Improving the health of adults with autism and their caregivers

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Chapter 1

General introduction

Background

People with an autism spectrum disorder (autism) have an approximately two-fold increased mortality risk (Hirvikoski et al., 2016; Hwang et al., 2019; Lunsky et al., 2022; Mouridsen et al., 2008; Pickett et al., 2011; Schendel et al., 2016). Moreover, psychiatric and somatic comorbidities are more common in people with autism than in the general population (Cashin et al., 2018; Croen et al., 2105; Hand et al., 2020). These comorbidities not only contribute to mortality risk, they also have a negative impact on quality of life, as in respectively cardiovascular diseases and gastrointestinal conditions (Bauman M.L., 2010; Hwang et al., 2019). Next to people with autism themselves, their caregivers and specifically mothers with a child with autism seem to have impaired health and an increased mortality risk (Fairthorne et al., 2014; Fairthorne et al., 2015). Lastly, considering the increased health risk of people with autism, reports on their experiences of barriers in healthcare access and unmet healthcare needs are alarming (Nicolaidis et al., 2013; Vogan et al., 2017). All in all, it is necessary to better understand these health(care) inequities in adults with autism and their caregivers when striving for improved health and decreased mortality in this population.

The objective of this dissertation is twofold. First, this dissertation aims to gain insight into the health of people with autism and their caregivers. This dissertation will specifically focus on psychological, behavioural, and biological (biopsychosocial) factors associated with metabolic syndrome and gastrointestinal symptoms in autistic adults. Moreover, caregiver strain in people who are caregivers for someone with autism (autism-caregivers) will be described using a biopsychosocial approach. Second, this dissertation aims to investigate how to improve primary healthcare for people with autism. This will result in an overview of barriers and recommendations to improve primary care, according to the perspectives of primary care providers (PCPs) and autistic adults.

Autism terminology in this dissertation

For this dissertation, it should be clear which autism terminology will be used. In the autism community, including people with autism, autism-caregivers, care providers, and researchers, there is growing attention for stigmatizing terminology and the evolving use of neutral language (Botha et al., 2020; Bury et al., 2023). The American Psychological Association (APA) stated that terminology in academic research should be based on the context and participants' preference (APA, 2020). Moreover, a recent study among autistic adults in the Netherlands showed that it is advised to mix the use of identity-first and person-first language in order to take different preferences into account (Buijsman et al., 2023). Thus, in this dissertation, both identity-first (autistic people) and person-first language (people with autism) will be used.

Biopsychosocial model

The biopsychosocial model of G. Engel is an often-used framework in psychiatric and medical research and clinical interventions (Engel, G.H., 1977). It consists of 1) biological variables, such as genetics and biomarkers; 2) psychological measures, such as mental distress and behavioural components; and 3) social aspects, such as socioeconomic status. It should be noted that this framework is not, in all cases or for all conditions, comprehensive and therefore still evolving (Adler, R. H., 2009; Ghaemi, S.N., 2009). We tailored the biopsychosocial model to the research questions in the first three studies in this dissertation (Chapters 2-4) by investigating psychological, behavioural and biological/physical factors, while also taking socioeconomic status into account.

Cardiovascular risk: metabolic syndrome in autism

When aiming to improve the health of autistic adults, reduction of cardiovascular risk could be one of the starting points, as cardiovascular diseases are one of the most common causes of death in people with autism (Hirvikoski et al., 2016; Hwang et al., 2019; Schendel et al., 2016; Shavelle et al., 2001). Moreover, cardiovascular risk is affected by several biopsychosocial factors. Therefore, in this dissertation, metabolic syndrome, a widely recognized cluster of major cardiovascular risk factors, was investigated. Metabolic syndrome is defined as the presence of three or more of the following cardiovascular aspects: hypertension, abdominal obesity (increased waist circumference), increased fasting glucose (diabetes type 2), and dyslipidaemia (Alberti et al., 2009).

While previous studies have each explored separate aspects of metabolic syndrome in autistic adults, the prevalence of the total entity of metabolic syndrome in adults with autistic traits has not been investigated yet. Besides, these previous studies seem to be inconsistent. With regard to hypertension in adults with autism, both increased risks and no differences compared to controls were found (Croen et al., 2015; Fortuna et al., 2016; Hand et al., 2020; Weir et al., 2020a). Another measure of metabolic syndrome is waist circumference. However, to our knowledge, no previous studies have examined the prevalence of an increased waist circumference or abdominal obesity in autistic adults compared to non-autistic adults. Regarding the risk for diabetes in autistic adults, varying results were observed, including decreased and increased risks compared to non-autistic adults (Croen et al., 2015; Fortuna et al., 2016; Hand et al., 2020; Vohra et al., 2017). The last aspect of metabolic syndrome, dyslipidaemia, consists of increased triglycerides levels and decreased HDL-cholesterol levels (Alberti et al., 2009). However, previous studies defined outcomes of dyslipidaemia inconsistently. For example, for hyperlipidaemia, unspecified lipid disorders, and unspecified dyslipidaemia, increased risks were reported in autistic adults compared to non-autistic adults (Croen et al., 2015; Fortuna et al., 2016; Vohra et al., 2017). Lastly, in autistic females, the prevalence of high cholesterol was found not to be different than in non-autistic females (Weir et al., 2020a).

All in all, an overview of the prevalence of metabolic syndrome in autistic adults is missing. Also, these studies did not further investigate the factors associated with some of the found increased cardiovascular risks. Therefore, in this dissertation, metabolic syndrome and its associated psychological, behavioural, and biological factors in adults with autistic traits will be explored. The relevance of including adults with autistic traits will be explained in the paragraph below titled ‘Autistic traits’.

Gastrointestinal symptoms in autism

One of the most prevalent somatic comorbidities in autism are gastrointestinal problems (Croen et al., 2015; Hand et al., 2020; Tye et al., 2019). Thus, a better understanding of the increased risk for gastrointestinal symptoms in autism might contribute to improved health of people with autism. In two previous studies including autistic adults, the observed prevalence of gastrointestinal disorders varied from 35-49% compared to 25-28% in adults without autism (Croen et al., 2015; Hand et al., 2020). As gastrointestinal problems are often functional or undiagnosed, this dissertation will focus on the presence of gastrointestinal symptoms (e.g., constipation, diarrhoea, heartburn, and abdominal discomfort), rather than the presence of an official gastrointestinal diagnosis (Bishop-Fitzpatrick & Rubenstein, 2019; Croen et al., 2015).

In order to prevent, recognize, and decrease gastrointestinal symptoms in autistic adults, it is important to gain more insight into the factors associated with the gut-brain axis in autistic adults. The gut-brain axis is a bidirectional signalling network between the gastrointestinal tract and the central nervous system. The hypothalamic-pituitary-adrenal (HPA) axis, a part of this gut-brain axis, is influenced by (mental) stress and can alter, for example, gut motility through the hormone cortisol, as well as dysregulate inflammatory blood markers such as leukocytes (De Palma et al., 2014; Hollins & Hodgson, 2019). Regarding the aetiology of gastrointestinal problems in autism, it is hypothesized that people with autism have increased gastrointestinal permeability, also known as ‘leaky gut’ (Li et al., 2017). Moreover, people with autism seem to have a lower diversity of gut microbiomes, which is associated with the presence of gastrointestinal symptoms (Chernikova et al., 2021). Other factors associated with gastrointestinal symptoms that have been found in autistic children are for example food intolerance, unusual eating habits, sleep disorders, oppositional or aggressive behaviour, social impairments, and limited expressive language (Ferguson et al., 2019; Gorrindo et al., 2012; Kang et al., 2014; Maenner et al., 2011). Lastly, it is known that intellectual disability is a risk factor for gastrointestinal disorders in autistic people (Bishop-Fitzpatrick & Rubenstein, 2019; Gilmore et al., 2021).

All in all, knowledge about the factors associated with gastrointestinal symptoms in autism is mainly based on studies investigating autistic children. For clinicians, it is helpful to understand the factors associated with gastrointestinal symptoms in autistic adults as well, because this knowledge can improve awareness and treatment for gastrointestinal symptoms in more specific groups of autistic adults. Therefore, in this dissertation, psychological, behavioural, and biological factors associated with gastrointestinal symptoms in autistic adults and adults with autistic traits will be investigated.

Autistic traits

The studies in this dissertation regarding cardiovascular risk and gastrointestinal symptoms will not only investigate associated factors in adults with a self-reported autism diagnosis, but also in the general population categorized by the amount of their self-reported autistic traits. We followed this dual analysis approach, firstly because of the diagnostic challenges in adults, specifically in women, leading to diagnostic delays and underdiagnoses in the general population (Lai & Cohen, 2015). Secondly, the comparison of adults with higher levels of autistic traits versus adults with lower levels of autistic traits might give more insight into the relationship between the amount of reported autistic traits and chronic physical health risks, such as cardiovascular diseases and gastrointestinal symptoms.

In Dutch clinical practice, an autism diagnosis is based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V; American Psychiatric Association, 2013). These criteria include several autistic traits, such as restricted or repetitive patterns of behaviour or interests, sensory over-responsivity, and difficulties in social and communication skills. Autistic traits can be roughly quantified with, for example, the Autism Spectrum Quotient-10 (AQ-10). This is a validated questionnaire to screen the degree of autistic traits in adults with average intelligence (Allison et al., 2012; Lundin et al., 2019; Warrier et al., 2020). While the AQ-10 was developed as a screening tool to enhance referral for complete autism diagnostics, the sensitivity and specificity of the AQ-10 and AQ-50 are very similar (Booth et al., 2013). The AQ-10 consists of 10 questions regarding attention to detail, attention switching, communication, imagination, and social skills.

Autism-caregivers' strain

Besides contributing to improved health for autistic adults, this dissertation aims to gain insight into the health of their caregivers (autism-caregivers). For a significant amount of people with autism, caregivers play an important role in supporting them on a daily basis. Besides, it is known that higher levels of perceived social support are associated with higher quality of life in autistic people (Bishop-Fitzpatrick et al., 2018; Renty & Roeyers, 2006). Moreover, improving the health of autism-caregivers is an urgent topic, as there is a growing body of evidence concluding that autism-caregiver strain is high. Even more concerning, a general population study in Australia showed that mothers who gave care to autistic children had an increased mortality risk of 1.44-1.69 compared to mothers of children without autism and without an intellectual disability (Fairthorne et al., 2014).

While there is no official definition for caregiver strain (also referred to as burden), it is suggested to be defined as 'the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical, and spiritual functioning' (Adelman et al., 2014; Zarit et al., 1986). Thus, a profound assessment of caregiver health is a significant component of recognizing and preventing caregiver strain (Adelman et al., 2014). Next, it is known that providing care to an autistic child or family member often comes with caregiver distress (Hayes & Watson, 2013). Autism-caregivers are often parents, and their parenting distress consists of three main domains: parent characteristics (including self-perceived competence, marital issues, and social support), stress from the parent-child interactions, and a child's behavioural characteristics (Zaidman-Zait et al., 2010). It has been suggested that the relationship between caregiver distress and the autistic child's internalizing and externalizing behaviours is bidirectional (Seltzer et al., 2010; Smith et al., 2014; Zaidman-Zait et al., 2011; Zaidman-Zait et al., 2014). Nonetheless, knowledge about biopsychosocial aspects of caregiver strain in autism-caregivers is still limited (Dijkstra-de Neijs et al., 2020; Marsack & Hopp, 2019; Ruiz-Robledillo & Moya-Albiol, 2013; Van der Lubbe et al., 2024), while this is needed to improve their health and reduce their mortality risk. Therefore, in the third study of this dissertation, psychological, behavioural, and biological aspects of caregiver strain were investigated in autism-caregivers compared to adults who are caregivers for someone with another condition (non-autism-caregivers).

Primary care for autistic adults

When aiming to improve the health of autistic adults, it is essential to not only increase knowledge about their increased health risks, but also to deliver more effective primary healthcare. Therefore, it is relevant to take a closer look into primary healthcare barriers that autistic adults and their primary care providers (PCPs) experience. These barriers can stand in the way of prevention, timely recognition, and adequate treatment of chronic diseases and might possibly lead to premature mortality (Doherty et al., 2022). From studies performed in the United Kingdom and the United States of America, it is known that healthcare barriers include barriers related to the care provider, barriers related to the person with autism (and its social support network), and barriers related to the organization of healthcare (Doherty et al., 2020; Mason et al., 2019; Nicolaidis et al., 2015; Walsh et al., 2020). One can think of the care provider's limited knowledge about autism, both the care provider's and the autistic person's communication skills, the autistic person' sensory sensitivities, or the limited time during a healthcare appointment.

In the Netherlands, the general practitioner (GP) works together with other primary care providers (PCPs), such as a general practice nurse who focuses on somatic care (in Dutch: *praktijkondersteuner; POH*) and a primary care mental health worker (PCMHW, in Dutch: *POH-GGZ*). The somatic GP-nurse and the primary care mental health worker assist the GP in the prevention and treatment of chronic conditions, such as cardiovascular diseases and psychiatric problems. Effective primary care is fundamental for prevention, early recognition and treatment, and referral to specialized secondary care. Thus, to receive any type of specialized care or diagnostics, a consultation with a PCP is necessary in the Netherlands. Consequently, the first aim of the Delphi-study was to explore which specific barriers play a role in Dutch primary care for autistic adults, since this has not been investigated yet. Next, it is relevant to investigate how Dutch PCPs and autistic adults want to improve primary care for autistic adults, which was the general aim of our Delphi-study.

Dissertation

All in all, this dissertation aims to increase insight into the health of adults with autism and their caregivers, considering different psychological, behavioural, and biological factors. Therefore, this dissertation will first focus on psychological, behavioural, and biological factors associated with metabolic syndrome and gastrointestinal symptoms respectively. Secondly, psychological, behavioural, and biological aspects of autism-caregivers' strain will be addressed. Quantitative methods were used to statistically analyse metabolic syndrome and gastrointestinal symptoms in adults with autism, adults with autistic traits, and autism-caregivers from the Lifelines Cohort. This is a prospective cohort of 167,729 participants recruited from the general population in the North of the Netherlands (provinces of Groningen, Friesland, and Drenthe). In the Lifelines Cohort, biomedical, sociodemographic, behavioural, physical, and psychological factors contributing to health and diseases in the general population were assessed (Scholtens et al., 2015). Lastly, possible ways to improve primary care for autistic adults will be explored. To determine how PCPs and autistic adults think their primary care could be improved, both qualitative and quantitative measures were applied by performing semi-structured interviews and a Delphi-study.

Three studies in this dissertation, namely the Lifelines studies regarding metabolic syndrome, gastrointestinal symptoms, and the Delphi-study on improvement of primary care, were created in collaboration with our project team of the Dutch 'Academic Workplace Autism' (*Academische Werkplaats Autisme (*AWA)*)*. This AWA was funded by The Netherlands Organization for Health Research and Development (ZonMw; project number 639003101). The AWA is a collaborative effort with different stakeholders, including autistic people, clinicians working with autistic people, and researchers, aiming to improve the lives of autistic people based on the results of co-created academic research. The participation of autistic people in the development of autism research leads to a more meaningful selection of study outcomes and could therefore be beneficial for the effective implementation of interventions. Thus, the involvement of (parents of) autistic people in research, from developing relevant research questions and inclusive study designs to interpreting results meaningfully, is key (Poulsen et al., 2022). Our project team consisted of two autistic adults, parents of a child with autism, different healthcare providers (child and adolescent psychiatrists, psychologists, and a physician specialized in care for people with a learning disability), and researchers. These project team members shared their insights into current concerns about the health of people with autism and into healthcare barriers, which led to the formulation of relevant research questions. For the three studies that were created in collaboration with the AWA, a more detailed description of the contributions of the project team can be found in each individual method section.

Outline

In Chapter 2, we first examine the cardiovascular risk (metabolic syndrome) of autistic adults. A quantitative database study was performed with the aim of comparing the prevalence of metabolic syndrome and associated psychological, behavioural, and biological factors between adults with higher and lower levels of autistic traits. The total included study population consisted of 17,705 adults from the Lifelines Cohort. The prevalence of metabolic syndrome was analysed in females and males from the quartile with the most autistic traits (female HQ-traits-group: n=2635; male HQ-traits-group: n=1803) compared to respectively females and males from the quartile with the least autistic traits (female LQ-traits-group: n=2635; male LQ-traits-group: n=1803). Using multivariable logistic regression, the associations between the presence of metabolic syndrome and the investigated psychological, behavioural, and biological factors were analysed in these groups.

Regarding the outcome of gastrointestinal symptoms, comparable analyses were conducted in the second Lifelines study in Chapter 3. The main goal of this study was to explore which psychological, behavioural, and biological factors are associated with gastrointestinal symptoms in adults with an autism diagnosis and in adults with different levels of autistic traits. A total of 31,185 adults from the Lifelines Study were included. The prevalence of gastrointestinal symptoms in the autism-group (n=309) was compared with the non-autism-group (n=30,876), as well as in the group with the highest levels of autistic traits (HQ-traits-group, n=7783) compared with the group with the lowest levels of autistic traits (LQ-traits-group, n=7783). With multivariable logistic regression, the associations between gastrointestinal symptoms and the investigated psychological, behavioural, and biological factors in the autism-group and HQ-traits-group were analysed.

Autism-caregivers' strain is the subject of Chapter 4. In total, 3354 adult caregivers from the Lifelines Cohort were included. This study population consisted of 722 people who were caregivers for someone with autism (autism-caregivers) and 2632 people who were caregivers for someone with another condition (non-autism-caregivers). The general aim was to compare the presence of the following psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers to non-autism-caregivers: stress, anxiety, depression, perceived health, smoking, alcohol use, physical activity, body mass index, waist circumference, and immunological markers of stress responses (leukocyte-counts). Multivariable regression models were used to compare these aspects of caregiver strain between the main groups of autism-caregivers and non-autism-caregivers. Two sub-analyses were performed to explore the different aspects of health in parental subgroups: 511 parental autism-caregivers versus 211 non-parental autism-caregivers, and 511 parental autism-caregivers versus 350 parental non-autism-caregivers. The goal of these sub-analyses was to investigate if the found differences between autism-caregivers and non-autism-caregivers could be attributed to the fact that autism-caregivers are more often parents who experience parental stress.

Chapter 5's central theme regards improved primary care for autistic people. A mixed-method study was executed first to identify barriers in Dutch healthcare for autistic adults and then to explore how PCPs and autistic adults suggest improving their primary healthcare. As a preparation for the Delphi-study, semi-structured interviews with five (parents of) autistic people and six care providers were first performed to evaluate barriers in Dutch healthcare. These interviews were transcribed, coded, and thematically analysed. Next, in a three-round Delphi-study, 21 autistic adults and 20 PCPs rated the impact of barriers and the usefulness and feasibility of recommendations to improve primary healthcare. The closed-ended questions (Likert scales) were numerically summarized, and the open-ended questions were thematically analysed. This resulted in recommendations to improve primary care for autistic adults, which were divided into three categories of recommendations focused on PCPs, on autistic adults, and on organization of general practice.

In Chapter 6, the significant psychological, behavioural, and biological factors associated with metabolic syndrome (Chapter 2), gastrointestinal symptoms (Chapter 3), and autism-caregiving (Chapter 4) will be summarized. Also, the evaluated healthcare barriers and recommendations to improve primary care for autistic adults (from Chapter 5) will be reviewed. The implications of these results for clinical practice, future research, and healthcare organization will be discussed.

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