60 ml/min/1.73 m^2) [198, 234, 271]. Data about smoking at least 1 cigarette/day (yes/no) were collected through a questionnaire completed by the participant's professional caregiver. Information on the use of antipsychotics was retrieved from the participant's medical record. Insufficient physical activity was defined as taking fewer than 7500 steps per day, measured by wearing pedometers for at least four days [39]. Participants who were unable to participate in this measurement (resistance to wearing the pedometer, comfortable walking speed <3.2 km/h, wheelchair dependent) were also classified as physically inactive. Cardiorespiratory fitness was measured with the 10-m incremental shuttle walking test [147, 161]. Gait speed was evaluated by measuring the time it took to cover 5 m, after 3 m for acceleration, with an additional 3 m at the end for deceleration at comfortable and fast gait speed [147, 272]. Grip strength was measured with the Jamar Hand Dynamometer (#5030J1, Sammons Preston Rolyan, USA) [147, 273]. If participants showed any form of resistance, the measurements were immediately stopped.

Cardiovascular disease

At baseline, the participants' own general practitioner or ID physician reviewed and recorded relevant medical history, based on available clinical information and medical records. This retrospective assessment specifically considered the presence of coronary artery disease, heart failure, and stroke (ischemic or haemorrhagic), allowing for the identification of pre-existing CVD at the time of

inclusion. At follow-up, researchers and research assistants reviewed participants' medical records to identify the presence of a confirmed diagnosis of myocardial infarction, heart failure, or stroke (ischemic or haemorrhagic) by an ID physician, general practitioner, or specialist, covering the period from baseline to follow-up measurements, as well as mortality and time of death.

Statistical analysis

Participant characteristics

Descriptive statistics were used to describe the participant characteristics and presence of CVD risk factors at baseline. To explore differences between participants in the present study and the total HA-ID study population, differences in participant characteristics between included and excluded HA-ID participants were analysed with independent t-tests for continuous variables, Fisher's exact tests (2-sided) for binary variables, and chi-square tests for categorical variables. Statistical significance was set at $p<0.05$.

Incidence of cardiovascular disease

Incidence rates for myocardial infarction were calculated by dividing the number of incident cases of myocardial infarction by the total number of person-years accumulated among participants without a history of myocardial infarction at baseline. To ensure accurate estimation of incident myocardial infarction, all participants with a documented history of coronary artery disease at baseline were excluded from the myocardial infarction incidence analyses. This approach was necessary because the baseline data captured only general coronary artery disease history, without distinguishing between specific diagnoses such as prior myocardial infarction. The follow-up period ended at the occurrence of a myocardial infarction, at death, or at the time of the medical record review during the follow-up measurements. If a participant experienced multiple myocardial infarctions during the follow-up period, only the first event was included in the analysis. Similarly, incidence rates were calculated for heart failure and stroke. The 95% confidence intervals (CI) were calculated based on the Poisson distribution. Incidence rates were calculated for men and women separately and for 10-year age categories.

Associated factors

To address missing data, single imputation was performed under the assumption of missing at random, using all variables included in the first competing risk analysis described below. For participants using a wheelchair, missing values were set to 0 for the fitness tests assessing cardiorespiratory fitness, comfortable gait speed, and fast gait speed, ensuring no imputation was applied to tests they were unable to perform.

After assumptions were checked, a competing risk analysis was conducted, using proportional subdistribution hazards models, to assess the associations between new CVD diagnoses (myocardial infarction, heart failure, or stroke) during follow-up (dependent variable) and baseline participant characteristics and CVD risk factors (independent variables), while accounting for mortality as a competing risk. The initial model included the following variables: age, sex, level of ID, Down syndrome, residential status, number of half-day activity programme sessions per week, mobility, hypertension, hypercholesterolemia, diabetes mellitus, waist-to-hip ratio, obesity, metabolic syndrome, inflammation, chronic kidney disease, smoking, antipsychotic use, physical inactivity, cardiorespiratory fitness, comfortable gait speed, fast gait speed, and grip strength. Lasso penalised regression was used for variable selection by shrinking regression coefficients towards zero. This approach allows for the assessment of each independent variable's unique contribution to the dependent variable while mitigating overfitting and multicollinearity. By applying a penalty to the regression coefficients, Lasso identifies the most predictive variables. In this study, the Lasso penalty parameter was set to select a number of variables corresponding to the available degrees of freedom, adhering to the rule of thumb of at least ten events per independent variable [284, 285].

Subsequently, to obtain unbiased hazard ratios (HRs), a second competing risk analysis was performed without Lasso, including age, sex, and the variables selected through the Lasso regression process. Statistical analysis was conducted using the R software environment (version R-4.3.3), with the mice and fastcmprsk packages.

RESULTS

Participant characteristics

By the end of the follow-up period, medical record data were available for 598 of the 1050 baseline participants (57.0%), of whom 266 (44.5%) were still alive and 332 (55.5%) had died. Reasons for exclusion were the absence of informed consent for follow-up data collection (n=395; 37.6%) and the unavailability of follow-up medical record data (n=57; 5.4%) (Figure 1). Baseline characteristics and differences between included and excluded HA-ID participants are shown in Table 1. The mean age at baseline of the 598 participants was 62.0 years (standard deviation (SD) 8.5; range 50-93 years) and 49.3% were women.

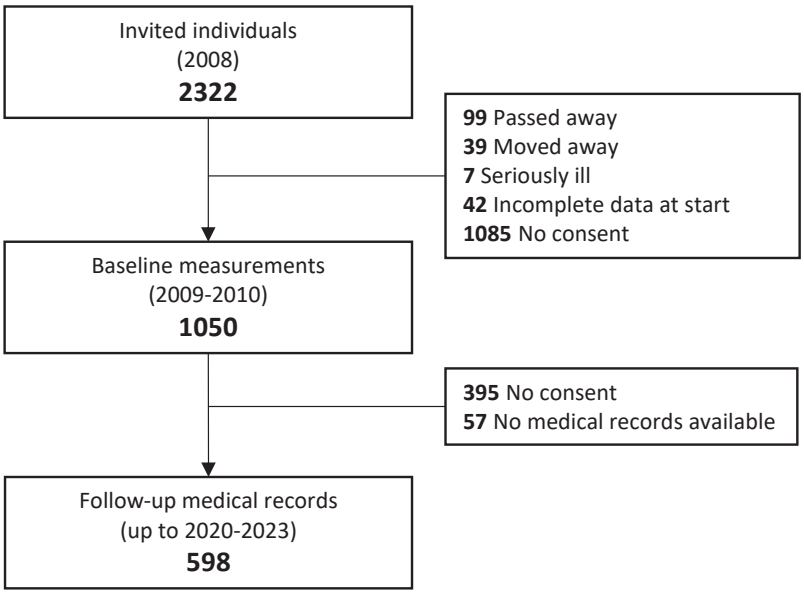

Figure 1 Flow-chart inclusion cardiovascular disease follow-up study

Table 1 Baseline characteristics of the study sample

		Study sample (n=598)	**Excluded HA-ID participants** (n=452)	***p*-value**
Age, mean (SD) (n=598; 452)		62.0 (8.5)	61.0 (7.3)	**0.03**
	50-59 years, *n* (%)	275 (46.0%)	218 (48.2%)	**0.04**
	60-69 years, *n* (%)	202 (33.8%)	168 (37.2%)	
	70-79 years, *n* (%)	101 (16.9%)	61 (13.5%)	
	80+ years, *n* (%)	20 (3.3%)	5 (1.1%)	
Sex, *n* (%) (n=598; 452)	Male	303 (50.7%)	235 (52.0%)	0.71
	Female	295 (49.3%)	217 (48.0%)	
Level of ID, *n* (%) (n=589; 434)	Borderline	13 (2.2%)	18 (4.1%)	**<0.001**
	Mild	102 (17.3%)	121 (27.9%)	
	Moderate	292 (49.6%)	214 (49.3%)	
	Severe	116 (19.7%)	56 (12.9%)	
	Profound	66 (11.2%)	25 (5.8%)	

Table 1 Continued

		Study sample (n=598)	**Excluded HA-ID participants** (n=452)	***p*-value**
Down syndrome, *n* (%) (n=532; 341)		107 (20.1%)	42 (12.3%)	**<0.01**
Residential status, *n* (%) (n=596; 443)	Central setting	397 (66.6%)	160 (36.1%)	**<0.001**
	Community based	184 (30.9%)	248 (56.0%)	
	Independent with ambulatory support	15 (2.5%)	28 (6.3%)	
	With relatives	0 (0%)	7 (1.6%)	
Number of half-day activity programme sessions per week, mean (SD) (n=547; 396)		6.4 (3.0)	6.4 (3.0)	0.95
	0 half-day sessions per week, *n* (%)	47 (8.6%)	30 (7.6%)	0.44
	1-3 half-day sessions per week, *n* (%)	43 (7.9%)	32 (8.1%)	
	4-6 half-day sessions per week, *n* (%)	160 (29.3%)	126 (31.8%)	
	7-9 half-day sessions per week, *n* (%)	215 (39.3%)	136 (34.3%)	
	≥ 10 half-day sessions per week, *n* (%)	82 (15.0%)	72 (18.2%)	
Mobility, *n* (%) (n=578; 411)	Independent	405 (70.1%)	326 (79.3%)	**<0.01**
	With walking aid	95 (16.4%)	56 (13.6%)	
	Wheelchair	78 (13.5%)	29 (7.1%)	
Hypertension, *n* (%) (n=531; 378)		240 (45.2%)		
Hypercholesterolemia, *n* (%) (n=444; 280)		92 (20.7%)		
Diabetes mellitus, *n* (%) (n=444; 280)		58 (13.1%)		
Waist to hip ratio, mean (SD) (n=458; 376)		0.9 (0.09)		
Obesity, *n* (%) (n=458; 376)		216 (47.2%)		
Metabolic syndrome, *n* (%) (n=339; 245)		135 (39.8%)		

Table 1 Continued

	Study sample (n=598)	**Excluded HA-ID participants** (n=452)	***p*-value**
C-reactive protein (>10 mg/L), *n* (%) (n=443; 280)	64 (14.4%)		
Chronic kidney disease, *n* (%) (n=382; 253)	65 (17.0%)		
Current smoking, *n* (%) (n=598; 452)	135 (22.6%)		
Antipsychotics use, *n* (%) (n=499; 338)	131 (26.3%)		
Physical inactivity, *n* (%) (n=296; 206)	246 (83.1%)		
Cardiorespiratory fitness in m, mean (SD) (n=317; 273)	233.4 (177.8)		
Comfortable gait speed in km/h, mean (SD) (n=372; 338)	3.3 (1.2)		
Fast gait speed in km/h, mean (SD) (n=278; 279)	6.2 (3.1)		
Grip strength in kg, mean (SD) (n=380; 345)	22.8 (9.5)		
History of coronary artery disease, *n* (%) (n=547; 357)	15 (2.7%)		
History of heart failure, *n* (%) (n=544; 357)	32 (5.9%)		
History of stroke, *n* (%) (n=547; 356)	34 (6.2%)		

ID = intellectual disability; kg = kilogram; km/h = kilometre per hour; m = metre; n = number of participants; *p*-value = $p<0.05$ is statistically significant, SD = standard deviation

The mean baseline age of included participants was higher than that of excluded participants (62.0 versus 61.0 years; $p=0.03$), with a greater proportion of individuals aged 80 and older in the participant group (3.3% versus 1.1%; $p=0.04$). Included participants had a lower prevalence of mild ID (17.3% versus 27.9%; $p<0.001$) and a higher prevalence of severe (19.7% versus 12.9%; $p<0.01$) and profound (11.2% versus 5.8%; $p<0.01$) ID and were more frequently diagnosed with Down syndrome (20.1% versus 12.3%; $p<0.01$). They were more likely to reside in a central setting (66.6% versus 36.1%; $p<0.001$) and less likely to live in community-based settings (30.9% versus 56.0%; $p<0.001$), independent living arrangements with ambulatory support (2.5% versus 6.3%; $p<0.01$), or with relatives (0% versus 1.6%; $p<0.01$). Included participants were less often able to walk independently (70.1% versus 79.3%; $p<0.01$) and more frequently used a wheelchair (13.5% versus 7.1%; $p<0.01$). No significant differences in sex or the number of day activity programme sessions were found.

Incidence of cardiovascular disease

The mean follow-up time for the 598 participants was 8.6 years (range 0-14.7 years). At the end of the follow-up period, 250 (41.8%) of them were still alive, while 348 (58.2%) had passed away. Table 2 presents the incidence rates for myocardial infarction, heart failure, and stroke, by sex and across 10-year age categories.

Myocardial infarction

At baseline, fifteen of the 598 participants (2.5%) had a history of coronary artery disease. Two participants had incomplete follow-up medical record data. After excluding these cases, twelve of the remaining 581 participants (2.1%) experienced a myocardial infarction during the follow-up period, with one of them (8.3%) dying as a result. We found an incidence rate of myocardial infarction of 2.3 per 1000py (95%CI 1.2-4.1 per 1000py) (Table 2).

Table 2 Incidence rates myocardial infarction

Age groups	**All**		**Men**		**Women**	
(years)	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*
50-59	4/2694	1.5 (0.4-3.8)	2/1357	1.5 (0.2-5.3)	2/1338	1.5 (0.2-5.4)
60-69	7/1700	4.1 (1.7-8.5)	7/941	7.4 (3.0-15.3)	0/760	0.0
70-79	0/654	0.0	0/249	0.0	0/404	0.0
80+	1/83	12.0 (0.3-67.0)	0/24	0.0	1/59	17.0 (0.4-94.9)
All	12/5131	2.3 (1.2-4.1)	9/2571	3.5 (1.6-6.6)	3/2561	1.2 (0.2-3.4)

CI = confidence interval; py = person-years

*Denotes per 1000 person-years

Heart failure

At baseline, 32 of the 598 participants (5.4%) had a history of heart failure. Three participants had incomplete follow-up medical record data. After excluding these cases, 36 of the remaining 563 participants (6.4%) were diagnosed with heart failure during the follow-up period, with nine of them (25.0%) dying as a result. We found an incidence rate of heart failure of 7.2 per 1000py (95%CI 5.0-10.0 per 1000py) (Table 3).

Table 3 Incidence rates heart failure

Age groups		**All**		**Men**		**Women**
(years)	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*
50-59	16/2636	6.1 (3.5-9.9)	8/1318	6.1 (2.6-12.0)	8/1318	6.1 (2.6-12.0)
60-69	7/1678	4.2 (1.7-8.6)	3/925	3.2 (0.7-9.5)	4/753	5.3 (1.4-13.6)
70-79	11/596	18.4 (9.2-33.0)	3/219	13.7 (2.8-40.1)	8/378	21.2 (9.1-41.7)
80+	2/87	23.0 (2.8-83.0)	1/19	52.7 (1.3-293.7)	1/68	14.7 (0.4-81.8)
All	36/4997	7.2 (5.0-10.0)	15/2481	6.0 (3.4-10.0)	21/2516	8.3 (5.2-12.8)

CI = confidence interval; py = person-years
*Denotes per 1000 person-years

Stroke

At baseline, 34 of the 598 participants (5.7%) had a history of stroke. Four participants had incomplete follow-up medical record data. After excluding these cases, 26 of the remaining 560 participants (4.6%) experienced a stroke during the follow-up period, with seven of them (26.9%) dying as a result. We found an incidence rate of stroke of 5.3 per 1000py (95%CI 3.5-7.8 per 1000py) (Table 4).

Table 4 Incidence rates stroke

Age groups		**All**		**Men**		**Women**
(years)	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*	Cases/py	Rate (95%CI)*
50-59	9/2616	3.4 (1.6-6.5)	4/1319	3.0 (0.8-7.8)	5/1297	3.9 (1.3-9.0)
60-69	11/1607	6.8 (3.4-12.2)	6/919	6.5 (2.4-14.2)	5/688	7.3 (2.4-17.0)
70-79	4/615	6.5 (1.8-16.7)	3/244	12.3 (2.5-36.0)	1/371	2.7 (0.1-15.0)
80+	2/67	29.8 (3.6-107.5)	0/20	0.0	2/47	42.3 (5.1-152.9)
All	26/4905	5.3 (3.5-7.8)	13/2501	5.2 (2.8-8.9)	13/2404	5.4 (2.9-9.2)

CI = confidence interval; py = person-years
*Denotes per 1000 person-years

Subgroups by sex and age

Although incidence rates differed between subgroups, all confidence intervals overlap, indicating no statistically significant differences. The only exception is the difference in heart failure incidence rates between the 60-69 and 70-79 age groups in the total population (men and women combined), with rates of 4.2 versus 18.4 per 1000py, respectively (Table 3).

Associated factors

Of the 598 participants, 69 were diagnosed with CVD at baseline. Of these, six had a history of coronary artery disease, 22 had heart failure, and 29 had a history of stroke. Additionally, at baseline, seven participants were diagnosed with both coronary artery disease and heart failure, two with both coronary artery disease and stroke, and three with both heart failure and stroke. After excluding these 69 cases, 529 participants remained, of whom 63 developed CVD during the follow-up period. Eleven participants experienced recurrent events during follow-up: five participants were diagnosed with two strokes, one participant with three strokes, three participants with both myocardial infarction and heart failure, one participant with myocardial infarction and stroke, and one participant with heart failure and stroke. Because of the limited number of recurrent events, the analyses focused solely on associations with the first diagnosed CVD event, excluding recurrent events.

With 63 first CVD events during follow-up, four independent variables could be included in the final competing risk analysis alongside age and sex. Lasso penalised regression identified hypertension, antipsychotic use, Down syndrome, and smoking as the four most predictive variables among all participant characteristics and CVD risk factors, ranked by importance. The final competing risk analysis identified significant associations with CVD events during follow-up for hypertension (HR 3.17; $p< 0.001$), Down syndrome (HR 2.66; $p<0.01$), and antipsychotic use (HR 1.98; $p=0.04$) (Table 5). Of the 202 participants with hypertension at baseline, thirty-seven (18.3%) developed CVD during follow-up, including three cases of myocardial infarction, sixteen of heart failure, fourteen of stroke, two with both myocardial infarction and heart failure, one with both myocardial infarction and stroke, and one with both heart failure and stroke. Fourteen (14.1%) participants of the participants with Down syndrome (n=99) developed CVD during follow-up, including ten cases of heart failure and four of stroke. Of the participants who used antipsychotics at baseline (n=116), sixteen (13.8%) developed CVD during follow-up, including two cases of myocardial infarction, seven of heart failure, six of stroke, and one with both myocardial infarction and heart failure.

Table 5 Competing risk analysis of CVD events during follow-up

Independent variables	HRs (95%CI)	*p*-value
Age	1.02 (0.99-1.06)	0.15
Sex	1.10 (0.64-1.90)	0.72
Hypertension	3.17 (1.75-5.74)	**<0.001**
Down syndrome	2.66 (1.36-5.20)	**<0.01**
Antipsychotics use	1.98 (1.05-3.76)	**0.04**
Smoking	1.52 (0.91-2.53)	0.11

CI = confidence interval; HR = hazard ratio; *p*-value = $p<0.05$ is statistically significant

DISCUSSION

This longitudinal study examined the incidence of CVD (myocardial infarction, heart failure, and stroke) in older adults with ID and explored its associations with participant characteristics and CVD risk factors. Over a mean follow-up time of 8.6 years among 598 individuals, we observed an incidence rate of 2.3 per 1000py for myocardial infarction, 7.2 per 1000py for heart failure, and 5.3 per 1000py for stroke. Hypertension (HR 3.17), Down syndrome (HR 2.66), and antipsychotic use (HR 1.98) were significantly associated with an increased risk of CVD during the follow-up period.

This study adds to the limited literature on CVD incidence in individuals with ID. The slightly higher myocardial infarction incidence rate in our study (2.3 per 1000py), compared to previous studies (0.3-1.9 per 1000py) in individuals with ID [19, 25, 106], may be attributed to the older population in our cohort. Similarly, our stroke incidence rate (5.3 per 1000py) exceeded that of an earlier study (2.7 per 1000py) [19], which may also be explained by age differences. The HA-ID study previously examined CVD incidence in a largely overlapping cohort but with a shorter follow-up [51]. Over three years, incidence rates were 2.8 per 1000py for myocardial infarction, 12.5 for heart failure, and 3.2 for stroke. Differences in rates between the two studies within the same study population may be explained by the fact that the earlier study assessed incidence rates for all included participants, whereas we considered only new diagnoses in those without prior CVD at baseline.

We compared the incidence data observed in this study with published data from the general Dutch population, derived from general practitioner registers [286]. myocardial infarction incidence was consistently lower in our cohort compared to the general population, e.g., 4.1 versus 8.4-10.7 per 1000py in the 60-69 age group [286]. In contrast, heart failure incidence was higher in our cohort across most age groups, except for the 80+ category, which matched the general population. For instance, in the 50-59 age group, our incidence rate was 6.1 versus 0.6-0.9 per 1000py in the general population [286]. Similarly, stroke incidence was higher in our cohort compared to the general population across most age categories, except for the 70-79 age group, which matched the general population. In the 80+ age group, for example, our incidence rate was 29.8 versus 12.0-17.2 per 1000py in the general population [286]. The high heart failure incidence in our cohort may be attributed to the higher prevalence of congenital heart defects among individuals with ID [122], which could potentially lead to heart failure at older ages. The finding that stroke is more prevalent than myocardial infarction in older adults with ID aligns with a previous study [69] and contrasts with data from the Dutch general population, where myocardial infarction is more prevalent than stroke [286]. This discrepancy may reflect undiagnosed myocardial infarctions in the older ID population. This is supported by earlier research showing a high rate of undiagnosed myocardial infarctions in older adults with ID using electrocardiography (ECG) [95]. Regarding subgroup differences, a significant difference in heart failure rates was found between the 60-69 and 70-79 age groups (4.2 versus 18.4 per 1000py). Consistent with this finding, a general trend of increasing incidence with age was observed, reflecting the age-related nature of the CVD diagnoses discussed in this study [132]. Although the numbers are small, the myocardial infarction incidence rate was nearly three times higher in men than in women (3.5 versus 1.2 per 1000py), consistent with trends seen in the general Dutch population [263].

Hypertension at baseline was the strongest factor associated with CVD over the follow-up period (HR 3.17, $p<0.001$). The European Society of Cardiology (ESC) identifies hypertension as a major causal risk factor for CVD [21], contributing to 9.4 million deaths annually and 7% of global disability-adjusted life years [287]. In this study, hypertension was defined as elevated blood pressure and/or the use of blood pressure lowering medication. This definition was chosen because the use of such medications reflects an elevated CVD risk, partly due to hypertension-mediated organ damage [21]. This approach aligns with established risk models, such as the Framingham Risk Score [288] and the QRISK score [289]. While combining treated and untreated hypertension may have introduced variability in CVD risk, hypertension remained the strongest risk factor in our cohort. As antihypertensive treatment reduces CVD risk [21], the observed HR in this study may underestimate the true risk associated with untreated hypertension.

Down syndrome was also significantly associated with CVD during follow-up (HR 2.66, $p<0.01$). Historically, CVD was thought to be less common in individuals with Down syndrome [133]. However, their life expectancy has risen significantly in recent decades, partly due to improved access to medical care, including surgical interventions for congenital heart defects [290]. Most longitudinal studies have not yet captured this aging population, limiting research on their health. Recent studies indicate a growing contribution of CVD to mortality in this group [291-295]. The higher CVD risk in individuals with Down syndrome in our cohort may be attributed by the high prevalence of congenital heart defects, affecting 40-50% of newborns with Down syndrome [296], which can lead to residual cardiac comorbidities later in life [103]. Thyroid disease, affecting about 50% of adults with Down syndrome [297], potentially contributes to cardiovascular issues, including ventricular dysfunction and heart failure [298-300]. Other contributing factors may include medication side effects [297], higher rates of overweight and obesity [301, 302], and lower physical activity [39] and fitness levels [303] compared to the general ID population. Additionally, Down syndrome is associated with moyamoya disease [304-306], a progressive cerebrovascular condition that increases stroke risk [307]. Given these factors, individuals with Down syndrome may have an increased CVD risk compared to the general ID population, as suggested by our findings. However, further research is needed to better understand the magnitude of CVD risk in older adults with Down syndrome and its underlying mechanisms.

Antipsychotic use at baseline was also significantly associated with CVD during follow-up (HR 1.98, $p=0.04$), consistent with findings from the three-year follow-up of the HA-ID study [51]. Antipsychotic use is notably high in individuals with ID, frequently prescribed off-label for behavioural problems like aggression or self-injurious behaviour [27], despite limited evidence of efficacy [29]. These medications can delay cardiac repolarisation, leading to QTc prolongation [30], which increases the risk of ventricular arrhythmias and CVD [31]. For this reason, the Dutch Multidisciplinary Guideline on Problem Behaviour in adults with ID recommends ECG monitoring when prescribing antipsychotics, particularly in those with additional risk factors [73]. Atypical antipsychotics further elevate CVD risk through side effects like weight gain and metabolic syndrome [32, 33]. Age, sex, and smoking were not significantly associated with CVD during the follow-up period, although HRs suggested a trend of increased risk with older age and smoking, aligning with general population data [21, 132].

This study's strengths include the prospective design, extensive baseline measurements in a setting familiar and close to where the participants live, the inclusion of a wide range of variables in the competing risk analysis, and the ability to monitor participants' cardiovascular health either until death or for at least ten years. To our knowledge, this is the first study to examine associations between CVD and participant characteristics, as well as CVD and CVD risk factors, in older adults with ID over such an extended period. However, some limitations should be noted. First, dropout resulted in a sample representing a group with greater support needs (e.g., older individuals, those with severe/profound ID or Down syndrome, and those living in care settings or using wheelchairs). As CVD risk factors are more prevalent in individuals with mild ID, who live more independently and make their own lifestyle choices [40], dropout may have led to an underestimation of CVD incidence. Second, the sample size and the number of CVD events resulted in wide CIs around the CVD incidence rates and limited our ability to include all participant characteristics and risk factors in the final competing risk analysis. However, by conducting two competing risk analyses, we were able to select the most important variables using Lasso penalised regression and report HRs for these variables. Third, CVD status was restricted to three major diagnostic categories: myocardial infarction, heart failure, and stroke. We recognise that this definition does not capture the full spectrum of atherosclerotic cardiovascular conditions and was based solely on medical record review, which may have led to an underestimation of the overall CVD burden. Fourth, our data were compared to the general population based on results from general practitioner registers, which may differ in data collection methods and could therefore have influenced the results of our comparisons. Fifth, certain factors such as ethnicity, family history, and clinical conditions like rheumatoid arthritis, could not be included in the competing risk analysis. Nevertheless, key risk factors (e.g., hypertension, hypercholesterolemia, diabetes, obesity, smoking) based on ESC guidelines [21] and established risk models like the Framingham Risk Score [288] and the Systematic Coronary Risk Evaluation [83], were included. Finally, several selection steps were performed in the competing risk analysis, introducing a degree of uncertainty, as alternative approaches might have yielded different results. This should be considered when interpreting the findings.

Given the limited research on CVD incidence and its risk factors in older adults with ID, large-scale longitudinal studies are needed to better assess risk and inform targeted prevention strategies. Aligning such studies with population-based cohort studies in the general population would allow for meaningful comparisons. Although further research is needed, certain clinical recommendations can be

made. When assessing CVD risk, established factors like hypertension should be considered, while also recognising the potentially increased risk in individuals with Down syndrome. Given the substantial underdiagnosis of hypertension in clinical practice [40], early detection through routine screening is essential to enable timely intervention to prevent the onset of CVD. The importance of regular blood pressure monitoring and effective management of elevated blood pressure in adults with ID is also emphasised in a recent systematic review examining evidence-based and research-informed strategies for CVD prevention in this population [308]. The elevated CVD risk associated with antipsychotic use necessitates careful evaluation of such prescriptions, particularly when used for non-psychiatric indications. In these cases, discontinuation should be considered where possible, in accordance with the Care and Coercion Act, which has been in effect in the Netherlands since January 2020 [309]. For individuals who do require antipsychotic treatment, proactive prevention strategies are essential. These include regular ECG monitoring and timely management of emerging CVD risk factors, in line with the Dutch Multidisciplinary Guideline on Problem Behaviour in Adults with Intellectual Disabilities [73]. To address potential underdiagnosis of myocardial infarction, we emphasise the importance of ECGs in clinical practice to enable early detection and timely preventive interventions.

In conclusion, this longitudinal cohort study found a lower incidence of myocardial infarction and a similar to higher incidence of heart failure and stroke in older adults with ID compared to the general population. Hypertension, Down syndrome, and antipsychotic use were significantly associated with an increased risk of CVD events during the follow-up period. Further research, including a focus on the association with Down syndrome, is needed. Meanwhile, proactive assessment and management of CVD risk factors, such as hypertension and antipsychotic use, are important for improving cardiovascular health in older adults with ID.

CHAPTER 7

General Discussion

GENERAL DISCUSSION

This thesis focused on the prevalence and incidence of cardiovascular diseases (CVD) in adults with intellectual disabilities (ID) and associated risk factors. We reviewed existing literature on CVD prevalence and incidence, assessed ECG feasibility and the prevalence of ECG abnormalities, examined the relationship between physical fitness and CVD, studied CVD incidence over a 10-year follow-up period, and analysed the predictive value of CVD risk factors. These objectives were addressed through a systematic review and analyses from the Healthy Ageing and Intellectual Disabilities (HA-ID) study, a prospective multicentre cohort study on older adults with ID receiving formal care. This chapter presents the principal findings of this dissertation, structured around the main research objectives. These findings are accompanied by a critical reflection, with particular attention to their implications and recommendations for clinical practice. The chapter concludes with proposed directions for future research and final remarks.

Literature synthesis on CVD in adults with ID

One key contribution of this dissertation is a comprehensive synthesis of studies on CVD prevalence and incidence in adults with ID, including subgroup data (Chapter 2). This up-to-date overview provides essential context for researchers, primary care providers, public health planners, and policymakers [43, 44]. To ensure reliability, we conducted a systematic review with independent and duplicate study selection, data extraction, and quality assessment. Our broad search strategy, without pre-specifying diagnoses, subgroups, source populations, or data collection methods, yielded 55 diverse studies. These reported wide prevalence ranges for coronary artery disease (0-12.9%), myocardial infarction (0-7.9%), heart failure (0.8-18.6%), cerebrovascular disease (0.7-15.0%), stroke (1.3-17.2%), peripheral arterial disease (0.4-20.7%), venous thrombosis (0.6-12.4%), and atrial fibrillation (0.8-6.3%) in adults with ID.

Substantial variation in methodological quality, combined with significant clinical and statistical heterogeneity, limited the feasibility of conducting meta-analyses. Clinical heterogeneity arose from differences in participants' age, level of ID, aetiology of ID, data collection methods, and source populations, making it challenging to draw generalisable conclusions for the overall adult ID population. This underscores the importance of the subgroup data we presented in the systematic literature review (Chapter 2), which allows for the identification of prevalence and incidence rates within specific subgroups. This is especially relevant to researchers studying certain groups, such as adults with Down syndrome, as

well as for healthcare providers. Notably, only six studies reported CVD incidence rates in person-years (py) [19, 25, 51, 85, 87, 106]. Given the importance of this data for optimising care and resource allocation, future research should prioritise longitudinal research in adults with ID. Based on the findings of our review, we provide specific recommendations in the 'Directions for Future Research' section.

CVD incidence in adults with ID

Given the limited literature on CVD incidence in adults with ID, as identified in our systematic review (Chapter 2), we undertook a prospective longitudinal study within the HA-ID study (described in detail in Chapter 3). Among 598 older adults (≥50 years) with ID, we observed an incidence rate of 2.3 per 1000py for myocardial infarction, 7.2 per 1000py for heart failure, and 5.3 per 1000py for stroke over a mean follow-up period of 8.6 years (Chapter 6). When we compared these to the incidence rates from our systematic review (Chapter 2), the slightly higher myocardial infarction incidence in our cohort (2.3 versus 0.3-1.9 per 1000py) [19, 25, 106] and higher stroke incidence (5.3 versus 2.7 per 1000py) [19] may be attributed to the older age of our sample.

We also compared our findings with data from the general Dutch population, derived from electronic general practitioner registers [286]. While myocardial infarction incidence was consistently lower in our cohort (e.g., 4.1 versus 8.4-10.7 per 1000py in the 60-69 age group) [286], heart failure and stroke incidences were higher across most age groups. For example, in the 50-59 age group, heart failure incidence was 6.1 in our cohort versus 0.6-0.9 per 1000py in the general population [286], and in the 80+ group, stroke incidence was 29.8 in our cohort versus 12.0-17.2 per 1000py in the general population [286].

Although we largely observed higher CVD incidence rates, there are indications that the actual incidence in our study may have been underestimated. This potential underestimation is partly attributable to the exclusive reliance on medical record reviews to determine CVD status, which could have led to underdiagnosis and, consequently, an undercount of actual cases. This issue is further addressed in the following section. Taken together, our results indicate a substantial CVD burden among older adults with ID, which may be even greater than was observed in our study.

CVD underdiagnosis in adults with ID

Research on the prevalence and incidence of CVD in older adults with ID faces the challenge of underdiagnosis. Diagnostic work-up in this population can be complex and challenging [66], as people may experience limitations

in understanding and articulating health problems, may present symptoms atypically, and may show limited cooperation and capacity during physical examination [67]. Referral policies for this vulnerable group are made with the utmost care in close consultation with physicians, representatives, healthcare staff, and other stakeholders. Careful consideration is given to the potential impact of diagnostic procedures on the individual's quality of life, which may, in some cases, lead to the decision to refrain from further diagnostic investigations [68]. The literature refers to this phenomenon as diagnostic and treatment overshadowing, whereby the interpretation of symptoms and behaviours, as well as the consideration of treatment options, may be influenced or constrained by the individual's ID and its manifestations [310]. This increases the likelihood of underdiagnosis in older adults with ID [51, 65, 67, 69] and highlights the need for objective measurements to establish the diagnosis.

To address this issue, our systematic review (Chapter 2) also examined the data collection methods used in the included studies, with particular attention to indications of potential underdiagnosis. The majority of included studies relied predominantly on data derived from medical records. Only three of the 55 studies employed objective measurements. Two studies used the ankle-brachial index to diagnose peripheral arterial disease (PAD) [70, 129], reporting significantly higher prevalence rates (8.4% to 20.7%) compared to studies that relied solely on medical record data (0% to 0.6%). One of these studies specifically examined underdiagnosis and reported a strikingly high rate among older adults with ID, revealing that 97% of those with PAD had not been previously diagnosed [70].

The third study, conducted as part of this dissertation, utilised ECG recording to assess the prevalence of ECG abnormalities in older adults with ID and to compare these findings with corresponding diagnoses in their medical records (Chapter 4) [95]. The most prevalent ECG abnormalities identified were prolonged P-wave duration (27.6%), QTc prolongation (18.7%), minor T-wave abnormalities (17.9%), first degree atrioventricular block (12.7%), and myocardial infarction (6.7%). Additionally, our findings revealed an underdiagnosis rate of 88.9% for prior myocardial infarction, twice as high as the rates reported in cohort studies in the general population, in which values of undiagnosed myocardial infarctions are reported up to 44% [262, 263]. Because people with a history of myocardial infarction face an increased risk of recurrent cardiovascular complications [263], and both diagnosed and undiagnosed cases share similar prognoses [262, 264, 265], the high underdiagnosis rate is particularly concerning. For QTc prolongation, the underdiagnosis was even more pronounced in our study, reaching 100%,

despite its known association with life-threatening ventricular arrhythmias [31]. Our findings highlight the extent of underdiagnosis in older adults with ID and illustrate the relevance of using objective measurements, such as ECGs.

ECG feasibility in adults with ID

The feasibility of ECG recording in adults with ID is not self-evident and has not been previously studied in this specific group. Challenges such as restlessness, anxiety, tics, or difficulty following instructions may hinder the ability to lie still, potentially affecting both the feasibility and interpretability of the ECG. For this reason, also in Chapter 4, we examined the feasibility of ECG recording in older adults with ID. Our findings indicate that ECG recording was feasible in 67.0% of the participants. However, feasibility was lower in certain subgroups, particularly among adults with severe ID and those who are wheelchair-dependent. Several factors negatively impacted feasibility, including physical disabilities, resistance, fear, difficulty understanding instructions, and restlessness.

During data collection, I observed firsthand that ECG recording was challenging for some participants. Nevertheless, I believe that the feasibility in clinical practice may be higher than the 67% reported in our study. On the day of the ECG recording, participants underwent multiple (physical) measurements in different rooms, administered by various professionals. This data collection process was demanding for some participants, which may have influenced the feasibility of the ECG recording. Additionally, some ECGs were not conducted due to technical issues, staff shortages, or the unavailability of appropriate lifting aids to accommodate participants' physical limitations. Furthermore, if a participant exhibited any resistance, the recording was immediately discontinued. Unlike routine clinical practice, no second attempts were made in such cases. In our study, predefined protocols were strictly followed, whereas in clinical settings, additional efforts may be undertaken to ensure a successful ECG recording. Consequently, the actual feasibility of ECG recording in older adults with ID in clinical practice may be higher than our study suggests.

To improve the likelihood of a successful ECG recording in this population, training and experience with people with ID is essential, though they may not be available in all clinical settings. Additionally, several factors should be considered to enhance feasibility in clinical practice: conducting the ECG in a quiet and familiar environment, selecting an optimal time of day for the participant, performing the recording with patience, ensuring the presence of a trusted person, providing appropriate lifting aids, and allowing for additional attempts or follow-up assessments when necessary.

CVD risk management in adults with ID

Given the substantial burden of CVD among adults with ID, coupled with the high rate of underdiagnosis, there is a clear need for more systematic and proactive management of CVD risk within this population. In the Netherlands, the diagnosis and treatment of CVD risk factors follow the general recommendations of the Dutch College of General Practitioners' Guideline on Cardiovascular Risk Management [311]. This guideline recommends assessing CVD risk in adults with a potentially elevated risk, such as those with a family history of premature CVD, known CVD risk factors, or pre-existing comorbidities associated with increased risk. Risk assessment involves a comprehensive cardiovascular profile, incorporating factors such as age, sex, smoking status, diet, psychosocial risk factors, alcohol consumption, physical activity, blood pressure, body mass index, serum lipid levels, glucose levels, and renal function parameters. Treatment decisions are based on the estimated 10-year risk of cardiovascular morbidity and mortality, calculated using the SCORE2 [312] or SCORE2-OP [313] risk chart. For adults with pre-existing CVD, diabetes mellitus, chronic kidney disease, severe hypertension, or familial hypercholesterolemia, risk assessment is performed using a separate dedicated table. This guideline promotes opportunistic screening and is not designed for the active and systematic detection of CVD risk factors. However, previous research within the HA-ID study has shown that CVD risk factors frequently go undiagnosed in older adults with ID, with reported underdiagnosis rates of 46% for hypercholesterolemia, 50% for hypertension, 54% for diabetes mellitus, and 94% for metabolic syndrome [40]. As a result, reliance on current standard healthcare practices may lead to substantial undertreatment in this population.

Currently, there are no specific guidelines for CVD risk management in adults with ID in the Netherlands. Developing tailored guidelines is essential to improve the quality of care for this population. In addition, creating such guidelines can help identify existing knowledge gaps, thereby guiding and prioritising future research initiatives. Canada already has a relevant guideline in place: the Canadian Consensus Guidelines for Primary Care of Adults with Intellectual and Developmental Disabilities [314]. These guidelines recommend earlier and more frequent screening for CVD risk factors than is recommended for the general population, with a strong emphasis on prevention. Following this example, it would be beneficial for the Netherlands to incorporate specific recommendations for adults with ID into the existing Dutch College of General Practitioners' Guideline on Cardiovascular Risk Management [311].

The Dutch Foundation for Quality Improvement in Long-Term Care is currently developing a multidisciplinary guideline on aging in adults with ID [315]. Given that CVD is the leading cause of disease burden in the Netherlands, as measured in disability-adjusted life years (DALYs) [316], it is expected that CVD risk management will also be addressed in this guideline. To inform its development, an inventory of key challenges was conducted in 2023 through surveys among healthcare professionals and representatives of adults with ID. One of the three primary themes that emerged was screening for age-related conditions, even in the absence of observable symptoms, centred around the key question: What should be screened, in whom, at what age, how frequently, and using which instruments [317]? Similar questions were raised by professionals working in the participating HA-ID care organisations when we engaged with them to identify research priorities for future studies. For instance, they questioned how CVD screening should be conducted in adults with ID and whether the SCORE2(-OP) chart, as recommended in the general guideline, is sufficiently applicable to this population.

Identifying CVD risk in adults with ID

Given the high levels of underdiagnosis of CVD and its risk factors, ID physicians and general practitioners should adopt a proactive approach to CVD risk management, including systematic screening and timely treatment of CVD risk factors. Considering the high prevalence of comorbidities at younger ages in older adults with ID [64], it may be appropriate to initiate such efforts earlier than in the general population, where systematic CVD risk screening is generally not recommended before the age of 40 in men and 50 in women [311]. This approach aligns with the Canadian Consensus Guidelines for Primary Care of Adults with Intellectual and Developmental Disabilities, which advocate for earlier screening in this population [314].

Based on the findings of this dissertation, some key directions for targeted CVD risk screening can be identified. In Chapter 6, hypertension at baseline emerged as the strongest significant risk factor for incident CVD during follow-up (HR 3.17; $p<0.001$). This finding aligns with the recognition by the European Society of Cardiology of hypertension as a major causal risk factor for CVD [21], responsible for an estimated 9.4 million deaths annually and 7% of global DALYs [287]. Given the substantial underdiagnosis of hypertension in clinical practice [40], early detection through routine screening is essential to enable timely intervention to prevent the onset of CVD. The importance of regular blood pressure monitoring and effective management of elevated blood pressure in adults with ID is also emphasised in a recent systematic review examining evidence-based and research-informed strategies for CVD prevention in this population [308].

In addition to hypertension, antipsychotic medication use at baseline was also significantly associated with CVD during follow-up (HR 1.98; p=0.04) (Chapter 6). Antipsychotic medication is frequently prescribed in people with ID, often off-label to manage challenging behaviours such as aggression or self-injurious behaviour [27], despite limited evidence for its efficacy in these contexts [29]. These medications can delay cardiac repolarisation, resulting in QTc prolongation [30], which increases the risk of ventricular arrhythmias and CVD [31]. In Chapter 4, we observed a markedly elevated prevalence of QTc prolongation within the HA-ID cohort (18.7%) compared to the general population (5.7-6.7%) [250, 260], with a concerning underdiagnosis rate of 100%. Atypical antipsychotics further elevate CVD risk through adverse metabolic effects, including weight gain and the development of metabolic syndrome [32, 33]. As a result, the Dutch Multidisciplinary Guideline on Problem Behaviour in adults with ID recommends ECG monitoring when prescribing antipsychotics, particularly in those with additional risk factors [73]. The elevated CVD risk associated with antipsychotic use necessitates careful evaluation of these prescriptions, with discontinuation when possible for non-psychiatric purposes, in accordance with the Care and Coercion Act, which has been in effect in the Netherlands since January 2020 [309]. For those requiring antipsychotics, proactive prevention strategies, including ECG monitoring and prompt management of any emerging CVD risk factors, are essential.

Finally, the high prevalence of undetected ECG abnormalities (Chapter 4) underscores the importance of ECG use in this population, as early detection may help prevent further cardiovascular complications. Previous findings from the HA-ID study by de Winter et al. (2016) further support this need, showing that half of the ultimately diagnosed myocardial infarctions were initially misattributed to epileptic seizures or abdominal pain, and that subtle symptoms of heart failure were also often overlooked [51]. These results emphasise the importance of raising awareness in clinical practice regarding the risk of underdiagnosed CVD in adults with ID, and the feasibility and potential added value of using ECGs in this context. Clinicians should be encouraged to remain vigilant when encountering atypical symptoms and to consider ECGs as a low-threshold, accessible diagnostic tool.

However, while these results offer important insights, they do not yet justify formal recommendations for systematic ECG screening. Any screening approach must carefully weigh potential benefits against possible harms. Overdiagnosis and the risk of overtreatment may lead to complications, especially when the

clinical relevance of detected abnormalities remains unclear. To guide the development of future clinical guidelines and ensure appropriate screening practices, further research is essential. Such research should not only explore the potential benefits of ECG screening but also assess its risks and long-term clinical impact within this specific population.

Lifestyle-oriented CVD prevention in adults with ID

In addition to screening, lifestyle-related prevention of CVD is essential in adults with ID. Research in the general population has shown that physical fitness, particularly cardiorespiratory fitness, is an important factor in the risk of CVD [52-56]. To examine this relationship in older adults with ID, we explored the cross-sectional association between physical fitness and CVD within this population (Chapter 5). Our findings showed that participants with CVD scored significantly lower on most physical fitness tests. They walked fewer metres on the cardiorespiratory fitness test (-81.4m; p=0.002) and demonstrated lower comfortable (-0.3km/h; p=0.04) and fast gait speeds (-1.1km/h; p=0.04) compared to those without CVD. Although the cross-sectional nature of the data limits causal interpretation, these results offer a first indication of a potential link between physical fitness and CVD in this population. Earlier research in the HA-ID cohort has already revealed very low physical fitness levels in older adults with ID, with performance comparable to or even worse than that of people in the general population who were 20 years older [61]. As hypothesised by Oppewal et al. (2020), even small gains in physical fitness may lead to substantial health benefits in this population [279]. This implicates that physical fitness might be a target for improvement of cardiovascular health in older adults with ID.

Beyond physical fitness, a recent systematic review [308] identified several effective lifestyle strategies to prevent CVD for this population, including the adoption of a healthy diet, engagement in regular physical activity, and smoking cessation. These approaches are well-established and consistent with those recommended for the general population. Nevertheless, people with ID are less likely to have the opportunity to participate in prevention and health promotion programs [318]. Generic health promotion initiatives, such as lifestyle campaigns, often fail to adequately reach this group or meet their specific needs [318, 319]. This is due to a range of factors, including cognitive and physical limitations, as well as comorbidities. As a result, tailored health promotion is essential. It requires customised lifestyle advice and programs that are specifically designed by professionals with expertise in working with people with ID. In addition, people with ID often rely on their immediate environment, such as relatives, caregivers, and healthcare providers, for support in adopting healthy behaviours [320]. This reliance underscores the

importance of fostering health-promoting environments [318] and ensuring that those involved in the care and support of people with ID are aware of their elevated CVD risk and actively contribute to lifestyle-oriented prevention strategies. Care-providing organisations also play a key role and should integrate targeted, tailored health promotion programs into routine care and daily practices. Encouragingly, several initiatives for people with ID have been developed in recent years [321-323], including two programs created within the HA-ID study: a physical activity and fitness program [324] and a progressive resistance exercise training program [325].

Directions for future research

Given the limited research on CVD incidence and its risk factors in older adults with ID, longitudinal studies are essential to improve risk assessment and inform targeted prevention strategies. Such knowledge is crucial for ID- and primary care providers, public health planners, and policymakers [43, 44], as it supports the optimisation of healthcare delivery [45] and enables more effective allocation of healthcare resources [46]. Although the HA-ID study represents a relatively large cohort for this specific population, its size (baseline n=1050; 10-year follow-up n=278) remains limited compared to cohorts from the general population, such as the Dutch Rotterdam Study, which includes nearly 18000 participants [326]. As a result, the prevalence estimates for ECG abnormalities (Chapter 4) and the incidence estimates for CVD (Chapter 6) were accompanied by wide confidence intervals, limiting the precision of our findings. In addition, we were unable to assess subgroup differences in the prevalence of ECG abnormalities (Chapter 4) and could not include all relevant variables related to physical fitness (Chapter 5) and CVD incidence (Chapter 6) in the multivariable models. These limitations underscore the need for large-scale longitudinal cohort studies in adults with ID to strengthen the existing evidence base. One potential approach to addressing this objective is through the integration of data from multiple international cohorts. To this end, the HA-ID study has established a collaboration with the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a longitudinal study investigating ageing among adults with ID aged 40 and over in Ireland [327]. Larger cohort studies facilitate more robust follow-up analyses of specific factors, such as physical fitness (Chapter 5) and Down syndrome (Chapter 6), for which this dissertation has identified cross-sectional or longitudinal associations with CVD.

Based on the findings of our systematic review (Chapter 2), it is also important to emphasise the need for high methodological quality in future studies. We observed considerable variation in methodological quality across the articles included. A substantial proportion of studies did not provide a sufficient description of the

study participants, and the validity and reliability of data collection methods was questionable. Given the implications for the generalisability, validity, and reliability of study findings, it is recommended that future research clearly describes the study population and utilise valid and reliable data collection methods, preferably objective measurements. Employing methodologies consistent with general population cohort studies enables meaningful comparisons between people with and without ID. Additionally, given the heterogeneity within this population, conducting subgroup analyses, such as focusing on people with Down syndrome, can yield valuable insights in future research.

This dissertation underscores the critical importance of incorporating objective measurements in CVD research involving adults with ID, reflecting their well-established value in the general population, as exemplified by studies such as the Rotterdam Study [326]. Given the increased risk of underdiagnosis in adults with ID, objective assessment methods are particularly essential. It provides insights that may not be fully captured through routine healthcare data alone. While large-scale database studies, including those led by Radboudumc in the Netherlands [123], provide valuable population-level perspectives, this limitation must be acknowledged when interpreting and comparing such data across populations. Therefore, cohort-based studies like the HA-ID study and large-scale database research should be regarded as complementary approaches. Together, they contribute to a more comprehensive and nuanced understanding of the cardiovascular health of adults with ID.

One of the key strengths of the HA-ID study (Chapter 3) is its comprehensive measurement protocol, enabling a thorough assessment of the health of older adults with ID. A common concern regarding this type of research is the potential for imposing an excessive burden on participants, some of whom are unable to provide informed consent themselves. However, these assumptions risk reinforcing a research gap that can contribute to health inequities. Every individual, regardless of intellectual ability, has the right to the highest attainable standard of health, as stated in the Convention on the Rights of Persons with Disabilities [328]. Objective methods are vital for identifying, preventing, and treating conditions such as CVD and improving care for adults with ID. Drawing on my experience with the 10-year follow-up of the HA-ID study, I can confirm that research involving older adults with ID presents significant challenges, though it is by no means impossible. When appropriate conditions are in place, this type of research is achievable in adults with ID. It is therefore important to challenge limiting assumptions and to promote the continued use of conventional, scientifically rigorous research methodologies

that involve direct participation in structured health assessments, while striving to minimise methodological compromises. Despite years of progress, research in this field still often feels pioneering, constantly evolving through new insights and methods. These lessons are essential for advancing future studies, including the next wave of the HA-ID cohort.

Concluding remarks

This dissertation contributes to the current knowledge on the prevalence and incidence of CVD and its risk factors in adults with ID. We presented an up-to-date synthesis of existing studies on CVD prevalence and incidence, including subgroup analyses, and contributed to the limited literature on CVD incidence in this population through a prospective longitudinal cohort study. Using data from the HA-ID cohort, we found a lower incidence of myocardial infarction but a similar to higher incidence of heart failure and stroke compared to the general population. Additionally, hypertension, Down syndrome, and antipsychotic use emerged as significant risk factors over time. We also demonstrated the feasibility of ECG recording in the majority of older adults with ID, which revealed substantial underdiagnosis of both myocardial infarction and QTc prolongation. These findings underscore the critical role of objective assessments, such as ECGs, in both research and clinical settings. Promoting lifestyle-related CVD prevention strategies and integrating tailored health promotion into routine care can contribute meaningfully to improved health outcomes. Furthermore, proactive screening and the management of modifiable CVD risk factors, particularly hypertension and antipsychotic use, represent essential steps toward improving cardiovascular health in older adults with ID. The scarcity of longitudinal research in this population emphasises the need for large-scale studies to further investigate CVD prevalence, incidence, and risk factors. Such efforts are vital for informing the development of targeted prevention guidelines and supporting improved cardiovascular health outcomes in adults with ID.

CHAPTER 8

Summary
Samenvatting

SUMMARY

Chapter 1 General introduction

Cardiovascular diseases (CVD) are a major health concern globally and are associated with high morbidity and mortality in adults with intellectual disabilities (ID). This population is at increased CVD risk due to a combination of syndrome-specific vulnerabilities, high rates of psychotropic drug use, and an elevated prevalence of lifestyle-related risk factors such as hypertension, type 2 diabetes, obesity, and physical inactivity. As life expectancy among adults with ID continues to rise, the burden of age-related CVD is growing. Despite this, epidemiological research on CVD prevalence and incidence in adults with ID remains limited. Accurate data are essential for ID physicians, primary care providers, public health planners, and policymakers to support the optimisation of healthcare delivery and effective allocation of healthcare resources.

A key challenge in studying CVD in adults with ID is underdiagnosis, partly due to the complexity of diagnostic procedures in this population. Difficulties in understanding and communicating health problems, atypical symptom presentation, and limited cooperation during physical examinations can hinder accurate diagnosis. Referral policies are made with great care, balancing medical need with potential impact on quality of life, which may at times lead to refraining from further diagnostic evaluation. Objective measures such as electrocardiograms (ECGs) may be valuable, as they can identify a broad range of cardiac abnormalities. However, their feasibility in adults with ID has not been previously studied, and data on the prevalence of ECG abnormalities in this population remain scarce.

Data on the predictive value of CVD risk factors in adults with ID also remains limited. Gaining insight into which risk factors predict CVD in adults with ID is essential for identifying high-risk groups and determining whether their risk profiles differ from those in the general population. If so, current CVD prevention guidelines may require adaptation to better meet the needs of this population. Evidence from studies in the general population indicate that physical fitness constitutes a significant risk factor for CVD, which may also hold relevance for people with ID.

This thesis aims to describe the prevalence and incidence of CVD in adults with ID and explore associated risk factors. We reviewed existing literature on CVD prevalence and incidence, assessed ECG feasibility and the prevalence of ECG abnormalities, examined the relationship between physical fitness and CVD, studied

CVD incidence over a 10-year follow-up period, and analysed the predictive value of CVD risk factors. These objectives were addressed through a systematic review and analyses from the Healthy Ageing and Intellectual Disabilities (HA-ID) study, a prospective multicentre cohort study on older adults with ID receiving formal care.

Chapter 2 Systematic review prevalence and incidence of CVD in adults with ID
With growing evidence of an elevated CVD risk in adults with ID, obtaining an accurate understanding of CVD prevalence and incidence in this population is essential. Such insights are crucial for ensuring optimal care and effective resource allocation. However, systematic reviews on this topic remain limited. To address this gap, in this chapter, we performed a systematic review to provide an overview of the available literature regarding CVD prevalence and incidence in adults with ID. Additionally, we focused on subgroup analyses to identify factors that may contribute to variations in CVD rates.

We conducted a systematic review following the PRISMA guidelines, synthesising data by specific CVD diagnoses and performing meta-analyses when applicable. Where possible, data were presented separately for different subgroups. In 55 articles, broad prevalence and incidence rates were reported for coronary artery disease (prevalence (prev) 0-12.9%; incidence (inc) 2.0-2.8 per 1000py), myocardial infarction (prev 0-7.9%; inc 0.3-2.8 per 1000py), heart failure (prev 0.8-18.6%; inc 12.5 per 1000py), cerebrovascular disease (prev 0.7-15.0%; inc 2.55 per 1000py), stroke (prev 1.3-17.2%; inc 2.7-3.2 per 1000py), peripheral arterial disease (prev 0.4-20.7%; inc 1.1 per 1000py), venous thrombosis (prev 0.6-12.4%; inc 0.8-4.1 per 1000py), and atrial fibrillation (prev 0.8-6.3%). Subgroup data have been reported based on age, sex, level of ID, aetiology of ID, living circumstances, CVD risk factors, data collection methods, and source populations. Overall, higher prevalence and incidence rates were observed in older people and in studies that used physical measurements for diagnosis.

We concluded that significant variability in methodological quality, clinical characteristics, and high statistical heterogeneity, makes it is challenging to draw generalisable conclusions for the overall adult ID population. The subgroup data, however, provide valuable insights into rates within specific subgroups. To enhance future research, it is important to conduct longitudinal studies using valid and reliable data collection methods (preferably objective measurements) that align with those used in the general population. Additionally, clear reporting of individual CVD diagnoses and subgroup analyses, will provide valuable additional insights into the CVD prevalence and incidence in adults with ID.

Chapter 3 HA-ID study: findings and 10-year follow-up protocol
The HA-ID study is a prospective multicentre cohort study on physical and mental health of older adults with ID. This chapter provides a summary of the previous findings from the HA-ID study and outlines the design of the 10-year follow-up, which involved the collection of extensive health data across five research themes: 1) cardiovascular disease; 2) physical activity, fitness and musculoskeletal disorders; 3) psychological problems and psychiatric disorders; 4) nutrition and nutritional state; and 5) frailty.

In short, the baseline results of the HA-ID study showed that older adults with ID experienced more health problems than their peers in the general population and that these issues occurred at younger ages. Given that Chapter 3 already functions as a summary, we therefore focus here primarily on aspects from this chapter that are directly relevant to the scope of this dissertation. The baseline measurements of the HA-ID study offered important insights into the prevalence of CVD risk factors, revealing higher rates of certain factors compared to the general population and significant underdiagnosis in clinical practice. During the 3-year follow-up, CVD incidence was assessed, reporting myocardial infarction (2.8 per 1000py), heart failure (12.5 per 1000py), and stroke (3.2 per 1000py). Obesity, atypical antipsychotic use, chronic kidney disease, and a history of heart failure or stroke were identified as predictors for CVD development. However, the study's limited statistical power highlighted the need for longer follow-up durations to strengthen future findings. The 10-year follow-up of the HA-ID cohort provides valuable opportunities to further explore CVD risk factors and the development of CVD over a longer period in older adults with ID. We have expanded the data collection during this follow-up to include several additional assessments, including ECGs.

Compared to the amount of research in the general population, epidemiological research into the health of older adults with ID is still in its infancy. Longitudinal data about the health of this vulnerable and relatively unhealthy group are needed so that policy and care can be prioritised and for guiding clinical decision making about screening, prevention and treatment to improve healthy ageing.

Chapter 4 Feasibility and findings of ECG recording in older adults with ID
Older adults with ID face a high risk of CVD. At the same time, diagnostic challenges increases the likelihood of underdiagnosis in this population. To reduce underdiagnosis, objective measures like ECGs could be useful. However,

little is known about the feasibility of ECG recordings or the prevalence of ECG abnormalities in this population. Therefore, we investigated the feasibility of ECG recording in older adults with ID, studied the prevalence of ECG abnormalities, and compared these findings with medical records.

We attempted a resting 12-lead ECG in 200 older adults with ID from the 10-year follow-up of the HA-ID study. ECG recording was considered feasible if the recording could be made and if the ECG could be interpreted. If myocardial infarction, atrial fibrillation, or QTc prolongation were identified on the ECG but not documented in the participant's medical record, it was classified as a previously undiagnosed condition. We found that ECG recording was feasible in 67% of the participants. Feasibility was lower with increasing severity of ID and for wheelchair users. The most prevalent ECG abnormalities included prolonged P-wave duration (27.6%), QTc prolongation (18.7%), minor T-wave abnormalities (17.9%), first degree atrioventricular block (12.7%), and myocardial infarction (6.7%). Notably, the vast majority of myocardial infarctions (88.9%) and all cases of QTc prolongation were previously undiagnosed.

We concluded that ECG recording is feasible in the majority of older adults with ID and identified a significant underdiagnosis of ECG abnormalities in clinical practice. Early detection of these abnormalities presents an opportunity for timely preventive interventions, and we would therefore like to emphasise the importance of ECG recording in this population. Furthermore, these findings highlight the need for further research into the potential benefits of opportunistic ECG screening in older adults with ID.

Chapter 5 Associations between physical fitness and CVD in older adults with ID
Reduced physical fitness is a well-known CVD risk factor in the general population and, therefore, represents a critical target for preventive measures and interventions aimed at enhancing cardiovascular health. However, it remains uncertain whether this association also holds true for older adults with ID, given their overall low physical fitness levels and high prevalence of comorbidities at an earlier age. To address this, we analysed differences in physical fitness between older adults with ID, with and without CVD.

We used cross-sectional data from 684 older adults with ID who participated in the baseline measurements of the HA-ID study and for whom medical file information and physical fitness test results were available. The CVD status was obtained from the participants' medical records. Physical fitness measures included

cardiorespiratory fitness (10-m shuttle walking test), comfortable and fast gait speed (over 5m), and grip strength (hand dynamometer). With multivariable linear regression we analysed associations between these physical fitness components and CVD presence, adjusting for participant characteristics. We found that participants with CVD had significantly lower physical fitness levels than those without CVD, for the physical fitness components cardiorespiratory fitness (-81.4m; p=0.002), comfortable gait speed (-0.3km/h; p=0.04), and fast gait speed (-1.1km/h; p=0.04). We found no statistically significant difference between the two groups for grip strength (-0.2kg; p=0.89).

We concluded that older adults with ID and CVD had significantly lower physical fitness levels compared to those without CVD, with the exception of grip strength. Longitudinal follow-up studies are needed to explore the relationship between physical fitness and CVD over time, allowing for insights into the direction and causality of this associations. Such research will also contribute to determining the extent to which physical fitness, similar to the general population, is an important factor in promoting cardiovascular health in older adults with ID.

Chapter 6 CVD incidence and risk factors in older adults with ID

Given that older adults with ID are at increased risk of CVD, longitudinal studies on CVD incidence and its associated risk factors are essential for optimising healthcare delivery and resource allocation in this population. Yet such studies remain limited. Therefore, we aimed to assess the incidence of CVD in older adults with ID and explore associations with participant characteristics and baseline risk factors.

We used longitudinal data from 598 older adults with ID who participated in the baseline measurements of the HA-ID study and had medical record data available at the 10-year follow-up. Baseline measurements were conducted in 2009-2010, with follow-up assessments, including medical record reviews, in 2020-2023. Incidence rates for myocardial infarction, heart failure, and stroke were calculated by sex and 10-year age categories. Competing risk analysis, accounting for mortality, was performed to examine associations between baseline risk factors and CVD diagnoses during follow-up. Over a mean follow-up period of 8.6 years, we observed incidence rates of 2.3 per 1000py for myocardial infarction, 7.2 for heart failure, and 5.3 for stroke. Hypertension (HR 3.17; p<0.001), Down syndrome (HR 2.66; p<0.01), and antipsychotic use (HR 1.98; p=0.04) were significantly associated with increased CVD risk during the follow-up period.

In conclusion, older adults with ID demonstrated a lower incidence of myocardial infarction and a similar to higher incidence of heart failure and stroke compared to the general population. Further research is warranted, including a focus on the association of CVD incidence with Down syndrome. Meanwhile, proactive assessment and management of CVD risk factors, such as hypertension and antipsychotic use, are important to improve cardiovascular health in older adults with ID.

Chapter 7 General discussion

This thesis enhances current knowledge on the prevalence and incidence of CVD and its associated risk factors in adults with ID. We provided an up-to-date synthesis of the literature, including subgroup analyses, based on 55 studies that reported wide-ranging prevalence and incidence rates across various CVD diagnoses. We demonstrated the feasibility of ECG recording in the majority of older adults with ID, reported the prevalence of ECG abnormalities, and identified substantial underdiagnosis of both myocardial infarction and QTc prolongation. Additionally, we found that older adults with ID and CVD exhibited significantly lower physical fitness levels on most physical fitness tests than those without CVD. Finally, we contributed to the limited literature on CVD incidence in this population. We found a lower incidence of myocardial infarction, but similar to higher rates of heart failure and stroke compared to the general population. Hypertension, Down syndrome, and antipsychotic use emerged as significant longitudinal risk factors.

Given the substantial burden of CVD and frequent underdiagnosis in adults with ID, there is a clear need for more systematic and proactive risk management. Tailored CVD guidelines are essential to improving care. ID physicians and general practitioners should adopt a proactive approach, including routine screening and timely management of key risk factors, including hypertension and antipsychotic use. The high prevalence of undetected ECG abnormalities highlights the importance of ECG use in this population, as early detection may prevent further cardiovascular complications. Any screening approach must carefully weigh the potential benefits against possible risks, such as overdiagnosis and overtreatment, as well as consider the long-term clinical implications for this specific population. Additionally, lifestyle-related CVD prevention is crucial and requires tailored health promotion programs developed by specialised professionals and integrated into routine care and daily practices by informed support networks and organisations.

This dissertation underscores the critical importance of incorporating objective measurements in CVD research involving adults with ID. Applying conventional, scientifically robust methodologies, including structured health assessments, is

vital to ensuring data quality and validity. Longitudinal studies are essential to improve risk prediction and guide effective prevention strategies. Future research should prioritise large-scale longitudinal data collection using valid and reliable methods aligned with general population cohort studies. These efforts are vital for developing targeted prevention guidelines and improving CVD outcomes in adults with ID.

SAMENVATTING

Hoofdstuk 1 Algemene inleiding

Hart- en vaatziekten (HVZ) zijn wereldwijd een groot gezondheidsprobleem en liggen ook bij volwassenen met een verstandelijke beperking (VB) ten grondslag aan ziekte en sterfte. Deze groep heeft een verhoogd risico op HVZ door een combinatie van factoren, zoals syndroomgerelateerde kwetsbaarheden, veelvuldig gebruik van psychofarmaca en een hoge prevalentie van leefstijlgerelateerde risicofactoren zoals hoge bloeddruk, diabetes type 2, obesitas en fysieke inactiviteit. Door de stijgende levensverwachting van mensen met een VB neemt ook de ziektelast door leeftijdsgebonden HVZ toe. Toch is er nog weinig epidemiologisch onderzoek naar de prevalentie en incidentie van HVZ bij deze doelgroep. Betrouwbare gegevens zijn essentieel voor artsen voor verstandelijk gehandicapten, huisartsen, beleidsmakers en gezondheidsplanners om de zorg te verbeteren en middelen effectief in te zetten.

Een belangrijk uitdaging bij onderzoek naar HVZ bij mensen met een VB is onderdiagnostiek. Een mogelijke verklaring hiervoor is de complexiteit van diagnostische procedures binnen deze doelgroep. Mensen met een VB kunnen moeite ervaren met het uiten van gezondheidsklachten, symptomen kunnen atypisch zijn en lichamelijk onderzoek verloopt soms moeizaam. Daarnaast maken artsen zorgvuldige afwegingen bij het doorverwijzen, waarbij medische noodzaak wordt afgewogen tegen mogelijke belasting. Dit kan ertoe leiden dat aanvullende diagnostiek niet altijd wordt ingezet. Objectieve metingen, zoals een hartfilmpje (ecg), kunnen helpen om hartafwijkingen vroegtijdig op te sporen. Er is echter nog weinig bekend over de haalbaarheid van hartfilmpjes bij mensen met een VB en hoe vaak afwijkingen voorkomen.

Inzicht in welke factoren het risico op HVZ bij mensen met een VB verhogen is belangrijk om risicogroepen te identificeren en te bepalen of hun risicoprofiel afwijkt van dat van de algemene bevolking. Op dit moment is over de voorspellende waarde van risicofactoren voor HVZ bij deze groep nog weinig bekend. Met deze kennis, zouden bestaande preventierichtlijnen voor HVZ mogelijk aangepast moeten worden. Op basis van onderzoek in de algemene bevolking lijkt onder andere lichamelijke fitheid een belangrijke risicofactor voor HVZ, mogelijk is deze ook relevant bij mensen met een VB.

In dit proefschrift wordt de prevalentie en incidentie van HVZ bij volwassenen met een VB beschreven en worden bijbehorende risicofactoren onderzocht. We hebben bestaande literatuur over de prevalentie en incidentie van HVZ bestudeerd, onderzochten de

haalbaarheid van het maken van hartfilmpjes, onderzochten de prevalentie van ecg-afwijkingen, bestudeerden de relatie tussen lichamelijke fitheid en HVZ, onderzochten de incidentie van HVZ over een periode van tien jaar en analyseerden de voorspellende waarde van risicofactoren voor HVZ. Deze onderzoeksvragen zijn beantwoord middels een systematisch literatuuronderzoek en analyses van gegevens uit het onderzoek 'Gezond Ouder worden met een verstandelijke beperking' (GOUD), een prospectieve multicenter cohortstudie onder ouderen met een VB.

Hoofdstuk 2 Systematische review prevalentie en incidentie van HVZ bij volwassenen met een VB

Er zijn steeds meer aanwijzingen dat volwassenen met een VB een verhoogd risico hebben op HVZ. Daarom is het belangrijk om helder inzicht te krijgen in de prevalentie en incidentie van HVZ binnen deze populatie. Dit is essentieel om optimale zorg te bieden en middelen effectief in te kunnen zetten. Systematische reviews over dit onderwerp zijn echter maar beperkt beschikbaar. Daarom hebben we in dit hoofdstuk een systematische review uitgevoerd om een overzicht te geven van de beschikbare literatuur over de prevalentie en incidentie van HVZ bij volwassenen met een VB. Daarnaast hebben we gekeken naar subgroepen om factoren te identificeren die mogelijk bijdragen aan verschillen in HVZ-cijfers.

We hebben het review uitgevoerd volgens de PRISMA-richtlijnen. Gegevens werden samengevat per specifieke HVZ-diagnose, en waar mogelijk werden meta-analyses uitgevoerd en werden resultaten afzonderlijk gepresenteerd voor verschillende subgroepen. We includeerden in totaal 55 artikelen waarin we grote verschillen vonden in de prevalentie en incidentie van coronaire hartziekten, hartinfarcten, hartfalen, cerebrovasculaire aandoeningen, beroerte, perifeer arterieel vaatlijden, veneuze trombose en atriumfibrilleren. Daarnaast rapporteerden we subgroepgegevens op basis van leeftijd, geslacht, mate van VB, oorzaak van de VB, woonsituatie, risicofactoren voor HVZ, methode van dataverzameling en kenmerken van de onderzochte populatie. We observeerden hogere prevalentie- en incidentiecijfers bij oudere volwassenen en in studies die fysieke metingen gebruikten voor het vaststellen van de diagnose.

We concludeerden dat de grote variatie in methodologische kwaliteit, de verschillen in klinische kenmerken en hoge statistische heterogeniteit het moeilijk maken om eenduidige conclusies te trekken over de prevalentie en incidentie van HVZ bij volwassenen met een VB. De subgroepgegevens bieden echter waardevolle inzichten in de prevalentie en incidentie van HVZ binnen specifieke groepen. Voor toekomstig onderzoek is het belangrijk om longitudinale studies uit te voeren met valide en betrouwbare dataverzamelingsmethoden (bij voorkeur objectieve

metingen) die overeenkomen met de methoden die in de algemene bevolking worden gebruikt. Daarnaast zal een gedetailleerde rapportage van afzonderlijke HVZ-diagnoses, samen met subgroepanalyses, waardevolle inzichten opleveren in de prevalentie en incidentie van HVZ bij volwassenen met een VB.

Hoofdstuk 3 Het GOUD onderzoek: bevindingen en protocol voor de 10-jaar follow-up

Het GOUD onderzoek is een prospectieve multicenter cohortstudie naar de fysieke en mentale gezondheid van ouderen met een VB. Dit hoofdstuk geeft een samenvatting van de eerdere bevindingen uit het GOUD onderzoek en beschrijft het ontwerp van de 10-jaar follow-up, waarbij uitgebreide gezondheidsgegevens werden verzameld rond vijf onderzoeksthema's: 1) hart- en vaatziekten; 2) lichamelijke activiteit, fitheid en musculoskeletale aandoeningen; 3) psychische problemen en psychiatrische stoornissen; 4) voeding en voedingstoestand; en 5) kwetsbaarheid.

In het kort lieten de resultaten van de eerste metingen van het GOUD onderzoek zien dat ouderen met een VB meer gezondheidsproblemen ervaren dan hun leeftijdsgenoten in de algemene bevolking en dat deze problemen zich op jongere leeftijd voordoen. Gezien het feit dat Hoofdstuk 3 al fungeert als samenvatting, richten we ons hier vooral op de aspecten uit dit hoofdstuk die direct relevant zijn voor het onderwerp van dit proefschrift. Het GOUD onderzoek heeft belangrijke inzichten gegeven in de prevalentie van risicofactoren voor HVZ, waarbij een hogere prevalentie van bepaalde risicofactoren werd vastgesteld in vergelijking met de algemene bevolking, evenals aanzienlijke onderdiagnostiek in de klinische praktijk. Tijdens de 3-jaar follow-up werd de incidentie van HVZ onderzocht, waarbij de volgende incidentiecijfers werden gerapporteerd: hartinfarct (2.8 per 1000 persoonjaren), hartfalen (12.5 per 1000 persoonjaren) en beroerte (3.2 per 1000 persoonjaren). Obesitas, het gebruik van atypische antipsychotica, chronische nierziekte en een voorgeschiedenis van hartfalen of beroerte werden geïdentificeerd als belangrijke risicofactoren voor de ontwikkeling van HVZ. De beperkte statistische power van de studie benadrukte de behoefte aan langere follow-up periodes om toekomstige bevindingen te versterken. De 10-jaar follow-up van het GOUD cohort biedt mogelijkheden om HVZ-risicofactoren en de ontwikkeling van HVZ over een langere periode bij ouderen met een VB verder te onderzoeken. We hebben de dataverzameling tijdens deze follow-up uitgebreid met verschillende aanvullende assessments, waaronder hartfilmpjes.

In vergelijking met het aantal onderzoeken in de algemene bevolking, staat epidemiologisch onderzoek naar de gezondheid van ouderen met een VB in de kinderschoenen. Longitudinale gegevens over de gezondheid van deze kwetsbare en relatief ongezonde groep zijn essentieel om beleid en zorg te kunnen prioriteren en klinische besluitvorming over screening, preventie en behandeling te ondersteunen, met als doel gezond ouder worden te bevorderen.

Hoofdstuk 4 Haalbaarheid en bevindingen van hartfilmpjes bij ouderen met een VB
Ouderen met een VB hebben een verhoogd risico op HVZ. Tegelijkertijd zorgen diagnostische uitdagingen voor een verhoogde kans op onderdiagnostiek in deze populatie. Objectieve metingen, zoals hartfilmpjes, kunnen helpen om onderdiagnostiek van HVZ te verminderen. Er is echter weinig bekend over de haalbaarheid het maken van een hartfilmpje en de prevalentie van ecg-afwijkingen in deze populatie. Daarom onderzochten we de haalbaarheid van het maken van hartfilmpjes bij ouderen met een VB, onderzochten we de prevalentie van ecg-afwijkingen en vergeleken we deze bevindingen met medische dossiers.

We voerden een rust-ecg uit bij 200 ouderen met een VB die deelnamen aan de 10-jaar follow-up van het GOUD onderzoek. Een hartfilmpje werd als haalbaar beschouwd wanneer het ecg kon worden geïnterpreteerd. Wanneer een hartinfarct, atriumfibrilleren of QTc-verlenging op het ecg werd vastgesteld, maar deze diagnose niet in het medische dossier van de deelnemer vermeld stond, werd dit geclassificeerd als een ongediagnosticeerde aandoening. Bij twee derde van de deelnemers bleek het haalbaar om een hartfilmpje te maken. De haalbaarheid nam af naarmate de ernst van de VB toenam en was tevens lager bij rolstoelgebruikers. De meest voorkomende ecg-afwijkingen waren verlengde P-golfduur, QTc-verlenging, milde T-golfafwijking, eerstegraads atrioventriculair blok en hartinfarct. Opvallend was dat de overgrote meerderheid van de hartinfarcten en alle gevallen van QTc-verlenging niet eerder waren gediagnosticeerd.

Wij concludeerden dat het bij de meerderheid van ouderen met een VB haalbaar is om hartfilmpjes te maken en dat er in de klinische praktijk tevens sprake is van aanzienlijke onderdiagnostiek van ecg-afwijkingen. Vroegtijdige detectie van deze afwijkingen biedt kansen voor tijdige preventieve interventies. Daarom willen we graag het belang van het maken van hartfilmpjes in deze populatie benadrukken. Daarnaast onderstrepen deze bevindingen de noodzaak van verder onderzoek naar de voordelen van opportunistische ecg-screening bij ouderen met een VB.

Hoofdstuk 5 Relatie tussen fysieke fitheid en HVZ bij ouderen met een VB
Lage fysieke fitheid is een bekende risicofactor voor HVZ in de algemene bevolking en vormt daarom een belangrijk aandachtsgebied voor preventie en interventies ter verbetering van de cardiovasculaire gezondheid. Het is echter onduidelijk of deze associatie ook van toepassing is op ouderen met een VB, gezien hun doorgaans lagere fysieke fitheid en hogere prevalentie van comorbiditeiten op jongere leeftijd. Om dit te onderzoeken, analyseerden we verschillen in fysieke fitheid tussen ouderen met een VB, met en zonder HVZ.

Hiervoor maakten we gebruik van cross-sectionele gegevens van 684 ouderen met een VB die deelnamen aan de baseline / nulmetingen van het GOUD onderzoek en van wie medische dossiergegevens en resultaten van de fitheidstesten beschikbaar waren. De HVZ-status werd verkregen uit de medische dossiers van de deelnemers. De fysieke fitheidsmetingen omvatte cardiorespiratoire fitheid (10-metre shuttle wandel test), comfortabele en snelle loopsnelheid (over 5 meter) en knijpkracht (met een handdynamometer). Met multivariabele lineaire regressie analyseerden we de associaties tussen deze componenten van fysieke fitheid en de aanwezigheid van HVZ, waarbij we corrigeerden voor kenmerken van de deelnemers. We constateerden dat deelnemers met HVZ aanzienlijk lagere fysieke fitheidsniveaus hadden dan degenen zonder HVZ, voor de componenten cardiorespiratoire fitheid, comfortabele loopsnelheid en snelle loopsnelheid. We vonden geen statistisch significant verschil tussen de twee groepen voor knijpkracht.

We concludeerden dat ouderen met een VB en HVZ aanzienlijk lagere fysieke fitheidsniveaus vertoonden dan degenen zonder HVZ, met uitzondering van knijpkracht. Longitudinale studies zijn noodzakelijk om de relatie tussen fysieke fitheid en HVZ in de tijd te onderzoeken, om meer inzicht te krijgen in de richting en causaliteit van deze associaties. Dergelijk onderzoek zal ook bijdragen aan het bepalen in hoeverre fysieke fitheid, net als in de algemene bevolking, een belangrijke rol speelt bij het bevorderen van de cardiovasculaire gezondheid van ouderen met een VB.

Hoofdstuk 6 Incidentie van HVZ en risicofactoren bij ouderen met een VB
Gegeven dat ouderen met een VB een verhoogd risico op HVZ hebben, zijn longitudinale studies naar de incidentie van HVZ en de bijbehorende risicofactoren essentieel om de zorg voor deze groep te verbeteren en beschikbare middelen efficiënt in te zetten. Toch is dergelijk onderzoek schaars. Daarom onderzochten wij de incidentie van HVZ bij ouderen met een VB en de relatie met risicofactoren.

Voor dit onderzoek maakten we gebruik van longitudinale gegevens van 598 ouderen met een VB die deelnamen aan de baseline/nulmetingen van het GOUD onderzoek en van wie medische dossiergegevens beschikbaar waren bij de 10-jaar follow-up. De baseline/nulmetingen werden uitgevoerd in 2009-2010 en de follow-up vond plaats in 2020-2023, inclusief medisch dossieronderzoek. We berekenden de incidentiecijfers voor hartinfarct, hartfalen en beroerte, uitgesplitst naar geslacht en leeftijd. Om de samenhang tussen risicofactoren bij aanvang en HVZ-diagnoses tijdens de follow-up te onderzoeken, voerden we een concurrerende risicoanalyse uit, waarbij sterfte als concurreren risico werd meegenomen. Gedurende een gemiddelde follow-up periode van 8.6 jaar vonden we incidentiecijfers van 2.3 per 1000 persoonsjaren voor hartinfarct, 7.2 voor hartfalen en 5.3 voor beroerte. Een verhoogde bloeddruk, downsyndroom en het gebruik van antipsychotica bleken significant geassocieerd met een verhoogd risico op HVZ gedurende de follow-upperiode.

Samenvattend vonden we dat ouderen met een VB een lagere incidentie van hartinfarct vertoonden, maar een vergelijkbare tot hogere incidentie van hartfalen en beroerte in vergelijking met de algemene bevolking. Vervolgonderzoek is noodzakelijk, met speciale aandacht voor de relatie tussen HVZ-incidentie en downsyndroom. Tegelijkertijd is het belangrijk om risicofactoren voor HVZ, zoals hoge bloeddruk en het gebruik van antipsychotica, tijdig te herkennen en doelgericht aan te pakken om de cardiovasculaire gezondheid van ouderen met een VB te verbeteren.

Hoofdstuk 7 Algemene discussie

Dit proefschrift vergroot de bestaande kennis over de prevalentie en incidentie van HVZ en de bijbehorende risicofactoren bij volwassenen met een VB. We gaven een actueel literatuuroverzicht op basis van 55 studies, inclusief subgroepanalyses, waarin uiteenlopende prevalentie- en incidentiecijfers voor diverse HVZ-diagnoses werden gerapporteerd. Daarnaast toonden we aan dat het maken van een hartfilmpje haalbaar is bij de meeste ouderen met een VB. We brachten in kaart hoe vaak ecg-afwijkingen voorkomen en constateerden dat zowel hartinfarcten als QTc-verlenging vaak onopgemerkt blijven. Ook bleek dat ouderen met een VB en HVZ op de meeste lichamelijke fitheidstesten beduidend lager scoorden dan leeftijdgenoten zonder HVZ. Verder leverden we een bijdrage aan de nog beperkte literatuur over de incidentie van HVZ in deze populatie. We vonden een lagere incidentie van hartinfarcten, maar een vergelijkbare tot hogere incidentie van hartfalen en beroertes in vergelijking met de algemene bevolking. Hoge bloeddruk, downsyndroom en het gebruik van antipsychotica kwamen naar voren als belangrijke risicofactoren over de tijd.

Gezien het aanzienlijke risico op HVZ en de frequente onderdiagnostiek bij volwassenen met een VB, is er een duidelijke behoefte aan systematisch en proactief risicomanagement. Op maat gemaakte richtlijnen voor HVZ zijn essentieel om de zorg te verbeteren. In de discussie pleit ik voor een proactieve aanpak, met routinematige screening en tijdige behandeling van belangrijke risicofactoren, zoals hoge bloeddruk en het gebruik van antipsychotica. De hoge prevalentie van ongedetecteerde ecg-afwijkingen benadrukt het belang van het gebruik van hartfilmpjes in deze populatie, aangezien vroege opsporing verdere cardiovasculaire complicaties kan helpen voorkomen.

Bij elke screeningsstrategie dienen de potentiële voordelen zorgvuldig te worden afgewogen tegen mogelijke risico's, zoals overdiagnose en overbehandeling, en dienen ook de langetermijngevolgen voor deze specifieke populatie in overweging te worden genomen. Daarnaast is preventie van HVZ door leefstijl essentieel. Dit vereist op maat gemaakte gezondheidsbevorderingsprogramma's voor mensen met een VB, ontwikkeld door gespecialiseerde professionals en geïntegreerd in de reguliere zorg en dagelijkse praktijk door ondersteuningsnetwerken en organisaties.

Dit proefschrift benadrukt het belang van het gebruik van objectieve metingen in onderzoek naar HVZ bij volwassenen met een VB. Het toepassen van wetenschappelijk onderbouwde methoden is essentieel om de kwaliteit en validiteit van de verzamelde gegevens te waarborgen. Longitudinale studies zijn noodzakelijk om het risico op HVZ beter te kunnen voorspellen en om effectieve preventiestrategieën te ontwikkelen. Toekomstig onderzoek zou zich moeten richten op grootschalige, longitudinale dataverzameling met valide en betrouwbare methoden, die aansluiten bij cohortstudies in de algemene bevolking. Dit is essentieel voor het ontwikkelen van gerichte preventierichtlijnen en het verbeteren van de cardiovasculaire gezondheid van volwassenen met een VB.

CHAPTER 9

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CHAPTER 10

Curriculum Vitae
Portfolio
Publications

CURRICULUM VITAE

Marleen Jolein de Leeuw werd op 23 september 1990 geboren in Dongen. In 2009 behaalde zij haar vwo-diploma aan het Cambreur College in Dongen. Aansluitend volgde zij de opleiding Ergotherapie aan de Hogeschool Rotterdam, waar zij in 2013 afstudeerde. Na haar afstuderen startte zij als ergotherapeut bij Rijndam Revalidatie in Rotterdam, waar zij werkzaam was binnen de poliklinische revalidatie voor volwassenen met niet-aangeboren hersenletsel en chronische pijn. Tegelijkertijd was zij als docent verbonden aan de opleiding Ergotherapie van de Hogeschool Rotterdam, waar zij haar Basiskwalificatie Onderwijs (BKO) en Basiskwalificatie Examinering (BKE) behaalde. In 2015 begon zij aan de master Evidence Based Practice in Health Care aan de Universiteit van Amsterdam. Haar masteronderzoek, uitgevoerd bij de afdeling Research & Development van Rijndam Revalidatie, richtte zich op factoren die samenhangen met zelfstandigheid in dagelijkse activiteiten bij kinderen met cerebrale parese. In 2017 rondde zij deze master tot klinisch epidemioloog cum laude af. Na haar master combineerde zij haar werk als docent met een functie als onderzoeker bij het Kenniscentrum Zorginnovatie van de Hogeschool Rotterdam. Daar was zij betrokken bij toegepast onderzoek naar de ontwikkeling en evaluatie van een gepersonaliseerde e-health interventie ter bevordering van arbeidsgereedheid en arbeidsparticipatie bij volwassenen met een autismespectrumstoornis. In 2018 startte Marleen haar promotieonderzoek bij de leerstoel Geneeskunde voor Verstandelijk Gehandicapten van het Erasmus MC in Rotterdam, met een aanstelling bij zorgorganisatie Amarant. Haar onderzoek vond plaats binnen de Academische werkplaats 'Gezond ouder worden met een verstandelijke beperking' (GOUD), een samenwerkingsverband tussen het Erasmus MC en de zorgorganisaties Abrona, Amarant en Ipse de Bruggen. Hier was Marleen betrokken bij de opzet en uitvoering van de 10-jaar follow-up van het GOUD onderzoek, een prospectieve multicenter cohortstudie naar de fysieke en mentale gezondheid van ouderen met een verstandelijke beperking. Haar proefschrift richtte zich op de prevalentie en incidentie van hart- en vaatziekten en doelgroep specifieke risicofactoren binnen deze populatie. Sinds augustus 2025 is Marleen werkzaam als senior adviseur wetenschappelijk onderzoek bij het Amphia Ziekenhuis in Breda.

PHD PORTFOLIO

Name PhD student	Marleen Jolein de Leeuw Department of General Practice, Intellectual Disability Medicine Research - Erasmus MC, University Medical Center Rotterdam
Research School	NIHES
PhD period	November 2018 - May 2025
Promotor	Prof. dr. P.J.E. Bindels
Supervisors	Dr. D.A.M. Maes-Festen Dr. A. Oppewal

	Year(s)	EC
Courses		
Basic course Rules and Organisation for Clinical researchers (BROK) – NFU	2019	1.50
EndNote & Systematic review in PubMed and other databases – Medical library, Erasmus MC	2019	1.00
Cardiovascular Epidemiology – NIHES, Erasmus MC	2019	0.90
Scientific Integrity – Graduate School, Erasmus MC	2020	0.30
Speaking skills for staff C1 – Language & Training Center, Erasmus University	2020	2.00
Patient Oriented Research – Graduate School, Erasmus MC	2021	0.30
Biomedical English Writing – Postgraduate School Molecular Medicine, Erasmus University	2021	2.50
Basic ECG principles – ProCare	2021	0.50
ECG interpretation – ProCare	2021	0.50
PhD day – Graduate School, Erasmus MC	2021	0.20
Cardiovascular Clinical Epidemiology – Graduate School, Erasmus MC	2021	0.20
Principles in Causal Inference – NIHES, Erasmus MC	2022	1.40
Re-registration Basic course Rules and Organisation for Clinical researchers – NFU	2023	0.25

	Year(s)	EC
Lectures and workshops		
Brainstorm sessions on cardiovascular disease research questions with staff and individuals with intellectual disabilities – Academic Collaborative Research Center Healthy Ageing and Intellectual Disabilities, Utrecht	2022	1.00
Lecture on findings from research on cardiovascular diseases in people with intellectual disabilities – Specialist training of physicians for people with Intellectual Disabilities, Erasmus MC	2023	0.50
Presentations		
Presenting at teams and departments Amarant, Abrona, and Ipse de Bruggen, care organisations	2018-2022	1.00
Presenting at Department of General Practice, Erasmus MC	2019-2022	2.00
Presenting findings from the HA-ID study on cardiovascular diseases in individuals with intellectual disabilities, Oorthuys overleg, Amsterdam UMC	2019	0.50
National and international conferences		
World Conference - International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD) (oral; Glasgow)	2019	2.00
European Conference - International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD) (oral; Amsterdam)	2021	2.00
Trinity Health and Education International Research Conference (THECONF2022) (oral; Dublin)	2022	2.00
European Geriatric Medicine Society congress (poster; Helsinki)	2023	2.00
Congres 'Zoek het uit! Praktijk en wetenschap dichter bij elkaar – Vilans (attendance; Nieuwegein)	2019	0.30
Research symposium – Amarant, care organisation (oral; Tilburg)	2019-2021	1.50

	Year(s)	EC
Supervising		
Critical reading – Department of General Practice, Erasmus MC	2019-2022	1.00
Medical student master theses – Intellectual Disability Medicine Research, Department of General Practice, Erasmus MC	2020-2021	2.00
Other		
Member of research group – Amarant, care organisation	2019-2025	1.00
Co-authoring HGOG grant application 'Diagnosis, prevalence and associated factors of osteoarthritis in adults with intellectual disabilities' – ZonMw (granted)	2019	2.00
Member organising committee 1st Research Day of the Associatie van Academische Werkplaatsen Verstandelijke Beperkingen – Rotterdam	2019-2020	3.00
Career orientation trajectory – Loopbaancentrum, Erasmus MC	2021	2.00
Symposium Career perspectives for junior epidemiologists – Netherlands Society for Epidemiology (attendance; Rotterdam)	2021	0.10
Peer review Journal of Intellectual Disability Research	2023	0.20
Total EC		**37.65**

PUBLICATIONS

This thesis

de Leeuw, M. J., Hilgenkamp, T. I. M., Maes-Festen, D. A. M., Bindels, P. J. E., Elbers, R. G., & Oppewal, A. (2025). Prevalence and Incidence of Cardiovascular Disease in Adults With Intellectual Disabilities: A Systematic Review. *Journal of Intellectual Disability Research*, Article jir.13254. Advance online publication. https://doi.org/10.1111/jir.13254

de Leeuw, M. J., Oppewal, A., Elbers, R. G., Knulst, M. W. E. J., Van Maurik, M. C., van Bruggen, M. C., Hilgenkamp, T. I. M., Bindels, P. J. E., & Maes-Festen, D. A. M. (2022). Healthy Ageing and Intellectual Disability study: summary of findings and the protocol for the 10-year follow-up study. *BMJ Open*, 12(2), Article e053499. https://doi.org/10.1136/bmjopen-2021-053499

de Leeuw, M. J., Böhmer, M. N., Leening, M. J. G., Kors, J. A., Bindels, P. J. E., Oppewal, A., & Maes-Festen, D. A. M. (2024). Feasibility and findings of electrocardiogram recording in older adults with intellectual disabilities: results of the Healthy Ageing and Intellectual Disabilities study. *Journal of Intellectual Disability Research*, 68(12), 1344-1357. https://doi.org/10.1111/jir.13181

de Leeuw, M. J., Oppewal, A., Elbers, R. G., Hilgenkamp, T. I. M., Bindels, P. J. E., & Maes-Festen, D. A. M. (2023). Associations between physical fitness and cardiovascular disease in older adults with intellectual disabilities: Results of the Healthy Ageing and Intellectual Disability study. *Journal of Intellectual Disability Research*, 67(6), 547-559. https://doi.org/10.1111/jir.13027

de Leeuw, M. J., Böhmer, M. N., Bindels, P. J. E., Maes-Festen, D. A. M., & Oppewal, A. (2025). Cardiovascular Disease Incidence and Risk Factors in Older Adults With Intellectual Disabilities: Results of the Healthy Ageing and Intellectual Disabilities Study. *Journal of Intellectual Disability Research*. Advance online publication. https://doi.org/10.1111/jir.70004

Other publications

Oppewal, A., **de Leeuw, M. J.**, van Bruggen, M. C., Elbers, R. G. (2022). De GOUD-X-studie: Gezond ouder worden met een verstandelijke beperking. *FysioPraxis*, 31(4), 36. https://issuu.com/kngfdefysiotherapeut/docs/fysiopraxis-_mei2022

van der Wel, K. L., Kleinjan, L., & **de Leeuw, M. J.** (2022). Letter to the Editor. *Medical Journal of Australia*, 216(3), 160. https://doi.org/10.5694/mja2.51389

de Leeuw, M. J., Schasfoort, F. C., Spek, B., van der Ham, I., Verschure, S., Westendorp, T., & Pangalila, R. F. (2021). Factors for changes in self-care and mobility capabilities in young children with cerebral palsy involved in regular outpatient rehabilitation care. *Heliyon*, 7(12), Article e08537. https://doi.org/10.1016/j.heliyon.2021.e08537

CHAPTER 11

Dankwoord

DANKWOORD

Wie denkt dat een proefschrift een soloproject is, heeft er waarschijnlijk nooit één geschreven. Graag wil ik iedereen bedanken die het tot stand komen van dit proefschrift mede mogelijk heeft gemaakt. Jullie begeleiding, samenwerking en steun waren onmisbaar!

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