Improving the health of adults with autism and their caregivers

Warreman, E.B.

Improving the health of adults with autism and their caregivers

Eva Warreman

Improving the health of adults with autism and their caregivers

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint

Cover design and layout by Henry Smaal (Persoonlijk Proefschrift), caregiver of a person with autism

Studies in this thesis were funded by The Netherlands Organization for Health Research and Development (ZonMw), project number Academische Werkplaats Autisme 639003101.

Improving the health of adults with autism and their caregivers

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 26 juni 2024
klokke 10.00 uur

door

Eva Britt Warreman
geboren te Woerden
in 1995

Promotor
Prof. dr. R.R.J.M. Vermeiren

Co-promotores
Dr. W.A. Ester
Dr. L.A. Nooteboom

Promotiecommissie
Prof. dr. A.M. van Hemert

Prof. dr. M.E. Numans

Prof. dr. W.G. Staal
Radboud University Medical Center

Prof. dr. W. Cahn
University Medical Center Utrecht

Contents

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.

References

Adelman, R. D., Tmanova, L. L., Delgado, D., Dion, S., & Lachs, M. S. (2014). Caregiver burden: a clinical review. JAMA, 311(10), 1052–1060. https://doi.org/10.1001/jama.2014.304

Adler R. H. (2009). Engel's biopsychosocial model is still relevant today. Journal of psychosomatic research, 67(6), 607–611. https://doi.org/10.1016/j.jpsychores.2009.08.008

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., Smith, S. C., Jr, International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, & International Association for the Study of Obesity (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Allison, C., Auyeung, B., & Baron-Cohen, S. (2012). Toward brief "Red Flags" for autism screening: The Short Autism Spectrum Quotient and the Short Quantitative Checklist for Autism in toddlers in 1,000 cases and 3,000 controls [corrected]. Journal of the American Academy of Child and Adolescent Psychiatry, 51(2), 202–212.e7. https://doi.org/10.1016/j.jaac.2011.11.003

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Bauman M. L. (2010). Medical comorbidities in autism: challenges to diagnosis and treatment. Neurotherapeutics, 7(3), 320–327. https://doi.org/10.1016/j.nurt.2010.06.001

Bishop-Fitzpatrick, L., Mazefsky, C. A., & Eack, S. M. (2018). The combined impact of social support and perceived stress on quality of life in adults with autism spectrum disorder and without intellectual disability. Autism, 22(6), 703–711. https://doi.org/10.1177/1362361317703090

Bishop-Fitzpatrick, L., & Rubenstein, E. (2019). The Physical and Mental Health of Middle Aged and Older Adults on the Autism Spectrum and the Impact of Intellectual Disability. Research in autism spectrum disorders, 63, 34–41. https://doi.org/10.1016/j.rasd.2019.01.001

Booth, T., Murray, A. L., McKenzie, K., Kuenssberg, R., O'Donnell, M., & Burnett, H. (2013). Brief report: an evaluation of the AQ-10 as a brief screening instrument for ASD in adults. Journal of autism and developmental disorders, 43(12), 2997–3000. https://doi.org/10.1007/s10803-013-1844-5

Botha, M., Dibb, B., & Frost, D. M. (2020). 'Autism is me': An investigation of how autistic individuals make sense of autism and stigma. Disability & Society, 37, 427–453. https://doi.org/10.1080/09687599.2020.1822782

Buijsman, R., Begeer, S., & Scheeren, A. M. (2023). 'Autistic person' or 'person with autism'? Person-first language preference in Dutch adults with autism and parents. Autism, 27(3), 788–795. https://doi.org/10.1177/13623613221117914

Bury, S. M., Jellett, R., Spoor, J. R., & Hedley, D. (2023). "It Defines Who I Am" or "It's Something I Have": What Language Do [Autistic] Australian Adults [on the Autism Spectrum] Prefer?. Journal of autism and developmental disorders, 53(2), 677–687. https://doi.org/10.1007/s10803-020-04425-3

Cashin, A., Buckley, T., Trollor, J. N., & Lennox, N. (2018). A scoping review of what is known of the physical health of adults with autism spectrum disorder. Journal of intellectual disabilities, 22(1), 96–108. https://doi.org/10.1177/1744629516665242

Chernikova, M. A., Flores, G. D., Kilroy, E., Labus, J. S., Mayer, E. A., & Aziz-Zadeh, L. (2021). The Brain-Gut-Microbiome System: Pathways and Implications for Autism Spectrum Disorder. Nutrients, 13(12), 4497. https://doi.org/10.3390/nu13124497

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. https://doi.org/10.1177/1362361315577517

De Palma, G., Collins, S. M., Bercik, P., & Verdu, E. F. (2014). The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both?. The Journal of physiology, 592(14), 2989–2997. https://doi.org/10.1113/jphysiol.2014.273995

Doherty, A. J., Atherton, H., Boland, P., Hastings, R., Hives, L., Hood, K., James-Jenkinson, L., Leavey, R., Randell, E., Reed, J., Taggart, L., Wilson, N., & Chauhan, U. (2020). Barriers and facilitators to primary health care for people with intellectual disabilities and/or autism: an integrative review. British Journal of General Practice open, 4(3), bjgpopen20X101030. https://doi.org/10.3399/bjgpopen20X101030

Doherty, M., Neilson, S., O'Sullivan, J., Carravallah, L., Johnson, M., Cullen, W., & Shaw, S. C. K. (2022). Barriers to healthcare and self-reported adverse outcomes for autistic adults: a cross-sectional study. BMJ Open, 12(2), e056904. https://doi.org/10.1136/bmjopen-2021-056904

Dijkstra-de Neijs, L., Leenen, P. J. M., Hays, J. P., Van der Valk, E. S., Kraaij, R., Van Rossum, E. F. C., Ester, W. A. (2020). Biological Consequences of Psychological Distress in Caregivers of Children with Autism Spectrum Disorder and its Potential Relevance to Other Chronic Diseases Including Cancer. Current Epidemiology Reports, 7, 139–148. https://doi.org/10.1007/s40471-020-00237-2

Engel G. L. (1977). The need for a new medical model: a challenge for biomedicine. Science (New York, N.Y.), 196(4286), 129–136. https://doi.org/10.1126/science.847460

Fairthorne, J., Hammond, G., Bourke, J., Jacoby, P., & Leonard, H. (2014). Early mortality and primary causes of death in mothers of children with intellectual disability or autism spectrum disorder: a retrospective cohort study. PloS One, 9(12), e113430. https://doi.org/10.1371/journal.pone.0113430

Fairthorne, J., Klerk, N., & Leonard, H. (2015). Health of mothers of children with Intellectual disability or autism spectrum disorder: A review of the literature. Medical Research Archives, 3(3). http://dx.doi.org/10.18103/mra.v0i3.204

Ferguson, B. J., Dovgan, K., Takahashi, N., & Beversdorf, D. Q. (2019). The Relationship Among Gastrointestinal Symptoms, Problem Behaviors, and Internalizing Symptoms in Children and Adolescents With Autism Spectrum Disorder. Frontiers in psychiatry, 10, 194. https://doi.org/10.3389/fpsyt.2019.00194

Fortuna, R. J., Robinson, L., Smith, T. H., Meccarello, J., Bullen, B., Nobis, K., & Davidson, P. W. (2016). Health Conditions and Functional Status in Adults with Autism: A Cross-Sectional Evaluation. Journal of general internal medicine, 31(1), 77–84. https://doi.org/10.1007/s11606-015-3509-x

Ghaemi S. N. (2009). The rise and fall of the biopsychosocial model. The British journal of psychiatry, 195(1), 3–4. https://doi.org/10.1192/bjp.bp.109.063859

Gilmore, D., Harris, L., Longo, A., & Hand, B. N. (2021). Health status of Medicare-enrolled autistic older adults with and without co-occurring intellectual disability: An analysis of inpatient and institutional outpatient medical claims. Autism, 25(1), 266–274. https://doi.org/10.1177/1362361320955109

Gorrindo, P., Williams, K. C., Lee, E. B., Walker, L. S., McGrew, S. G., & Levitt, P. (2012). Gastrointestinal dysfunction in autism: parental report, clinical evaluation, and associated factors. Autism research, 5(2), 101–108. https://doi.org/10.1002/aur.237

Hand, B. N., Angell, A. M., Harris, L., & Carpenter, L. A. (2020). Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism, 24(3), 755–764. https://doi.org/10.1177/1362361319890793

Hayes, S. A., & Watson, S. L. (2013). The impact of parenting stress: a meta-analysis of studies comparing the experience of parenting stress in parents of children with and without autism spectrum disorder. Journal of autism and developmental disorders, 43(3), 629–642. https://doi.org/10.1007/s10803-012-1604-y

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. The British journal of psychiatry, 208(3), 232–238. https://doi.org/10.1192/bjp.bp.114.160192

Hollins, S. L., & Hodgson, D. M. (2019). Stress, microbiota, and immunity. Current Opinion in Behavioral Sciences, 28, 66-71. https://doi.org/10.1016/j.cobeha.2019.01.015

Hwang, Y. I. J., Srasuebkul, P., Foley, K. R., Arnold, S., & Trollor, J. N. (2019). Mortality and cause of death of Australians on the autism spectrum. Autism research, 12(5), 806–815. https://doi.org/10.1002/aur.2086

Kang, V., Wagner, G. C., & Ming, X. (2014). Gastrointestinal dysfunction in children with autism spectrum disorders. Autism research, 7(4), 501–506. https://doi.org/10.1002/aur.1386

Lai, M. C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. The Lancet Psychiatry, 2(11), 1013–1027. https://doi.org/10.1016/S2215-0366(15)00277-1

Li, Q., Han, Y., Dy, A. B. C., & Hagerman, R. J. (2017). The Gut Microbiota and Autism Spectrum Disorders. Frontiers in cellular neuroscience, 11, 120. https://doi.org/10.3389/fncel.2017.00120

Lundin, A., Kosidou, K., & Dalman, C. (2019). Measuring Autism Traits in the Adult General Population with the Brief Autism-Spectrum Quotient, AQ-10: Findings from the Stockholm Public Health Cohort. Journal of autism and developmental disorders, 49(2), 773–780. https://doi.org/10.1007/s10803-018-3749-9

Lunsky, Y., Lai, M. C., Balogh, R., Chung, H., Durbin, A., Jachyra, P., Tint, A., Weiss, J., & Lin, E. (2022). Premature mortality in a population-based cohort of autistic adults in Canada. Autism research, 15(8), 1550–1559. https://doi.org/10.1002/aur.2741

Maenner, M. J., Arneson, C. L., Levy, S. E., Kirby, R. S., Nicholas, J. S., & Durkin, M. S. (2012). Brief report: Association between behavioral features and gastrointestinal problems among children with autism spectrum disorder. Journal of autism and developmental disorders, 42(7), 1520–1525. https://doi.org/10.1007/s10803-011-1379-6

Marsack, C. N., & Hopp, F. P. (2019). Informal Support, Health, and Burden Among Parents of Adult Children With Autism. The Gerontologist, 59(6), 1112–1121. https://doi.org/10.1093/geront/gny082

Mason, D., Ingham, B., Urbanowicz, A., Michael, C., Birtles, H., Woodbury-Smith, M., Brown, T., James, I., Scarlett, C., Nicolaidis, C., & Parr, J. R. (2019). A Systematic Review of What Barriers and Facilitators Prevent and Enable Physical Healthcare Services Access for Autistic Adults. Journal of autism and developmental disorders, 49(8), 3387–3400. https://doi.org/10.1007/s10803-019-04049-2

Mouridsen, S. E., Brønnum-Hansen, H., Rich, B., & Isager, T. (2008). Mortality and causes of death in autism spectrum disorders: an update. Autism, 12(4), 403–414. https://doi.org/10.1177/1362361308091653

Nicolaidis, C., Raymaker, D. M., Ashkenazy, E., McDonald, K. E., Dern, S., Baggs, A. E., Kapp, S. K., Weiner, M., & Boisclair, W. C. (2015). "Respect the way I need to communicate with you": Healthcare experiences of adults on the autism spectrum. Autism, 19(7), 824–831. https://doi.org/10.1177/1362361315576221

Nicolaidis, C., Raymaker, D., McDonald, K., Dern, S., Boisclair, W. C., Ashkenazy, E., & Baggs, A. (2013). Comparison of healthcare experiences in autistic and non-autistic adults: a cross-sectional online survey facilitated by an academic-community partnership. Journal of general internal medicine, 28(6), 761–769. https://doi.org/10.1007/s11606-012-2262-7

Pickett, J., Xiu, E., Tuchman, R., Dawson, G., & Lajonchere, C. (2011). Mortality in individuals with autism, with and without epilepsy. Journal of child neurology, 26(8), 932–939. https://doi.org/10.1177/0883073811402203

Poulsen, R., Brownlow, C., Lawson, W., & Pellicano, E. (2022). Meaningful research for autistic people? Ask autistics!. Autism, 26(1), 3–5. https://doi.org/10.1177/13623613211064421

Renty, J. O., & Roeyers, H. (2006). Quality of life in high-functioning adults with autism spectrum disorder: The predictive value of disability and support characteristics. Autism, 10(5), 511–524. https://doi.org/10.1177/1362361306066604

Ruiz-Robledillo, N., & Moya-Albiol, L. (2013). Self-reported health and cortisol awakening response in parents of people with asperger syndrome: the role of trait anger and anxiety, coping and burden. Psychology & health, 28(11), 1246–1264. https://doi.org/10.1080/08870446.2013.800517

Seltzer, M. M., Greenberg, J. S., Hong, J., Smith, L. E., Almeida, D. M., Coe, C., & Stawski, R. S. (2010). Maternal cortisol levels and behavior problems in adolescents and adults with ASD. Journal of autism and developmental disorders, 40(4), 457–469. https://doi.org/10.1007/s10803-009-0887-0

Schendel, D. E., Overgaard, M., Christensen, J., Hjort, L., Jørgensen, M., Vestergaard, M., & Parner, E. T. (2016). Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. JAMA pediatrics, 170(3), 243–250. https://doi.org/10.1001/jamapediatrics.2015.3935

Scholtens, S., Smidt, N., Swertz, M. A., Bakker, S. J., Dotinga, A., Vonk, J. M., van Dijk, F., van Zon, S. K., Wijmenga, C., Wolffenbuttel, B. H., & Stolk, R. P. (2015). Cohort Profile: LifeLines, a three-generation cohort study and biobank. International journal of epidemiology, 44(4), 1172–1180. https://doi.org/10.1093/ije/dyu229

Shavelle, R. M., Strauss, D. J., & Pickett, J. (2001). Causes of death in autism. Journal of autism and developmental disorders, 31(6), 569–576. https://doi.org/10.1023/a:1013247011483

Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2014). The family context of autism spectrum disorders: influence on the behavioral phenotype and quality of life. Child and adolescent psychiatric clinics of North America, 23(1), 143–155. https://doi.org/10.1016/j.chc.2013.08.006

Tye, C., Runicles, A. K., Whitehouse, A. J. O., & Alvares, G. A. (2019). Characterizing the Interplay Between Autism Spectrum Disorder and Comorbid Medical Conditions: An Integrative Review. Frontiers in psychiatry, 9, 751. https://doi.org/10.3389/fpsyt.2018.00751

Van der Lubbe, A., Swaab, H., Vermeiren, R. R. J. M., & Ester, W. A. (2024). Stress, Eating Behavior and Adverse Health in Parents of Young Children with Autism Spectrum Disorder. Journal of autism and developmental disorders, 54(2), 662–672. https://doi.org/10.1007/s10803-022-05825-3

Vohra, R., Madhavan, S., & Sambamoorthi, U. (2017). Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism, 21(8), 995–1009. https://doi.org/10.1177/1362361316665222

Vogan, V., Lake, J. K., Tint, A., Weiss, J. A., & Lunsky, Y. (2017). Tracking health care service use and the experiences of adults with autism spectrum disorder without intellectual disability: A longitudinal study of service rates, barriers and satisfaction. Disability and health journal, 10(2), 264–270. https://doi.org/10.1016/j.dhjo.2016.11.002

Walsh, C., Lydon, S., O'Dowd, E., & O'Connor, P. (2020). Barriers to Healthcare for Persons with Autism: A Systematic Review of the Literature and Development of A Taxonomy. Developmental Neurorehabilitation, 23:7, 413-430. https://doi.org/10.1080/17518423.2020.1716868

Warrier, V., Greenberg, D. M., Weir, E., Buckingham, C., Smith, P., Lai, M. C., Allison, C., & Baron-Cohen, S. (2020). Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nature communications, 11(1), 3959. https://doi.org/10.1038/s41467-020-17794-1

Weir, E., Allison, C., Warrier, V., & Baron-Cohen, S. (2021a). Increased prevalence of non-communicable physical health conditions among autistic adults. Autism, 25(3), 681–694. https://doi.org/10.1177/1362361320953652

Zaidman-Zait, A., Mirenda, P., Duku, E., Szatmari, P., Georgiades, S., Volden, J., Zwaigenbaum, L., Vaillancourt, T., Bryson, S., Smith, I., Fombonne, E., Roberts, W., Waddell, C., Thompson, A., & Pathways in ASD Study Team (2014). Examination of bidirectional relationships between parent stress and two types of problem behavior in children with autism spectrum disorder. Journal of autism and developmental disorders, 44(8), 1908–1917. https://doi.org/10.1007/s10803-014-2064-3

Zaidman-Zait, A., Mirenda, P., Zumbo, B. D., Georgiades, S., Szatmari, P., Bryson, S., Fombonne, E., Roberts, W., Smith, I., Vaillancourt, T., Volden, J., Waddell, C., Zwaigenbaum, L., Duku, E., Thompson, A., & Pathways in ASD Study Team (2011). Factor analysis of the Parenting Stress Index-Short Form with parents of young children with autism spectrum disorders. Autism research, 4(5), 336–346. https://doi.org/10.1002/aur.213

Zaidman-Zait, A., Mirenda, P., Zumbo, B. D., Wellington, S., Dua, V., & Kalynchuk, K. (2010). An item response theory analysis of the Parenting Stress Index-Short Form with parents of children with autism spectrum disorders. Journal of child psychology and psychiatry, and allied disciplines, 51(11), 1269–1277. https://doi.org/10.1111/j.1469-7610.2010.02266.x

Zarit, S. H., Todd, P. A., & Zarit, J. M. (1986). Subjective burden of husbands and wives as caregivers: a longitudinal study. The Gerontologist, 26(3), 260–266. https://doi.org/10.1093/geront/26.3.260

Chapter 2

Psychological, behavioural, and biological factors associated with metabolic syndrome in autistic adults and adults with autistic traits

Eva Warreman, Laura Nooteboom, Pieter Leenen, Hilde Geurts, Mary Beth Terry, Jens Bos, Eelko Hak, Wijbrand Hoek, Liesbeth van Rossum, Robert Vermeiren, Wietske Ester
Frontiers in Psychiatry, 2023, 14, 1303840
https://doi.org/10.3389/fpsyt.2023.1303840

Abstract

Background

While cardiovascular diseases are highly prevalent and an important cause of mortality in autistic adults, knowledge on their increased cardiovascular risk is limited. Hence, this study aimed to investigate psychological, behavioural, and physical factors associated with metabolic syndrome (MetS) in adults with autistic traits.

Methods

In total, 17,705 adults from the Lifelines Cohort were included and categorized using Autism Spectrum Quotient-10 sum-scores. The quartiles with highest (HQ-traits-group females: n=2635; males: n=1803) and lowest levels of autistic traits (LQ-traits-group, n=idem) were analysed. Using multivariable logistic regression, the associations between MetS and (self-reported and interviewed) psychological, behavioural, and physically measured factors in these stratified groups were investigated.

Results

Among females, MetS was more common in the HQ-traits-group than in the LQ-traits-group (10.0% versus 7.5%, $p<0.01$), while this was not the case among males (HQ-traits-group 13.8% versus LQ-traits-group 13.1%, $p=0.52$). In both the female and male HQ-traits-group, the presence of MetS was associated with poorer self-reported health, less daily physical activity, and altered leukocyte counts.

Conclusion

These findings underline the relevance of adequate cardiovascular prevention in adults with higher levels of autistic traits. Future research could gain more insight into the relationship between cardiovascular risk and autistic traits in females, and into tailored cardiovascular prevention.

Introduction

Autism spectrum disorder (ASD) is associated with an approximate two-fold increased mortality risk (Hirvikoski et al., 2016; Hwang et al., 2019; Schendel et al., 2016). In particular, cardiovascular diseases are amongst the most common causes of death in adults with ASD (Hirvikoski et al., 2016; Hwang et al., 2019; Schendel et al., 2016; Shavelle et al., 2001). Several studies have reported an elevated risk for cardiovascular diseases in adults with ASD compared to adults without ASD, with odds ratios varying approximately from 1.3 to 2.5 (Croen et al., 2015; Hand et al., 2020; Weir et al., 2021a). Thus, the need to reduce their cardiovascular risk is evident. Furthermore, it is relevant to investigate cardiovascular risk in the general population in order to take those adults with autistic traits, specifically females, with a late or missed ASD-diagnosis into account, by analysing them on the presence of autistic traits, rather than only on the presence of an ASD-diagnosis (Lai & Baron-Cohen, 2015).

Metabolic syndrome (MetS) is a globally recognized set of major cardiovascular risk factors, namely hypertension, central obesity, increased fasting glucose, and dyslipidaemia (Alberti et al., 2009). The prevalence of hypertension is not higher in autistic adults than in non-autistic adults, based on a recent meta-analysis (Dhanasekara et al., 2023). To our knowledge, the prevalence of central obesity, defined by increased waist circumference, has not been studied in autistic adults or in adults with autistic traits. Regarding the prevalence of diabetes in autistic people, mixed outcomes have been reported (Croen et al., 2015; Hand et al., 2020; Fortuna et al., 2016; Vohra et al., 2017). Previous studies including autistic adults investigated different or undefined outcome measures of dyslipidaemia, resulting in contradicting results (Croen et al., 2015; Weir et al., 2021a; Fortuna et al., 2016; Vohra et al., 2017). Thus, the total prevalence of MetS, defined as the presence of at least three of five criteria (Alberti et al., 2009), in adults with autistic traits remains unclear.

For future development of preventive cardiovascular interventions, more insight into the psychological, behavioural, and physical factors associated with cardiovascular risk (i.e., MetS) in autistic adults is needed (Weir et al., 2021a; Dhanasekara et al., 2023). Therefore, the biopsychosocial factors that will be assessed in this study include stress, anxiety, depression, alcohol consumption, smoking, physical activity, and immunological blood markers (Denollet et al., 2009; Harshfield et al., 2020; Rosengren et al., 2004; Yusuf et al., 2004; Cole et al., 2008; Dhabhar et al., 2012).

We hypothesize that an increased cardiovascular risk in adults with autistic traits is associated with the degree of autistic traits and related to biopsychosocial factors. Moreover, autistic males and females have different cardiovascular risk profiles (Weir et al., 2021a). Therefore, the aim of this study is to investigate the prevalence of MetS and which psychological, behavioural, and physical factors are associated with MetS in female and male adults with autistic traits.

Methods

Study population

Our database consisted of data from two database: the Lifelines database and the IADB.nl pharmacy database. We first included adults from the general population in the Dutch Lifelines Cohort Study. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioural, biological and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The Lifelines protocol was approved by the UMCG Medical ethical committee under number 2007/152 (Scholtens et al., 2015). We used the second assessment of the Lifelines Study, which took place between 2014-2017.

Next, the Lifelines data from the 37,924 participants who submitted an autism questionnaire (AUTQ) in 2019 were combined with the medication data from the University of Groningen IADB.nl pharmacy prescription database. This is a growing database that contains prescription data for more than 20 years from 1996 till 2016 from approximately 90 community pharmacies and covers an estimated population of 900,000 patients. Registration in the database is irrespective of health care insurance and age, gender and prescription rates among the database population have been found to be representative of the Netherlands as a whole, and the database has been widely used for research (Visser et al., 2013). Each person is individually tracked throughout the database period and prescription records contain information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician and the Anatomical Therapeutic Chemical code (ATC code). Each patient has a unique anonymous identifier; date of birth and gender are known. Due to the high patient-pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete, except for over the counter (OTC) drugs and medication dispensed during hospitalization (Sediq et al., 2018).

For the current study (Figure 1), we included 17,705 participants, ≥18 years old at the onset of the second Lifelines assessment, who self-reported whether they had an ASD-diagnosis, and completed the short version of the Autism Spectrum Quotient (AQ-10). The 17,705 included participants were sex-stratified (10,539 females and 7212 males) and then categorised in quartiles based on their AQ-10 sum-scores, resulting in a female quartile with highest AQ-10 sum-scores (female HQ-traits-group: n=2635), female quartile with lowest AQ-10 sum-scores (LQ-traits-group: n=2635), male quartile with highest AQ-10 sum-scores (male HQ-traits-group: n=1803), and male quartile with lowest AQ-10 sum-scores (LQ-traits-group: n=1803).

Of the 17,705 included participants, 198 reported having an ASD-diagnosis (1.1%). In the ASD-group (n=198), 21 participants (10.6%) met the criteria for having MetS. However, G*Power analysis showed that for logistic regression using MetS as outcome and with a power of at least 0.8, in the ASD-group at least 43 participants needed to meet the criteria for MetS. Thus, the power in the diagnosed ASD-group was insufficient for performing regression.

Autistic community involvement

During several brainstorm sessions, our research team was advised about relevant research questions and variables by a project-group of the Dutch '*Academic Workplace Autism'*, which consisted of both adults with ASD and clinicians with experience treating people with ASD.

Measures

Autistic traits

The AQ-10 is a valid instrument to roughly quantify the level of autistic traits in adults with average intelligence (Allison et al., 2012). It is not designed to determine the presence of an ASD-diagnosis, but it can indeed be used to investigate the degree of autistic traits in population samples (Ashwood et al., 2016; Lundin et al, 2019; Sizoo et al., 2015; Warrier et al., 2020). The AQ-10 consists of ten questions about the following five domains of autistic traits: attention to detail, attention switching, communication, imagination, and social skills (Allison et al., 2012). The questions are scored with a four-point Likert-scale. The minimum AQ-10 score is zero and the maximum score is 10; a higher score represents the presence of more autistic traits.

Metabolic syndrome (MetS)

The definition of MetS was the presence of at least three of five criteria (Alberti et al., 2009): an increased waist circumference (in males: 102 cm, in females: 88 cm; measured by trained Lifelines' staff), increased fasting glucose (serum level 5.6 mmol/L and/or use of blood glucose-lowering drugs), decreased HDL-cholesterol (in males:1.0 mmol/L, in females:1.3 mmol/L, and/or use of lipid-modifying drugs), increased triglycerides (1.7 mmol/L and/or use of lipid-modifying drugs), and/or hypertension (systolic blood pressure 130 mmHg, and/or diastolic blood pressure 85 mmHg, and/or use of antihypertensive drugs). The ATC-codes used to assess the use of blood glucose-lowering drugs, lipid-modifying drugs, and antihypertensive drugs can be found in supplemental Table S1. The use of these drugs was based on prescription in the IADB.nl database within a period of 180 days before the physical visit of the second Lifelines assessment.

Psychological factors
The presence of depression and anxiety were determined with a face-to-face Mini International Neuropsychiatric Interview (MINI; based on the DSM-IV-TR, Sheehan et al., 1998). Depression was defined as any current depressive disorder: major depressive disorder or dysthymia. The definition of anxiety included any current anxiety disorder: panic disorder, agoraphobia, social phobia, or generalized anxiety disorder. Long-term Difficulties Inventory (LDI) sum-scores were used to assess self-reported stress. Self-reported health was quantified with the following 5-point Likert scale RAND-question: 'How would you rate your health generally speaking?'.

Behavioural factors
Physical activity was determined with the following question from the Short Questionnaire to Assess Health-enhancing physical activity: "Adding everything up, on how many days per week on average are you involved in cycling, doing odd jobs, gardening, sport, or other strenuous activities for at least 30 minutes?". The prevalence of an average alcohol intake of at least three glasses per day (heavy drinking (Wouters et al., 2020; Rausch et al., 2022)) was measured with a question from the Flower Food Frequency questionnaire (FFQ): "During the past month, how many glasses of alcoholic drinks did you drink per day on average?". Smoking was assessed with self-report regarding smoking in the past month.

Biological factors
Leukocyte- and subtype-counts were analysed because they are measures of (low-grade) inflammation and a biological stress response. Chronic low-grade inflammation is an essential pathogenic factor for MetS (Del Giudice & Gangestad, 2018; Dijkstra-de Neijs et al., 2020). Blood samples were drawn by trained Lifelines' staff during a physical visit.

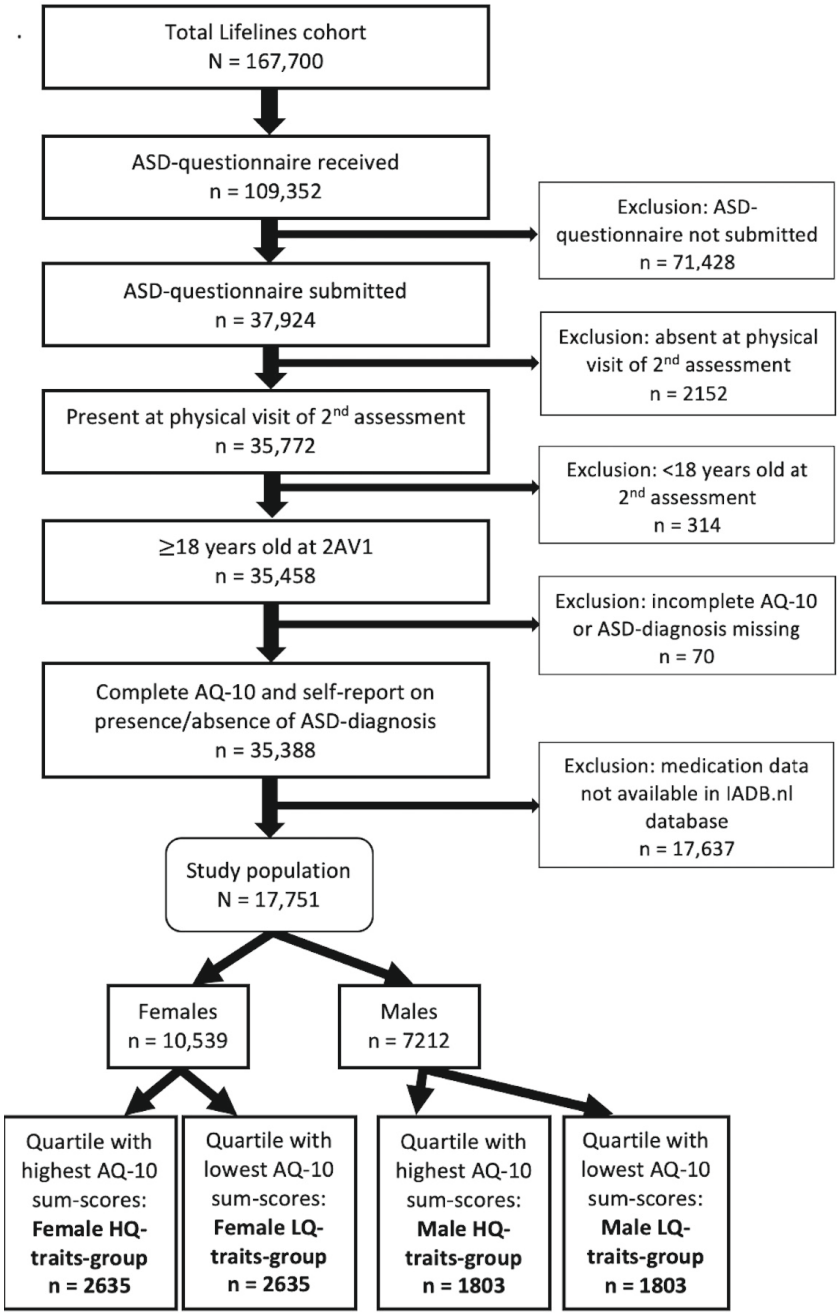
Covariates
Self-reported employment status and educational attainment were combined to determine socioeconomic status. Employment was defined as doing paid work for one or more hours per week. Low educational attainment included no education, primary, lower or preparatory vocational education, or lower general secondary education. Middle educational attainment was defined as: intermediate vocational education or apprenticeship, higher general secondary education, or pre-university secondary education. High educational attainment entailed higher vocational education or university. As several types psychotropic drugs can have weight gain as side effect, potentially weight-increasing antidepressants, antipsychotics, and anticonvulsants were assessed. None of the included participants used anticonvulsants. A list of the Anatomical

Therapeutic Chemical (ATC) codes to identify the use of antidepressants and antipsychotics can be found in supplementary Table S1.

Statistical analysis

We used IBM SPSS Statistics version 25 for all data analyses. Basic characteristics, including the prevalence of MetS, were compared with univariable analyses in the following groups: female HQ-traits-group versus female LQ-traits-group and male HQ-traits-group versus male LQ-traits-group (Table 1). These univariable analyses involved Chi-square tests for categorical variables and Student *t* tests or Mann-Whitney U tests for continuous variables. Next, multivariable analyses were performed in the female and male HQ- and LQ-traits-groups: psychological, behavioural, and biological factors were compared between these sex-stratified groups using multivariable regression, with correction for age and socioeconomic status (Table 2). Lastly, multivariable logistic regression with the presence of MetS as outcome measure was conducted (Table 3). These logistic regression models were executed for each of the included psychological, behavioural, and biological variables in the sex-stratified HQ-traits- and LQ-traits-groups. Age and socioeconomic status (employment and education) were included as covariates. Because of some missing data in the employment and educational attainment (see Supplemental Table S2), we performed step-by-step with three models (model 1 adjusted for age; model 2 adjusted for age and employment; model 3 adjusted for age, employment, and educational attainment). Model 3 was the most suitable as the point estimates remained similar. From the investigated potentially weight gain-inducing psychotropic drugs, only antidepressants were frequently used in our study population. Therefore, the latter logistic regression models were also performed with correction for the use of antidepressants. However, this did not result in outcomes leading to different conclusions, since the same significant outcomes were found. Transformation of skewed data was not indicated, because the assumptions of logistic regression were met based on the nature of the distributions and the large sample sizes.

Figure 1. Flow diagram of study population



Results

Basic characteristics

The basic characteristics of the females and males in the HQ- and LQ-traits-groups are shown in Table 1. The mean ages were not different within the female and male groups. In both the female and male HQ-traits-groups, the socioeconomic status was lower than in the female and male LQ-traits-groups.

Metabolic syndrome

MetS was more common in the female HQ-traits-group than in the female LQ-traits-group (10.0% versus 7.5%, p<0.01; see Table 1). In contrast, among males, the prevalence of MetS in the HQ-traits-group was not different from the LQ-traits-group (13.8% versus 13.1%, p=0.52). The prevalence of MetS was higher in the male HQ-traits-group than in the female HQ-traits-group (13.8% versus 10.0%, p<0.01).

Psychological, behavioural and biological factors associated with MetS

The psychological, behavioural, and biological factors in the female and male HQ- and LQ-traits-groups can be found in Table 2.

Table 3 shows the associations between these psychological, behavioural, and biological factors and the presence of MetS. In the female HQ-traits-group, the presence of MetS was associated with higher stress levels, poorer self-reported health, and the presence of a depressive disorder (OR 1.07, 95% CI 1.01-1.13; OR 0.53, 95% CI 0.43-0.66; OR 1.65, 95% CI 1.03-2.63; see Table 3). To explain, for example, a one-point higher score on the LDI stress questionnaire increases the odds of having MetS 1.07 times. Regarding behavioural factors, the presence of MetS was associated with less physical activity and smoking in the female HQ-traits-group (OR 0.88, 95% CI 0.91-0.95; OR 1.53, 95% CI 1.01-2.30). In other words, one more day of at least 30 minutes of physical activity per week decreases the odds of having MetS 0.88 times. In addition, higher total leukocyte-, neutrophil-, lymphocyte-, and monocyte-counts were associated with MetS in the female HQ-traits-group. However, in the female HQ-traits-group, the presence of anxiety disorders, alcohol use of more than two glasses per day, eosinophil-counts, and the neutrophil-to-lymphocyte ratio were not associated with the presence of MetS.

In the male HQ-traits-group (see Table 3), the presence of MetS was associated with poorer self-reported health, less physical activity, and higher total leukocyte-, neutrophil-, lymphocyte-, and monocyte-counts (OR 0.59, 95% CI 0.48-0.72; OR 0.84, 95% CI 0.78-0.92; OR 1.31, 95% CI 1.21-1.43; OR 1.39, 95% CI 1.24-1.57; OR 2.00, 95% CI 1.54-2.59; OR 13.83, 95% CI 5.39-35.49). In this male HQ-group, MetS was not associated with stress levels, the presence of anxiety or depressive disorders, alcohol use, smoking, eosinophil-counts, and the neutrophil-to-lymphocyte ratio.

Table 1. Basic characteristic of HQ-traits-group, LQ-traits-group, and sex-stratified subgroups

	Females			Males		
	HQ-traits-group n=2635	**LQ-traits-group n=2635**	P-value [a]	**HQ-traits-group n=1803**	**LQ-traits-group n=1803**	P-value [a]
Age (mean, SD)	49.1 (12.8)	48.6 (11.7)	N.S.	51.7 (12.9)	51.9 (11.7)	N.S.
AQ-10 [b] sum score (median, IQR)	4 (4-5)	0 (0-1)	<0.01	5 (5-6)	1 (0-1)	<0.01
Ethnicity (N, %)						
Eastern or Western European	2421 (91.9)	2484 (94.3)	N.S.	1656 (91.8)	1677 (93.0)	N.S.
Mediterranean or Arabic	<10 (<0.4)	<10 (<0.4)		<10 (<0.6)	<10 (<0.6)	
Black	<10 (<0.4)	<10 (<0.4)		<10 (<0.6)	<10 (<0.6)	
Asian	<10 (<0.4)	<10 (<0.4)		<10 (<0.6)	<10 (<0.6)	
Other	28 (1.1)	15 (0.6)		11 (0.6)	<10 (<0.6)	
Educational attainment (N, %)						
Low	581 (22.0)	302 (11.5)	<0.01	389 (21.6)	186 (10.3)	<0.01
Middle	863 (32.8)	713 (27.1)	<0.01	517 (28.7)	412 (22.9)	<0.01
High	733 (27.8)	1171 (44.4)	<0.01	546 (30.3)	860 (47.7)	<0.01
Employment (N, %)	1665 (63.2)	2006 (76.1)	<0.01	1201 (66.7)	1348 (74.8)	<0.01
Use of antipsychotics [c]	<10 (<0.4)	<10 (<0.4)	-	<10 (<0.6)	<10 (<0.6)	-
Use of antidepressants [d]	63 (2.4)	27 (1.0)	<0.01	21 (1.2)	<10 (<0.6)	-
Metabolic syndrome [e] (N, %)	264 (10.0)	197 (7.5)	<0.01	248 (13.8)	236 (13.1)	N.S.
WC ≥ threshold (N, %)	1135 (43.1)	1005 (38.1)	<0.01	463 (25.7)	417 (23.1)	N.S.
Hypertension (N, %)	960 (36.4)	839 (31.8)	<0.01	954 (52.9)	972 (53.9)	N.S.
Triglycerides ≥ threshold (N, %)	273 (10.4)	209 (7.9)	<0.01	425 (23.6)	421 (23.3)	N.S.
HDL-cholesterol < threshold (N, %)	386 (14.6)	309 (11.7)	<0.01	196 (10.9)	163 (9.0)	N.S.
Use of lipid-modifying drugs (N, %)	35 (1.3)	26 (1.0)	N.S.	41 (2.3)	54 (3.0)	N.S.
Increased fasting glucose (N, %)	<10 (<0.4)	<10 (<0.4)	N.S.	10 (0.6)	13 (0.7)	N.S.

a. Unadjusted p-values: Chi-square tests for categorical variables and Student *t* tests or Mann-Whitney U tests for continuous variables. b. AQ-10 = short version of the Autism Spectrum Quotient. c. Only antipsychotics which are likely to have weight gain as side effect were included (corresponding ATC-codes: see Table S1). d. Only antidepressants which are likely to have weight gain as side effect were (corresponding ATC-codes: see Table S1). e. Metabolic syndrome was defined as the presence of three or more of the following criteria: 1) waist circumference (WC) above threshold: ≥88 cm in females and ≥102 cm in males, 2) hypertension: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, and/or use of antihypertensive drugs, 3) triglycerides ≥1.7 mmol/L and/or use of lipid-modifying drugs, 4) HDL-cholesterol <1.3 mmol/L in females and <1.0 in males, and/or use of lipid-modifying. drugs, 5) fasting serum glucose ≥5.6 mmol/L and/or use of blood glucose-lowering drugs.

Table 2. Psychological, behavioural and biological factors: HQ-traits-group versus LQ-traits-group.

	Females				Males			
	HQ-traits-group n=2635	**LQ-traits-group n=2635**	p-value [a]	Adjusted OR (95% CI) [b]	**HQ-traits-group n=1803**	**LQ-traits-group n=1803**	p-value [a]	Adjusted OR (95% CI) [b]
Psychological								
Stress (median, IQR)	2 (1-4)	2 (1-3)	<0.01	1.17 (1.14-1.21)	2 (0-3)	1 (0-3)	<0.01	1.17 (1.13-1.22)
Self-reported health (median, SD)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	<0.01	0.64 (0.59-0.70)	3.0 (3.0-4.0)	4.0 (3.0-4.0)	<0.01	0.65 (0.59-0.71)
Anxiety disorder (N, %)	331 (12.6)	127 (4.8)	<0.01	2.80 (2.23-3.52)	146 (8.1)	41 (2.3)	<0.01	3.48 (2.39-5.05)
Depressive disorder (N, %)	190 (7.2)	55 (2.1)	<0.01	3.39 (2.42-4.74)	80 (4.4)	27 (1.5)	<0.01	2.85 (1.77-4.59)
Behavioural								
Alcohol use, >2 glasses/day (N, %)	259 (9.8)	275 (10.4)	N.S.	0.98 (0.80-1.21)	412 (22.9)	502 (27.8)	0.02	0.70 (0.58-0.84)
Physical activity, days/week (median, IQR)	4.5 (3.0-6.0)	5.0 (3.0-6.0)	<0.01	0.94 (0.91-0.98)	4.0 (2.5-6.0)	4.5 (3.0-6.0)	<0.01	0.95 (0.91-0.99)
Smoking (N, %)	308 (11.7)	255 (9.7)	0.02	1.14 (0.93-1.39)	212 (11.8)	250 (13.9)	N.S.	0.73 (0.58-0.91)
Biological								
Total leukocytes (10^E9/L) (median, IQR)	5.80 (4.90-6.90)	5.70 (4.90-6.80)	<0.01	1.04 (1.00-1.08)	5.80 (4.90-6.83)	5.80 (5.00-6.90)	N.S.	0.99 (0.95-1.03)
Neutrophils (10^E9/L) (median, IQR)	3.11 (2.48-3.92)	3.03 (2.43-3.78)	0.01	1.05 (0.99-1.10)	3.03 (2.49-3.76)	3.05 (2.50-3.77)	N.S.	1.00 (0.93-1.06)
Lymphocytes (10^E9/L) (median, IQR)	1.92 (1.58-2.33)	1.91 (1.55-2.32)	N.S.	1.00 (0.91-1.11)	1.89 (1.55-2.27)	1.90 (1.54-2.28)	N.S.	0.89 (0.78-1.02)
Monocytes (10^E9/L) (median, IQR)	0.46 (0.38-0.55)	0.45 (0.37-0.54)	<0.01	1.94 (1.24-3.04)	0.52 (0.43-0.62)	0.51 (0.42-0.62)	N.S.	0.93 (0.57-1.51)
Eosinophils (10^E9/L) (median, IQR)	0.15 (0.10-0.23)	0.15 (0.10-0.23)	N.S.	1.01 (0.62-1.65)	0.17 (0.11-0.26)	0.18 (0.12-0.27)	N.S.	1.13 (0.65-1.96)
Neutrophil-to-lymphocyte ratio (median, IQR)	1.62 (1.26-2.12)	1.60 (1.21-2.05)	N.S.	1.06 (0.98-1.14)	1.64 (1.25-2.14)	1.63 (1.27-2.08)	N.S.	1.04 (0.95-1.14)

a. Unadjusted p-values: Chi-square tests for categorical variables and Student *t* tests or Mann-Whitney U tests for continuous variables. b. Adjusted for age and socioeconomic status (employment and educational attainment).

Table 3. Multivariable logistic regression with the presence of metabolic syndrome as outcome

	Females		Males	
	HQ-traits-group n=2635	LQ-traits-group n=2635	**HQ-traits-group n=1803**	LQ-traits-group n=1803
	Metabolic syndrome (OR, 95% CI) [a]	Metabolic syndrome (OR, 95% CI) [a]	Metabolic syndrome (OR, 95% CI) [a]	Metabolic syndrome (OR, 95% CI) [a]
Psychological				
Stress	1.07 (1.01-1.13)	1.05 (0.97-1.13)	1.01 (0.94-1.08)	1.12 (1.03-1.22)
Self-reported health	0.53 (0.43-0.66)	0.54 (0.44-0.68)	0.59 (0.48-0.72)	0.47 (0.38-0.58)
Anxiety disorder	1.13 (0.74-1.72)	1.68 (0.91-3.10)	1.44 (0.88-2.38)	1.42 (0.58-3.50)
Depressive disorder	1.65 (1.03-2.63)	1.93 (0.79-4.69)	1.58 (0.85-2.91)	1.06 (0.31-3.65)
Behavioural				
Alcohol use of >2 glasses/day	1.00 (0.57-1.78)	1.87 (1.12-3.12)	1.28 (0.85-1.95)	1.84 (1.25-2.70)
Physical activity (days/week)	0.88 (0.91-0.95)	0.90 (0.83-0.98)	0.84 (0.78-0.92)	0.85 (0.78-0.92)
Smoking	1.53 (1.01-2.30)	1.51 (0.93-2.45)	1.05 (0.66-1.66)	1.69 (1.12-2.53)
Biological				
Total leukocytes (10^E9/L)	1.41 (1.30-1.52)	1.42 (1.29-1.55)	1.31 (1.21-1.43)	1.20 (1.09-1.31)
Neutrophils (10^E9/L)	1.49 (1.34-1.65)	1.56 (1.38-1.77)	1.39 (1.24-1.57)	1.45 (1.28-1.65)
Lymphocytes (10^E9/L)	2.32 (1.87-2.87)	1.64 (1.29-2.09)	2.00 (1.54-2.59)	1.47 (1.15-1.87)
Monocytes (10^E9/L)	6.76 (2.81-16.28)	7.11 (2.35-21.50)	13.83 (5.39-35.49)	9.50 (3.71-24.35)
Eosinophils (10^E9/L)	2.40 (0.84-6.87)	2.94 (0.98-8.89)	1.84 (0.69-4.86)	2.28 (0.71-7.33)
Neutrophil-to-lymphocyte ratio	1.07 (0.90-1.26)	1.25 (1.04-1.49)	1.12 (0.94-1.34)	1.17 (0.99-1.39)

[a.] Adjusted for age and socioeconomic status (employment and educational attainment).

Discussion

Our study showed that in the general population, MetS is more common in females with higher levels of autistic traits than in females with lower levels of autistic traits. When comparing males with higher and lower levels of autistic traits, their prevalence of MetS was not different. These findings are concordant with a previous sex-stratified study including adults with an ASD-diagnosis (Weir et al., 2021a).

With respect to the investigated psychological factors, in both females and males with higher levels of autistic traits, the presence of MetS was strongly associated with poorer self-reported health. Also, stress levels and

the presence of anxiety disorders were moderately associated with MetS in females with higher levels of autistic traits. To our knowledge, these findings cannot directly be compared to other studies, since the relation between these psychological variables and MetS in adults with autistic traits has not been examined previously. It does seem that autistic traits, self-reported health, stress and anxiety disorders are interrelated, based on previous research (Moseley et al., 2021; Amos et al., 2019; Warreman et al., 2023).

Regarding the assessed behavioural factors, the presence of MetS was strongly associated with less physical activity in both females and males with higher levels of autistic traits. Moreover, females and males with higher levels of autistic traits were less physically active than females and males with lower levels of autistic traits. In previous studies, adults either with an ASD-diagnosis or autistic traits also reported less physical activity (McCoy et al., 2016; Hillier et al., 2020). Smoking was moderately associated with MetS in the females with higher levels of autistic traits from our study. However, in our study, females with higher levels of autistic traits did not smoke more than females with lower levels of autistic traits, which is in line with previous research in autistic adults (Weir et al., 2021b). Together, especially enhancement of physical activity should be taken into account in the prevention of cardiovascular risk for adults with autistic traits.

From the investigated biological factors, MetS was strongly associated with leukocyte and several -subtype counts in both males and females with higher levels of autistic traits. This association could be explained by increased chronic stress levels in adults with higher levels of autistic traits, as psychological stress can alter these immunological variables through the hypothalamic-pituitary-adrenal axis (Dhabhar et al., 2012). Altered immune responses due to chronic stress are interrelated with metabolic activity and increased risk for cardiovascular diseases (Dijkstra-de Neijs et al., 2020; Babio et al., 2013; Dominguez-Andres & Netea, 2019). However, MetS itself is also related to low-grade systemic inflammation, since the total leukocyte and -subtype counts were also associated with MetS in males and females with lower levels of autistic traits.

Strengths and limitations

The large sample size is the main strength of this study, reporting on a wide range of biopsychosocial variables in adults from a general population cohort. Furthermore, our analyses based on the participants' level of autistic traits is a first step to better understand the increased risk for cardiovascular diseases in autistic adults and to identify cardiovascular risk profiles associated with higher level of autistic traits. Another strength of this study is the use of physically measured variables (e.g., blood pressure, fasting glucose, waist

circumference, cholesterol levels) and linked medication data from the IADB.nl database to define the presence of MetS in participants.

Temporality was not examined in our study, because of the cross-sectional design. Also, the AQ-10 scores were assessed on a later moment in time (on average four years later) than the measures of MetS and psychological, behavioural, and biological factors. However, it has previously been investigated that the AQ-10 test-retest reliability was adequate with a time interval of 6 to 12 months (Broadbent et al., 2013). It could be debated whether differences in AQ-10 scores between males and females had an effect on the found associations. However, the statistical AQ-10 variance was smaller in males than in females from the HQ-traits-groups. Also, the adult AQ-10 was validated for both men and women (Allison et al., 2012). Moreover, categorization of our study population in reversed order (first into HQ-/LQ-traits-groups and then sex-categorization) did not lead to other main study results. Next, it should be noted that in the Lifelines Cohort, only people with the ability to fill in self-report questionnaires were eligible for inclusion. Thus, our study results cannot be generalized to adults with (cognitive) disabilities impacting self-report. Lastly, since 25 (12.6%) of the participants with ASD from the 198 participants with ASD in the total study population were not included in the final analysis of female and male HQ- and LQ-traits-groups, our study was not able to cover all people diagnosed with ASD in our Lifelines Cohort sample.

Implications

Healthcare providers, such as general practitioners and psychiatrists, should be alert to assess cardiovascular risk factors when providing care for females with autistic traits, because of their increased prevalence of MetS. This implies that a wider range of females with higher levels of autistic traits, other than only those with an ASD-diagnosis based on previous research (Weir et al., 2021a), should be included in timely cardiovascular preventive interventions. Next, adults with autistic traits and their healthcare providers should be educated about the factors associated with MetS in this population. Future studies could gain more insight into the pathway through which autistic traits, biopsychosocial factors, and cardiovascular risk factors interact, especially in females.

Conclusion

In females with higher levels of autistic traits, the prevalence of MetS is higher than in females with lower levels of autistic traits. In both males and females with higher levels of autistic traits, the presence of MetS is strongly associated with poorer self-reported health, less physical activity, and altered leukocyte and -subtype counts. Earlier and adequate cardiovascular preventive measures are indicated for adults with relatively more autistic traits. To decrease morbidity and mortality of adults with high levels of autistic traits, future research should focus on implementation of cardiovascular prevention for adults with autistic traits.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Eva Warreman: conceptualization, methodology, formal analysis, writing of original draft and editing, visualization. Laura Nooteboom: conceptualization, writing review and editing, supervision. Pieter Leenen: conceptualization, writing review and editing. Hilde Geurts: conceptualization, writing review and editing. Mary Beth Terry: conceptualization, methodology, writing review and editing, supervision. Jens Bos: data curation, writing review and editing. Eelko Hak: writing review and editing. Wijbrand Hoek: writing review and editing, funding acquisition. Liesbeth van Rossum: conceptualization, writing review and editing. Robert Vermeiren: conceptualization, writing review and editing, supervision. Wietske Ester: conceptualization, methodology, writing review and editing, supervision.

Funding

This work, the Lifelines initiative, was supported by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Centre Groningen and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen) (Scholtens et al., 2015). Our study was supported by a grant from the Netherlands Organisation for Health Research and Development (NWO-ZonMw) (project number 639003101). The IADB.nl and the PharmLines Initiative are funded by the University of Groningen, Groningen Research Institute of Pharmacy (Visser et al., 2013).

Acknowledgements

We wish to acknowledge the services of the Lifelines Cohort Study, all study participants, the contributing research centres delivering data to Lifelines, and the participating IADB.nl pharmacies for providing their data for research. We also thank the members of Dutch 'Academic Workplace for Autism' for contributing to this study by sharing useful insights regarding the importance of selected study outcomes for the autistic population.

Table S1. Included Anatomical Therapeutic Chemical (ATC) codes

	ATC codes
Antihypertensive drugs	C02, C03, C04, C07, C08, C09
Lipid-modifying drugs	C10A, C10B
Blood glucose-lowering drugs	A10A, A10B
Anticonvulsant drugs	N03AF01, N03AG01, N03AX12, N03AX16
Antidepressants	N06AA09, N06AB08, N06AB10, N06AA21, N06AF03, N06CA01, N06AA01, N06AB03, N06AX11, N06AB06, N06AB04, N06AA12, N06CA03, N06AA10, N06AF04, N06AA04, N06AX21, N06AA02, N06AB05, N06AA06
Antipsychotics	N05AX12, N05AX13, N05AC02, N05AD01, N05AA01, N05AN, N05AB03, N05AF04, N05AH02, N05AN01, N05AH04, N05AB06, N05AB02, N05AH03, N05AX08, N05AE04

Table S2. Number of missing data in covariates and main outcomes

	Females		Males	
	HQ-traits-group n=2635	**LQ-traits-group n=2635**	**HQ-traits-group n=1803**	**LQ-traits-group n=1803**
Covariates	N (%)	N (%)	N (%)	N (%)
Age	0 (0)	0 (0)	0 (0)	0 (0)
Educational attainment	458 (17.4)	449 (17.0)	351 (19.5)	345 (19.1)
Employment	197 (7.5)	176 (6.7)	135 (7.5)	135 (7.5)
Main outcomes				
Metabolic syndrome	0 (0)	0 (0)	4 (0.2)	0 (0)
WC ≥ threshold	0 (0)	0 (0)	4 (0.2)	0 (0)
Hypertension	0 (0)	0 (0)	0 (0)	0 (0)
Triglycerides ≥ threshold	0 (0)	0 (0)	0 (0)	0 (0)
HDL-cholesterol < threshold	0 (0)	0 (0)	0 (0)	0 (0)
Use of lipid-modifying drugs	0 (0)	0 (0)	0 (0)	0 (0)
Increased fasting glucose	0 (0)	0 (0)	0 (0)	0 (0)
Stress	205 (7.8)	181 (6.9)	146 (8.1)	141 (7.8)
Self-reported health	193 (7.3)	174 (6.6)	137 (7.6)	135 (7.5)
Anxiety disorder	663 (25.2)	585 (22.2)	483 (26.8)	477 (26.5)
Depressive disorder	663 (25.2)	585 (22.2)	483 (26.8)	477 (26.5)
Alcohol use, >2 glasses/day	1217 (46.2)	1137 (43.1)	646 (35.8)	551 (30.6)
Physical activity, days/week	211 (8.0)	183 (6.9)	152 (8.4)	143 (7.9)
Smoking	311 (11.8)	321 (12.2)	255 (14.1)	218 (12.1)
Total leukocytes	121 (4.6)	114 (4.3)	77 (4.3)	74 (4.1)
Neutrophils	138 (5.2)	134 (5.1)	92 (5.1)	87 (4.8)
Lymphocytes	138 (5.2)	134 (5.1)	92 (5.1)	87 (4.8)
Monocytes	138 (5.2)	134 (5.1)	92 (5.1)	87 (4.8)
Eosinophils	157 (6.0)	152 (5.8)	108 (6.0)	100 (5.6)
Neutrophil-to-lymphocyte ratio	138 (5.2)	134 (5.1)	92 (5.1)	87 (4.8)

References

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., Smith, S. C., Jr, International Diabetes Federation Task Force on Epidemiology and Prevention, Hational Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, & International Association for the Study of Obesity (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Allison, C., Auyeung, B., & Baron-Cohen, S. (2012). Toward brief "Red Flags" for autism screening: The Short Autism Spectrum Quotient and the Short Quantitative Checklist for Autism in toddlers in 1,000 cases and 3,000 controls [corrected]. Journal of the American Academy of Child and Adolescent Psychiatry, 51(2), 202–212.e7. https://doi.org/10.1016/j.jaac.2011.11.003

Amos, G. A., Byrne, G., Chouinard, P. A., & Godber, T. (2019). Autism Traits, Sensory Over-Responsivity, Anxiety, and Stress: A Test of Explanatory Models. Journal of autism and developmental disorders, 49(1), 98–112. https://doi.org/10.1007/s10803-018-3695-6

Ashwood, K. L., Gillan, N., Horder, J., Hayward, H., Woodhouse, E., McEwen, F. S., Findon, J., Eklund, H., Spain, D., Wilson, C. E., Cadman, T., Young, S., Stoencheva, V., Murphy, C. M., Robertson, D., Charman, T., Bolton, P., Glaser, K., Asherson, P., Simonoff, E., ... Murphy, D. G. (2016). Predicting the diagnosis of autism in adults using the Autism-Spectrum Quotient (AQ) questionnaire. Psychological medicine, 46(12), 2595–2604. https://doi.org/10.1017/S0033291716001082

Babio, N., Ibarrola-Jurado, N., Bulló, M., Martínez-González, M. Á., Wärnberg, J., Salaverría, I., Ortega-Calvo, M., Estruch, R., Serra-Majem, L., Covas, M. I., Sorli, J. V., Salas-Salvadó, J., & PREDIMED Study Investigators (2013). White blood cell counts as risk markers of developing metabolic syndrome and its components in the PREDIMED study. PloS one, 8(3), e58354. https://doi.org/10.1371/journal.pone.0058354

Broadbent, J., Galic, I., & Stokes, M. A. (2013). Validation of autism spectrum quotient adult version in an Australian sample. Autism research and treatment, 2013, 984205. https://doi.org/10.1155/2013/984205

Cole S. W. (2008). Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. Brain, behavior, and immunity, 22(7), 1049–1055. https://doi.org/10.1016/j.bbi.2008.02.006

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. https://doi.org/10.1177/1362361315577517

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain, behavior, and immunity, 70, 61–75. https://doi.org/10.1016/j.bbi.2018.02.013

Denollet, J., Maas, K., Knottnerus, A., Keyzer, J. J., & Pop, V. J. (2009). Anxiety predicted premature all-cause and cardiovascular death in a 10-year follow-up of middle-aged women. Journal of clinical epidemiology, 62(4), 452–456. https://doi.org/10.1016/j.jclinepi.2008.08.006

Dhabhar, F. S., Malarkey, W. B., Neri, E., & McEwen, B. S. (2012). Stress-induced redistribution of immune cells--from barracks to boulevards to battlefields: a tale of three hormones--Curt Richter Award winner. Psychoneuroendocrinology, 37(9), 1345–1368. https://doi.org/10.1016/j.psyneuen.2012.05.008

Dhanasekara, C. S., Ancona, D., Cortes, L., Hu, A., Rimu, A. H., Robohm-Leavitt, C., Payne, D., Wakefield, S. M., Mastergeorge, A. M., & Kahathuduwa, C. N. (2023). Association Between Autism Spectrum Disorders and Cardiometabolic Diseases: A Systematic Review and Meta-analysis. JAMA pediatrics, 177(3), 248–257. https://doi.org/10.1001/jamapediatrics.2022.5629

Dominguez-Andres, J., & Netea, M. G. (2019). Long-term reprogramming of the innate immune system. Journal of leukocyte biology, 105(2), 329–338. https://doi.org/10.1002/JLB.MR0318-104R

Fortuna, R. J., Robinson, L., Smith, T. H., Meccarello, J., Bullen, B., Nobis, K., & Davidson, P. W. (2016). Health Conditions and Functional Status in Adults with Autism: A Cross-Sectional Evaluation. Journal of general internal medicine, 31(1), 77–84. https://doi.org/10.1007/s11606-015-3509-x

Hand, B. N., Angell, A. M., Harris, L., & Carpenter, L. A. (2020). Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism, 24(3), 755–764. https://doi.org/10.1177/1362361319890793

Harshfield, E. L., Pennells, L., Schwartz, J. E., Willeit, P., Kaptoge, S., Bell, S., Shaffer, J. A., Bolton, T., Spackman, S., Wassertheil-Smoller, S., Kee, F., Amouyel, P., Shea, S. J., Kuller, L. H., Kauhanen, J., van Zutphen, E. M., Blazer, D. G., Krumholz, H., Nietert, P. J., Kromhout, D., ... Emerging Risk Factors Collaboration (2020). Association Between Depressive Symptoms and Incident Cardiovascular Diseases. JAMA, 324(23), 2396–2405. https://doi.org/10.1001/jama.2020.23068

Hillier, A., Buckingham, A., & Schena, D., 2nd (2020). Physical Activity Among Adults With Autism: Participation, Attitudes, and Barriers. Perceptual and motor skills, 127(5), 874–890. https://doi.org/10.1177/0031512520927560

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. The British journal of psychiatry: the journal of mental science, 208(3), 232–238. https://doi.org/10.1192/bjp.bp.114.160192

Hwang, Y. I. J., Srasuebkul, P., Foley, K. R., Arnold, S., & Trollor, J. N. (2019). Mortality and cause of death of Australians on the autism spectrum. Autism research, 12(5), 806–815. https://doi.org/10.1002/aur.2086

Lai, M. C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. The lancet. Psychiatry, 2(11), 1013–1027. https://doi.org/10.1016/S2215-0366(15)00277-1

Lundin, A., Kosidou, K., & Dalman, C. (2019). Measuring Autism Traits in the Adult General Population with the Brief Autism-Spectrum Quotient, AQ-10: Findings from the Stockholm Public Health Cohort. Journal of autism and developmental disorders, 49(2), 773–780. https://doi.org/10.1007/s10803-018-3749-9

McCoy, S. M., Jakicic, J. M., & Gibbs, B. B. (2016). Comparison of Obesity, Physical Activity, and Sedentary Behaviors Between Adolescents With Autism Spectrum Disorders and Without. Journal of autism and developmental disorders, 46(7), 2317–2326. https://doi.org/10.1007/s10803-016-2762-0

Moseley, R. L., Turner-Cobb, J. M., Spahr, C. M., Shields, G. S., & Slavich, G. M. (2021). Lifetime and perceived stress, social support, loneliness, and health in autistic adults. Health psychology: official journal of the Division of Health Psychology, American Psychological Association, 40(8), 556–568. https://doi.org/10.1037/hea0001108

Rausch, C., van Zon, S. K. R., Liang, Y., Laflamme, L., Möller, J., de Rooij, S. E., & Bültmann, U. (2022). Geriatric Syndromes and Incident Chronic Health Conditions Among 9094 Older Community-Dwellers: Findings from the Lifelines Cohort Study. Journal of the American Medical Directors Association, 23(1), 54–59.e2. https://doi.org/10.1016/j.jamda.2021.02.030

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., Blackett, K. N., Sitthi-amorn, C., Sato, H., Yusuf, S., & INTERHEART investigators (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet, 364(9438), 953–962. https://doi.org/10.1016/S0140-6736(04)17019-0

Schendel, D. E., Overgaard, M., Christensen, J., Hjort, L., Jørgensen, M., Vestergaard, M., & Parner, E. T. (2016). Association of Psychiatric and Neurologic Comorbidity With Mortality Among Persons With Autism Spectrum Disorder in a Danish Population. JAMA pediatrics, 170(3), 243–250. https://doi.org/10.1001/jamapediatrics.2015.3935

Scholtens, S., Smidt, N., Swertz, M. A., Bakker, S. J., Dotinga, A., Vonk, J. M., van Dijk, F., van Zon, S. K., Wijmenga, C., Wolffenbuttel, B. H., & Stolk, R. P. (2015). Cohort Profile: LifeLines, a three-generation cohort study and biobank. International journal of epidemiology, 44(4), 1172–1180. https://doi.org/10.1093/ije/dyu229

Sediq, R., van der Schans, J., Dotinga, A., Alingh, R. A., Wilffert, B., Bos, J. H., Schuiling-Veninga, C. C., & Hak, E. (2018). Concordance assessment of self-reported medication use in the Netherlands three-generation Lifelines Cohort study with the pharmacy database iaDB.nl: The PharmLines initiative. Clinical epidemiology, 10, 981–989. https://doi.org/10.2147/CLEP.S163037

Shavelle, R. M., Strauss, D. J., & Pickett, J. (2001). Causes of death in autism. Journal of autism and developmental disorders, 31(6), 569–576. https://doi.org/10.1023/a:1013247011483

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry, 59 Suppl 20, 22–57.

Sizoo, B. B., Horwitz, E. H., Teunisse, J. P., Kan, C. C., Vissers, C., Forceville, E., Van Voorst, A., & Geurts, H. M. (2015). Predictive validity of self-report questionnaires in the assessment of autism spectrum disorders in adults. Autism : the international journal of research and practice, 19(7), 842–849. https://doi.org/10.1177/1362361315589869

Visser, S. T., Schuiling-Veninga, C. C., Bos, J. H., de Jong-van den Berg, L. T., & Postma, M. J. (2013). The population-based prescription database IADB.nl: its development, usefulness in outcomes research and challenges. Expert review of pharmacoeconomics & outcomes research, 13(3), 285–292. https://doi.org/10.1586/erp.13.20

Vohra, R., Madhavan, S., & Sambamoorthi, U. (2017). Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism, 21(8), 995–1009. https://doi.org/10.1177/1362361316665222

Warreman, E. B., Nooteboom, L. A., Terry, M. B., Hoek, H. W., Leenen, P., van Rossum, E., Ramlal, D., Vermeiren, R., & Ester, W. A. (2023). Psychological, behavioural and biological factors associated with gastrointestinal symptoms in autistic adults and adults with autistic traits. Autism, 27(7), 2173–2186. https://doi.org/10.1177/13623613231155324

Warrier, V., Greenberg, D. M., Weir, E., Buckingham, C., Smith, P., Lai, M. C., Allison, C., & Baron-Cohen, S. (2020). Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nature communications, 11(1), 3959. https://doi.org/10.1038/s41467-020-17794-1

Weir, E., Allison, C., Warrier, V., & Baron-Cohen, S. (2021a). Increased prevalence of non-communicable physical health conditions among autistic adults. Autism, 25(3), 681–694. https://doi.org/10.1177/1362361320953652

Weir, E., Allison, C., & Baron-Cohen, S. (2021b). Understanding the substance use of autistic adolescents and adults: a mixed-methods approach. The lancet. Psychiatry, 8(8), 673–685. https://doi.org/10.1016/S2215-0366(21)00160-7

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., & INTERHEART Study Investigators (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet, 364(9438), 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9

Chapter 3

Psychological, behavioural, and biological factors associated with gastrointestinal symptoms in autistic adults and adults with autistic traits

Eva Warreman, Laura Nooteboom, Mary Beth Terry, Wijbrand Hoek, Pieter Leenen, Liesbeth van Rossum, Anand Ramlal, Robert Vermeiren, Wietske Ester
Autism, 2023, 27(7), 2173-2186
https://doi.org/10.1177/13623613231155324

Abstract

Background

Gastrointestinal (GI) symptoms and their relation to physical and mental aspects in adults with an autism spectrum disorder (ASD) are poorly understood, despite their high prevalence. Therefore, the aim of this study is to examine psychological, behavioural, and biological factors associated with GI-symptoms in adults with ASD(-traits).

Methods

We included 31,185 adults from the Lifelines Study. Using multivariable logistic regression, we analysed the association between GI-symptoms and psychological, behavioural (questionnaire-assessed), and physically measured biological factors in adults with ASD (n=309), without ASD (n=30,876), and in the quartiles with highest (n=7783) and lowest (n=7783) Autism Spectrum Quotient-10 (AQ-10) sum-scores.

Results

In the ASD-group, GI-symptoms were associated with psychiatric comorbidity (odds ratio (OR) 2.71, 95% confidence interval (CI) 1.51-4.85), more stress (OR 1.15, 95% CI 1.06-1.26), and worse perceived health (OR 2.32, 95% CI 1.62-3.34). In the quartile with highest AQ-10 sum-scores, GI-symptoms were also associated with these psychological factors, and with less physical activity (OR 0.95, 95% CI 0.92-0.98).

Conclusion

Our study demonstrates that not only adults with ASD but also adults with ASD-traits are at increased risk for GI-symptoms, which is associated with psychological and behavioural factors. This suggests that an integrated psychosomatic approach of GI-symptoms in adults with ASD(-traits) is needed.

Lay abstract

Background

Little is known about factors related to the increased risk for gastrointestinal (GI) symptoms in adults with an autism spectrum disorder (ASD), while the negative impact of GI-symptoms is evident. Especially, the relationship between GI-symptoms and psychological, behavioural, and biological risk factors in adults with ASD(-traits) is unclear. Autistic peer support workers and autism-advocates also emphasized the importance of identifying risk factors, because of the high prevalence of GI-problems in people with ASD. Therefore, our study investigated which psychological, behavioural, and biological factors are associated with GI-symptoms in adults with ASD or with ASD-traits.

Methods

We analysed data from 31,185 adults in the Dutch Lifelines Study. Questionnaires were used to evaluate the presence of an ASD-diagnosis, autistic traits, GI-symptoms, psychological, and behavioural factors. Biological factors were examined with body measurements.

Results

We found that not only adults with ASD, but also adults with higher levels of autistic traits were at increased risk for GI-symptoms. Adults with ASD who experienced psychological problems (psychiatric problems, worse perceived health, chronic stress) had a higher risk for GI-symptoms than adults with ASD without these psychological problems. Moreover, adults with higher levels of autistic traits were less physically active, which was also associated with having GI-symptoms.

Conclusion

In conclusion, our study highlights the relevance of identifying psychological problems and evaluating physical activity when trying to help adults with ASD or autistic traits and GI-symptoms. This suggests that healthcare professionals should be more aware of behavioural and psychological risk factors when evaluating GI-symptoms in adults with ASD(-traits).

Introduction

Gastrointestinal (GI) problems are more prevalent in people with an autism spectrum disorder (ASD) than in the general population (McElhanon et al., 2014; Croen et al., 2015; Hand et al., 2020). However, previous studies concerning GI-symptoms mainly included children with ASD (Holingue et al., 2018; Lefter et al., 2019; McElhanon et al., 2014). Consequently, in-depth knowledge about GI-symptoms in autistic adults is lacking. A case-control study reported a prevalence of 35% GI-disorders in adults with ASD (mean age 29 years old) compared to 28% in adults without ASD (Croen et al., 2015). In older adults with ASD (65+ years old), GI-disorders seem to be more common than in non-autistic adults (49% versus 25%), as are other GI-conditions such as gastroenteritis or constipation (Hand et al., 2020). It is also known that the risk for GI-disorders is increased in adults with both ASD and intellectual disability (Bishop-Fitzpatrick and Rubenstein, 2019; Gilmore et al., 2021). However, to our knowledge, there are no previous studies investigating other factors (e.g., psychological, behavioural and biological) associated with GI-symptoms in adults with ASD. Thus, comprehensive knowledge on GI-symptoms in autistic adults is limited, while a better understanding of their increased risk for GI-problems is needed (Leader et al., 2021). In this study, we investigated the presence of GI-symptoms, rather than diagnosed GI-disorders, because of the high prevalence of functional GI-problems in a broader sense in adults with ASD (Bishop-Fitzpatrick and Rubenstein, 2019; Croen et al., 2015).

When investigating factors associated with GI-symptoms, psychological factors such as stress, anxiety, and depression, should be taken into account. Stress is a mediator in GI-symptoms, as stress influences both gut function and microbiota composition through the hypothalamic-pituitary-adrenal (HPA) axis, and reduces gut motility via the noradrenergic system (Cacioppo et al., 2007; De Palma et al., 2014). The individual's immune status is also closely intertwined with HPA axis activity, personal stress levels, the gastrointestinal condition and microbiota (Hollins and Hodgson, 2019). Relevant immunological markers that are altered by stress are for example C-reactive protein (CRP) and leukocyte counts (Del Giudice et al., 2018; Dijkstra-de Neijs et al., 2020). In addition, in children with ASD, a positive association between the concentration of the stress hormone cortisol and lower GI-tract symptoms was found (Ferguson et al., 2016). Moreover, stress is related to psychiatric symptoms, such as depression and anxiety (Tafet and Nemeroff, 2015). People with ASD often experience high levels of stress (Baron et al., 2006; Bishop-Fitzpatrick et al., 2015; Hirvikoski et al., 2015) and psychiatric comorbidities are very common (Lai et al., 2014; Hand et al., 2020). Also, anxiety has been associated with GI-problems in children with ASD (Ferguson et al., 2017).

Furthermore, behavioural factors, such as physical (in)activity and alcohol abuse, can have an impact on GI-symptoms through the gut-brain axis (Bilski et al., 2018; Chen and Haber, 2021). It is also known that children with ASD are more susceptible for food selectivity and insufficient oral intake, which can affect the intestinal microbiome (Bandini et al., 2010; Murtaza et al., 2017).

Next to the above-mentioned immunological markers that can be altered in relation to stress and GI-symptoms, other biological factors that are of concern when investigating GI-symptoms are body mass index (BMI) and waist circumference (to measure abdominal obesity). Increased BMI and abdominal obesity are associated with GI-problems, such as irritable bowel syndrome (IBS) and gastroesophageal reflux (Emerenziani et al., 2019; Foxx-Orenstein, 2010; Lee et al., 2015).

In summary, psychological, behavioural, and biological factors affecting the gut-brain axis should be taken into account when researching GI-symptoms in autistic adults.

While adults with ASD tend to have more GI-symptoms than the general population, an integrated approach analysing psychological, behavioural, and biological factors associated with GI-symptoms in autistic adults is missing. A better understanding of these factors and their putative associations in adults with ASD is relevant to optimise prevention and treatment of these GI-symptoms. The underlying theory entails that autistic traits and related factors, such as stress, depression, anxiety, sensory dysregulation, and food selectivity contribute to GI-symptoms (Amos et al., 2019; Harris et al., 2021; Mazurek et al., 2013; Williams and Gotham, 2021). Therefore, the main goal of this study is to use an integrated approach to explore which psychological, behavioural, and biological factors are associated with GI-symptoms in adults with ASD and in adults with autistic traits. In addition, our study leads to more insights regarding psychological, behavioural, and biological characteristics in both adults with ASD and in the general adult population with autistic traits.

Methods

Study population

All data were extracted from the Lifelines database. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, biological and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity

and complex genetics (Scholtens et al., 2015). Baseline assessment took place between 2007 and 2013, and the second assessment was performed from 2014 until 2017. Subsequently, in 2019 an autism questionnaire (AUTQ) was sent to 109,352 Lifelines participants. The AUTQ consisted of the short version of the Autism Spectrum Quotient (AQ-10) and a self-report question regarding the presence of an ASD-diagnosis. Thus, to be eligible for this study, participants had to be able to submit self-report surveys.

We included 31,185 participants (Figure 1), aged 18 years or older at the start of the second Lifelines assessment, who reported the presence or absence of an ASD-diagnosis, and provided any answer to one or more questions regarding GI-symptoms in the respective questionnaire (see below). These 31,185 included participants were first divided into two groups: ASD (n=309) and non-ASD (n=30,876). Next, for formation of groups based on AQ-10 sum-scores, cases with an incomplete AQ-10 were excluded from the whole included population (Figure 1). The remaining participants were categorized in quartiles, based on their AQ-10 sum-scores. The highest quartile (HQ-traits-group: n=7783), consisting of 25% of participants with the highest AQ-10 sum-scores, and the lowest quartile (LQ-traits-group: n=7783), consisting of 25% of participants with the lowest AQ-10 sum-scores, were used for analyses.

Measures

Autistic traits

The AQ-10 is an instrument to quantify the degree of autistic traits in adults with average intelligence (Allison et al., 2012). It should not be used to predict an ASD-diagnosis, since studies found varying sensitivity- and specificity-values of 62-80% and 28-87%, respectively (Sizoo et al., 2015; Booth et al., 2013; Ashwood et al., 2016). However, the AQ-10 is indeed a valid measure in epidemiological studies to grade the level of autistic symptoms in adult participants (Lundin et al., 2019; Warrier et al., 2020).

Gastrointestinal symptoms

The Rome III IBS Diagnostic Questionnaire addresses different variables concerning GI-symptoms (Thompson et al., 2006). In our study, we defined GI-symptoms as the self-report of one or more of the following complaints: abdominal discomfort/pain, diarrhoea, constipation, and/or heartburn. The presence of each symptom was rated on a 5- or 7-point Likert-scale. Cut-off points (described in Figure 2) were based on clinical relevance and definitions of functional bowel disorders (Longstreth et al., 2006; Palsson et al., 2016). As supplementary analysis, the prevalence of GI-diseases (Crohn's disease, ulcerative colitis, coeliac disease, gastric ulcer, and/or gallstones) was compared between adults with and without ASD.

Psychological factors
Psychiatric comorbidity was defined as the presence of one or more of the following diagnoses: any current depressive disorder (major depressive disorder, dysthymia) and/or any current anxiety disorder (panic disorder, agoraphobia, social phobia, generalized anxiety disorder), as determined in a face-to-face Mini International Neuropsychiatric Interview (MINI; based on the DSM-IV-TR). Another psychological measure included self-reported stress, using the Long-term Difficulties Inventory (LDI). LDI sum-scores were calculated to compare stress levels between groups. We assessed perceived health with a RAND-question about general health as a continuous variable, asking participants to answer on a 5-point Likert scale: 'How would you rate your health generally speaking?'

Behavioural factors
Physical activity was measured using the following question from the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH): 'Adding everything up, on how many days per week on average are you involved in cycling, doing odd jobs, gardening, sport, or other strenuous activities for at least 30 minutes?'. Alcohol use was assessed with this question from the Flower Food Frequency questionnaire (FFQ): 'During the past month, how many glasses of alcoholic drinks did you drink per day on average?'. For this variable, the cut-off for binary analyses was set at an average alcohol intake of more than two glasses per day (Wouters et al., 2020; Rausch et al., 2022).

Biological factors
Waist circumference and height and weight (for calculation of BMI) were measured by trained Lifelines' personnel during a physical visit of the second assessment. In addition to the level of psychological stress as determined by the LDI, we evaluated counts of different types of leukocytes and CRP levels as measures of inflammation and therefore indirect physical components of perceived stress (Del Giudice et al., 2018; Dijkstra-de Neijs et al., 2020). Blood samples were also drawn during a physical visit of the second assessment. CRP levels were processed using a nephelometric assay in a Roche Modular analyser (Roche, Basel, Switzerland).

Covariates
Socioeconomic status was determined with self-reported employment status and educational attainment. Employment status was a dichotomous question on whether the participant, at that moment, did paid work for one or more hours per week. Educational attainment was categorized as low (no education, primary, lower or preparatory vocational education, or lower general secondary education), middle (intermediate vocational education or apprenticeship, higher

general secondary education, or pre-university secondary education), high (higher vocational education or university), or other.

Autistic community involvement
The research team was advised by members of the Dutch Academic Workplace for Autism' (including autistic adults and clinicians) about the research question, selection of relevant variables, and interpretation of the results.

Statistical analyses

We used IBM SPSS Statistics version 25 for all data analyses. Before we performed our main analyses, we executed non-response analyses. The goal of the first non-response analysis was to map characteristics of the 71,428 Lifelines' participants that did receive the AUTQ, but did not submit this questionnaire (and could therefore not be included in our study). The second non-response analysis was performed to compare the total included study population (N=31,185) with the participants that were excluded because of an incomplete GI-questionnaire (n=6726).

Then, we first analysed basic characteristics with univariable analyses comparing the ASD- versus non-ASD-group, and the HQ-traits- versus LQ-traits-group. After that, psychological, behavioural, and biological factors were also compared for the ASD- versus non-ASD-group and the HQ-traits- versus LQ-traits-group, with univariable and multivariable analyses. In univariable analyses, categorical variables were analysed with Chi-square tests or Fisher's exact tests, and continuous variables with Student *t* tests or Mann-Whitney U tests. P-values below 0.05 were considered statistically significant. Correction for age, sex, and socioeconomic status was carried out with multivariable logistic regression for categorical variables and multivariable linear regression for continuous variables.

Next, multivariable logistic regression with the presence of (one or more) GI-symptoms as outcome measure was performed. These logistic regression models were executed for each of the included psychological behavioural, and biological factors in the ASD-, non-ASD-, HQ-traits-, and LQ-traits-group. Age, sex, and socioeconomic status were included as confounders in multiple logistic regression (Bytzer et al., 2001; Knutsson et al., 2010). Transformation of skewed data was not indicated, because the assumptions of logistic regression were met based on the nature of the distributions. In these logistic regression models, exclusion of participants with ASD from the HQ-traits-group did not result in different outcomes. Therefore, these participants were not excluded from the HQ-traits-group.

Primary interaction term analysis was executed in the total included study population (N=31,185), to identify the significance of the interaction effect of an ASD-diagnosis for each investigated psychosocial, behavioural, and biological

factor with GI-symptoms as dependent variable. Secondary interaction analysis was performed in the combined HQ-traits- and LQ-traits-group (n=15,566), to identify the significance of the interaction effect of reporting the highest levels of autistic traits (HQ-traits-group).

Imputation of missing data was not needed, because prevalence of missing data did not differ between ASD and the control group, and the origin of these missing data was regarded as random. CRP levels were not analysed in the ASD-group, since these data were only available for 3 participants in this group. This was due to the fact that from the total Lifelines cohort (N=167,700), only in approximately 500 participants CRP levels were determined during the second assessment.

Ethical approval

Ethical approval for the Lifelines study (reference number NL17981.042.07) was obtained from the medical ethical committee of the University Medical Center Groningen, The Netherlands.

Figure 1. Flow diagram of study population

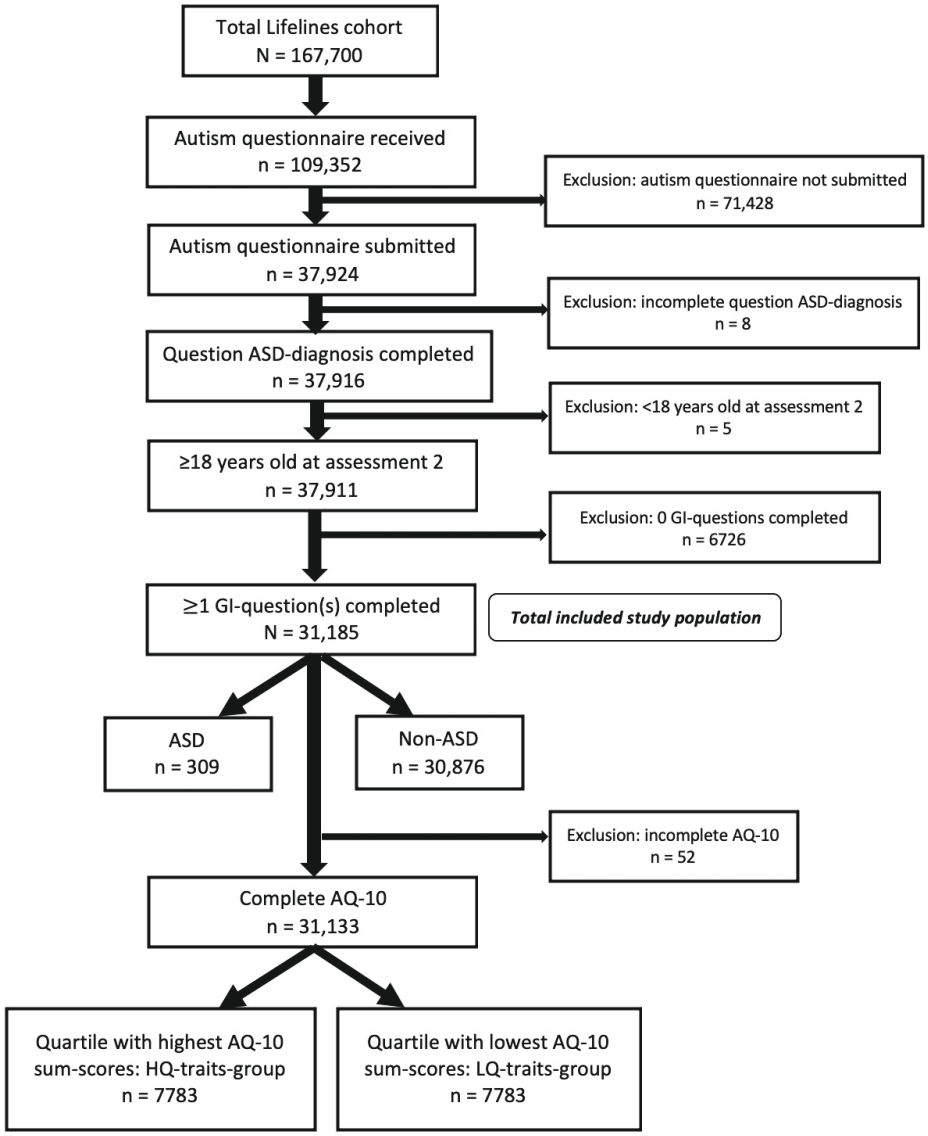
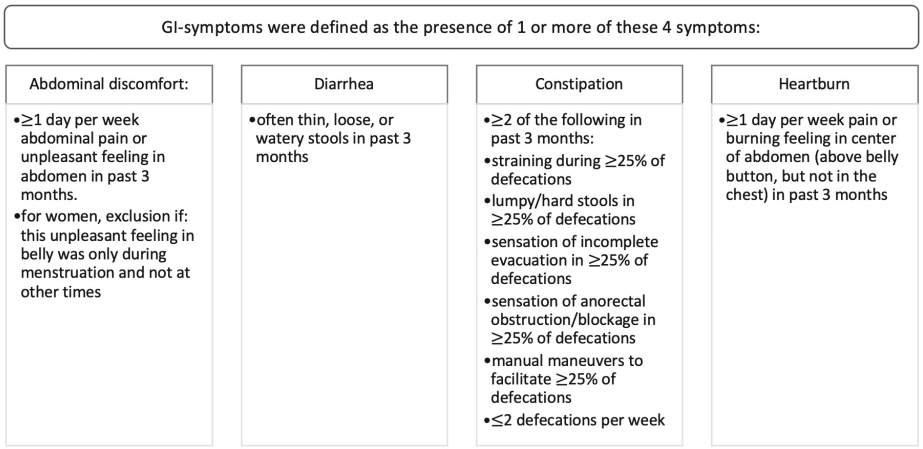


Figure 2. Definition of gastrointestinal (GI) symptoms



Results

Basic characteristics

In the total study population of 31,185 adults, 1% (n=309) reported an ASD-diagnosis (Table 1). Of these 309 adults with ASD, 86.4% (n=267) was categorized in the HQ-traits-group (i.e., group with highest AQ-10 sum-scores). Moreover, in adults with ASD, the median AQ-10 sum-score of 6.0 (interquartile range (IQR) 4.5-7.5) was 4.0 points higher than in adults without reported ASD ($p<0.01$). Socioeconomic status was lower in adults with ASD compared with adults without ASD, and in the HQ-traits-group compared with the LQ-traits-group.

The first non-response analysis revealed that the 71,428 participants who were not included because they did not submit the AUTQ, were younger in age and consisted of more men compared to the 37,924 participants who submitted the AUTQ. The second non-response analysis showed that the 6726 participants who were excluded because they did not answer any of the questions in the GI-questionnaire, more frequently had an ASD-diagnosis (n=128; 1.9%) compared to the total included study population of 31,185 participants (n=309; 1.0%). Nonetheless, the median AQ-10 sum-score in the excluded 6726 participants was not different from the median AQ-10 sum-score in the included study population.

Gastrointestinal symptoms

The prevalence of GI-symptoms (abdominal discomfort/pain, diarrhoea, constipation, and/or heartburn) was significantly higher in adults with ASD compared with adults without ASD (36% versus 21%, $p<0.01$) (Table 1). This tendency was also observed in the quartiles: 25% in the HQ-traits-group compared with 19% in the LQ-traits-group ($p<0.01$). In adults with ASD, three out of four investigated GI-symptoms were more frequently reported (p-values < 0.01). Subsequently, in the HQ-traits-group all four investigated GI-symptoms were more frequent, compared with the LQ-traits-group (p-values < 0.01). In addition, GI-diseases (Crohn's disease, ulcerative colitis, coeliac disease, gastric ulcer, and/or gallstones) were not more prevalent in adults with ASD compared with adults without ASD.

Psychological, behavioural and biological factors

In Table 2A (ASD- versus non-ASD-group) and in Table 2B (HQ-traits- versus LQ-traits-group) the outcomes of differences within groups (based on univariable and multivariable analyses) regarding psychological, behavioural, and biological factors are presented.

Psychiatric comorbidity (anxiety and/or depression) was more common in the ASD-group (OR 5.29, 95% CI 3.94-7.10). Adults with ASD reported higher stress

levels (OR 1.22, 95% CI 1.18-1.27) and worse perceived health (OR 1.71, 95% CI 1.47-2.00; as a higher score resembles worse perceived health), compared with adults without ASD. When comparing the HQ-traits and LQ-traits-group, the same differences were observed: psychiatric comorbidity was more prevalent in the HQ-traits-group (OR 3.27, 95% CI 2.83-3.79), stress levels were higher (OR 1.15, 95% CI 1.13-1.17), and perceived health was worse (OR 1.48, 95% CI 1.41-1.55).

Regarding behavioural factors, the level of physical activity and prevalence of alcohol use of more than two glasses per day in adults with ASD did not differ from adults without ASD. Multivariable analyses, correcting for differences in age, sex and socioeconomic status, also revealed no difference in prevalence of alcohol use between the HQ-traits- and LQ-traits-group. These analyses did demonstrate that adults in the HQ-traits-group were less physically active (OR 0.95, 95% CI 0.93-0.97) than adults in the LQ-traits-group.

Multivariable analyses of biological measurements showed that mean BMI and waist circumference were not different between both the ASD- and non-ASD-group and the HQ-traits- and LQ-traits-group. Similar approaches of immune parameters revealed no differences between the ASD- and non-ASD-group and the HQ-traits- and LQ-traits-group regarding the total leukocyte and leukocyte-subset counts as well as CRP levels.

Factors associated with gastrointestinal symptoms

Assessing GI-symptoms in the distinct groups and associated factors (Table 3), we observed that GI-symptoms were associated with all investigated psychological variables (psychiatric comorbidity, stress, and perceived health) in the ASD-, non-ASD-, HQ-traits-, and LQ-traits-group. In the ASD-group, GI-symptoms were not associated with behavioural variables (alcohol use and physical activity). In the HQ-traits-group, being less physically active was associated with GI-symptoms (OR 0.95, 95% CI 0.92-0.98). No association was found between alcohol use and GI-symptoms in the HQ-traits-group. Most biological variables (BMI, waist circumference, eosinophils, monocytes, and basophils) were not associated with GI-symptoms in any of the investigated groups. However, in the HQ-traits-group as well as in the non-ASD-group, GI-symptoms were positively associated with total leukocyte, lymphocyte, and neutrophil counts.

Interaction term analyses demonstrated that there were no interactions between the variable ‘ASD or non-ASD’ and the included psychological, behavioural, and biological factors. The only significant interaction was between the variable ‘HQ-traits- or LQ-traits-group’ and lymphocyte counts (OR 1.16, 95% CI 1.01-1.33).

Table 1. Basic characteristics: ASD- versus non-ASD-group and HQ-traits- versus LQ-traits-group

	ASD n = 309		non-ASD n = 30,876		p-value [a]	HQ-traits-group [b] n = 7783		LQ-traits-group [c] n = 7783		p-value [a]
Age, years (mean, SD)	41.2	(12.0)	50.7	(12.1)	<0.01	50.9	(12.7)	49.8	(11.4)	<0.01
Female sex (N, %)	124	(40.1)	18,089	(58.6)	<0.01	3534	(45.4)	5385	(69.2)	<0.01
ASD diagnosis (N, %)	309	(100)	0			267	(3.4)	2	(0.0)	<0.01
AQ-10 sum score [d] (median, IQR)	6.0	(4.5-7.5)	2.0	(0.5-3.5)	<0.01	5.0	(4.0-6.0)	1.0	(0.0-1.0)	<0.01
Ethnicity (N, %)										
Eastern or Western European	275	(89.0)	29,047	(94.1)	N.S.	7254	(93.2)	7392	(95.0)	0.03
Mediterranean, Arabic, Black or Asian	0		175	(0.6)		33	(0.4)	38	(0.5)	
Other	<10	(<3.2)	174	(0.6)		61	(0.8)	29	(0.4)	
Educational attainment (N, %)										
Low	47	(15.2)	6242	(20.2)	0.03	2025	(26.0)	1009	(13.0)	<0.01
Middle	120	(38.8)	9775	(31.7)		2578	(33.1)	2334	(30.0)	
High	90	(29.1)	10,012	(32.4)		1978	(25.4)	3202	(41.1)	
Employment (N, %)	191	(61.8)	21,502	(69.6)	0.01	5085	(65.3)	5853	(75.2)	<0.01
Gastrointestinal symptoms [e] (N, %)	112	(36.2)	6446	(20.9)	<0.01	1919	(24.7)	1467	(18.8)	<0.01
Constipation	56	(18.1)	2491	(8.1)	<0.01	760	(9.8)	560	(7.2)	<0.01
Diarrhoea	33	(10.7)	2067	(6.7)	<0.01	629	(8.1)	484	(6.2)	<0.01
Heartburn	15	(4.9)	963	(3.1)	N.S.	292	(3.8)	211	(2.7)	<0.01
Abdominal pain/ discomfort	53	(17.2)	3151	(10.2)	<0.01	936	(12.0)	687	(8.8)	<0.01

a. Univariable analysis with Chi-square test, independent sample t-test or Mann-Whitney U test. b. HQ-traits-group = 25% of participants with the highest Autism Quotient (AQ-10) sum-scores. c. LQ-traits-group = 25% of participants with the lowest AQ-10 sum-scores. d. AQ-10 = short version of the Autism Spectrum Quotient. e. Gastrointestinal symptoms = presence of 1 or more of these symptoms: constipation, diarrhoea, heartburn, abdominal pain/discomfort.

Table 2A. Psychological, behavioural and biological factors in ASD- versus non-ASD-group

	ASD n = 309		non-ASD n = 30,876		p-value [a]	Adjusted OR (95% CI) [b]
Psychological						
Psychiatric comorbidity [c] (N, %)	88	(28.5)	2042	(6.6)	<0.01	5.29 (3.94-7.10)
Anxiety	75	(24.3)	1735	(5.6)	<0.01	4.98 (3.67-6.76)
Depression	49	(15.9)	812	(2.6)	<0.01	5.50 (3.81-7.92)
Stress (median, IQR) [d]	3	(2-6)	1	(0-3)	<0.01	1.22 (1.18-1.27)
Perceived health (mean, SD) [e]	2.9	(0.9)	2.6	(0.8)	<0.01	1.71 (1.47-2.00)
Behavioural						
Alcohol use, >2 glasses/day (N, %)	67	(21.7)	7638	(24.7)	N.S.	0.57 (0.41-0.80)
Physical activity, days/week (mean, SD)	4.3	(2.0)	4.4	(1.9)	N.S.	N.S.
Biological						
Body mass index (mean, SD)	25.8	(4.9)	25.9	(4.2)	N.S.	N.S.
Waist circumference (cm) (mean, SD)	90.4	(14.2)	90.0	(12.4)	N.S.	N.S.
Leukocytes (10^E9/L) (median, IQR)	6.00	(5.10-6.90)	5.80	(4.90-6.80)	<0.05	N.S.
Neutrophils (10^E9/L) (median, IQR)	3.09	(2.60-3.84)	3.06	(2.27-3.80)	N.S.	N.S.
Lymphocytes (10^E9/L) (median, IQR)	1.97	(1.59-2.36)	1.90	(1.57-2.31)	N.S.	N.S.
Monocytes (10^E9/L) (median, IQR)	0.49	(0.42-0.60)	0.48	(0.39-0.58)	<0.05	N.S.
Eosinophils (10^E9/L) (median, IQR)	0.16	(0.09-0.24)	0.16	(0.11-0.24)	N.S.	N.S.
Basophils (10^E9/L) (median, IQR)	0.04	(0.03-0.06)	0.04	(0.03-0.06)	N.S.	N.S.

a. Univariable analysis with Chi-square test, Fisher's exact test, independent sample t-test or Mann-Whitney U test. b. Multivariable logistic regression, adjusted for age, sex, socioeconomic status (SES: employment and educational attainment); odds ratio = OR; 95% confidence interval = 95% CI. c. Psychiatric comorbidity = any current depressive disorder and/or any current anxiety disorder. d. Long-term Difficulties Inventory sum-score. A higher score equals more perceived stress. e. A higher score equals worse perceived general health.

Table 2B. Psychological, behavioural and biological factors in HQ-traits- versus LQ-traits-group

	HQ-traits-group [a] n = 7783		LQ-traits-group [b] n = 7783		p-value [c]	Adjusted OR (95% CI) [d]
Psychological						
Psychiatric comorbidity [e] (N, %)	855	(11.0)	316	(4.1)	<0.01	3.27 (2.83-3.79)
Anxiety (N, %)	714	(9.2)	269	(3.5)	<0.01	3.20 (2.74-3.75)
Depression (N, %)	396	(5.1)	107	(1.4)	<0.01	3.92 (3.10-4.95)
Stress (median, IQR) [f]	2.0	(0.0-3.0)	1.0	(0.0-3.0)	<0.01	1.15 (1.13-1.17)
Perceived health (mean, SD) [g]	2.8	(0.8)	2.5	(0.8)	<0.01	1.48 (1.41-1.55)
Behavioural						
Alcohol use, >2 glasses / day (N, %)	2088	(26.8)	1752	(22.5)	<0.01	N.S.
Physical activity, days / week (mean, SD)	4.2	(1.9)	4.5	(1.9)	<0.01	0.95 (0.93-0.97)
Biological						
Body mass index (mean, SD)	26.1	(4.3)	25.6	(4.2)	<0.01	N.S
Waist circumference (cm) (mean, SD)	91.5	(12.6)	88.4	(12.1)	<0.01	N.S.
Leukocytes (10^E9/L) (median, IQR)	5.80	(5.00-6.90)	5.70	(4.90-6.80)	<0.01	N.S.
Neutrophils (10^E9/L) (median, IQR)	3.09	(2.50-3.83)	3.04	(2.43-3.78)	<0.01	N.S.
Lymphocytes (10^E9/L) (median, IQR)	1.90	(1.56-2.31)	1.90	(1.57-2.29)	N.S.	N.S.
Monocytes (10^E9/L) (median, IQR)	0.49	(0.40-0.59)	0.47	(0.39-0.56)	<0.01	N.S.
Eosinophils (10^E9/L) (median, IQR)	0.16	(0.11-0.24)	0.16	(0.11-0.24)	<0.01	N.S.
Basophils (10^E9/L) (median, IQR)	0.04	(0.03-0.06)	0.04	(0.03-0.06)	N.S.	N.S.
CRP (median, IQR)	1.1	(0.6-3.0)	1.0	(0.5-2.2)	N.S.	N.S.

a. HQ-traits-group = 25% of participants with the highest Autism Quotient (AQ-10) sum-scores. b. LQ-traits-group = 25% of participants with the lowest AQ-10 sum-scores. c. Univariable analysis with Chi-square test, Fisher's exact test, independent sample t-test or Mann-Whitney U test. d. Multivariable logistic regression, adjusted for age, sex, socioeconomic status (SES: employment and educational attainment); odds ratio = OR; 95% confidence interval = 95% CI. e. Psychiatric comorbidity = any current depressive disorder and/or any current anxiety disorder. f. Long-term Difficulties Inventory sum-score. A higher score equals more perceived stress. g. A higher score equals worse perceived general health.

Table 3. Multivariable logistic regression with GI-symptoms as outcome, adjusted for confounders [a]

	ASD n = 309	non-ASD n = 30,876	**HQ-traits-group [b] n = 7783**	LQ-traits-group [c] n = 7783
	GI-symptoms [d] (OR, 95% CI) [e]	GI-symptoms [d] (OR, 95% CI) [e]	GI-symptoms [d] (OR, 95% CI) [e]	GI-symptoms [d] (OR, 95% CI) [e]
Psychological				
Psychiatric comorbidity [f]	2.78 (1.51-5.01) *	2.72 (2.46-3.01) *	2.68 (2.27-3.15) *	2.45 (1.91-3.13) *
Stress [g]	1.15 (1.06-1.26) *	1.20 (1.18-1.21) *	1.18 (1.15-1.21) *	1.20 (1.16-1.23) *
Perceived health [h]	2.32 (1.62-3.34) *	2.07 (1.99-2.16) *	2.16 (1.98-2.35) *	2.06 (1.89-2.24) *
Behavioural				
Alcohol use, >2 glasses/ day	0.77 (0.38-1.59)	1.07 (0.99-1.16)	1.04 (0.90-1.21)	1.18 (1.00-1.39)
Physical activity	0.92 (0.80-1.05)	0.96 (0.95-0.98) *	0.95 (0.92-0.98) *	0.96 (0.93-1.00)
Biological				
Body mass index	1.01 (0.96-1.07)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.02 (1.00-1.03)
Waist circumference	1.00 (0.98-1.02)	1.01 (1.00-1.01)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
Leukocytes	0.99 (0.85-1.14)	1.04 (1.02-1.06) *	1.05 (1.01-1.08) *	1.04 (1.00-1.08)
Neutrophils	1.06 (0.84-1.34)	1.07 (1.04-1.09) *	1.07 (1.02-1.12) *	1.07 (1.01-1.12) *
Lymphocytes	0.76 (0.49-1.19)	1.08 (1.03-1.13) *	1.11 (1.01-1.22) *	0.98 (0.89-1.09)
Monocytes	0.36 (0.05-2.85)	1.23 (0.99-1.52)	0.94 (0.63-1.40)	1.25 (0.80-1.96)
Eosinophils	2.87 (0.48-17.22)	0.96 (0.76-1.21)	1.01 (0.65-1.57)	1.43 (0.92-2.20)
Basophils	0.80 (0.00-597051.25)	2.09 (0.52-8.44)	6.86 (0.51-92.77)	1.34 (0.08-23.88)
CRP	-	1.16 (0.57-2.36)	1.24 (0.31-5.04)	(0.13-3.66)

a. In each of the 4 groups (ASD-, non-ASD-, HQ-traits-, and LQ-traits-group) separate multivariable logistic regression models were performed with the presence of 1 or more GI-symptom(s) as dependent outcome measure. For each of the independent psychological, behavioural, and biological variables a separate multivariable logistic regression model was performed, including adjustment for confounders (age, sex, employment and educational attainment). Thus, the groups were not compared in these analyses. b. HQ-traits-group = 25% of participants with the highest Autism Quotient (AQ-10) sum-scores. c. LQ-traits-group = 25% of participants with the lowest AQ-10 sum-scores. d. Gastrointestinal (GI) symptoms = presence of 1 or more of these symptoms: constipation, diarrhoea, heartburn, abdominal pain/discomfort. e. Odds ratio = OR. 95% confidence interval = 95% CI. Statistically significant odds ratios are marked: *. f. Psychiatric comorbidity = any current depressive disorder and/or any current anxiety disorder. g. Long-term Difficulties Inventory sum-score. A higher score equals more perceived stress. h. A higher score equals worse perceived general health.

Discussion

Our results demonstrated an elevated risk for the GI-symptoms abdominal discomfort/pain, diarrhoea, constipation, and/or heartburn in adults with ASD compared to adults without ASD. This increased risk was also found in adults with higher levels of autistic traits compared to adults with lower levels. In both adults with ASD and adults with higher levels of autistic traits, GI-symptoms were strongly associated with psychiatric comorbidity (anxiety and/or depressive disorder), increased perceived psychological stress levels, and worse perceived health. In adults with higher levels of autistic traits, there was a moderate association between GI-symptoms and less physical activity and increased leukocyte, lymphocyte, and neutrophil counts.

With regard to psychological factors, we found no previous studies specifically investigating the association between GI-symptoms in adults with ASD or autistic traits and stress or psychiatric comorbidities. Nonetheless, interactions between autistic traits and several psychological parameters have already been acknowledged (Green and Ben-Sasson et al., 2010; Amos et al., 2019), for example sensory over-responsivity, which could lead to stress and anxiety. Through the gut-brain axis, psychological factors such as stress and anxiety can cause alterations in the GI-tract (e.g., bowel movement and gut microbiota), and vice versa (Chidambaram et al., 2020). Such GI-alterations are related to GI-symptoms. On a biological basis, this bilateral interaction between the physique and the psyche in the gut-brain axis supports the associations we observed between GI-symptoms and psychiatric comorbidity and stress in autistic adults. The current study also showed that in adults with ASD and in adults with higher levels of autistic traits, worse perceived health was associated with GI-symptoms. This result could be explained by the relation between worse perceived health and stress, as found in autistic adults (Moseley et al. 2021).

Regarding investigated behavioural factors, alcohol use of more than two glasses per day was not associated with GI-symptoms in our adults with ASD or autistic traits. Previous studies demonstrated that alcohol (ab)use is less prevalent in adults with ASD (Croen et al., 2015; Vohra et al., 2017; Tolchard et al., 2018; Weir et al., 2020), as also observed in our multivariable analysis. When it comes to physical activity, previous literature has pointed out that children and adults with ASD on average perform less physical exercise (McCoy et al., 2016; Memari et al., 2015; Hillier et al, 2020). Moreover, the current study displayed that being less physically active was associated with GI-symptoms in adults with higher levels of autistic traits. Therefore, it is advisable to take physical activity into account when assessing GI-problems in autistic adults.

With respect to biological factors, BMI is associated with GI-symptoms in the general population (Eslick GD, 2012) and weight problems are an

increasing epidemic in people with ASD (Li et al., 2020; Croen et al., 2015; Hand et al., 2020). In our study, mean BMI and waist circumference did not differ between adults with and without ASD, and both were not associated with GI-symptoms. Regarding immunological factors, we investigated leukocyte and subtype counts, because stress is a mediator in GI-symptoms and stress hormones (such as cortisol) are known to regulate these leukocyte counts (De Palma et al., 2014; Dhabhar et al., 2012). Therefore, we hypothesised that altered immunological blood markers might help to understand the correlation between chronic exposure to stress in individuals with ASD and the occurrence of GI-symptoms (Hirvikoski et al., 2015; Bishop-Fitzpatrick et al., 2015; Baron et al., 2006). Our study demonstrated a moderate association between immunological factors, in particular lymphocyte and neutrophil counts, and GI-symptoms in adults with higher levels of autistic traits. In adults with lower levels of autistic traits neutrophil but not lymphocyte counts were found to be associated with GI-symptoms. Thus, we cannot conclude that these total leukocyte and subtype counts clearly highlight the relationship between stress and GI-symptoms in our target population.

In summary, our findings suggest that stress, psychiatric comorbidities, perceived health, and physical activity are important factors to integrate in the assessment of GI-symptoms in adults with ASD or autistic traits. It should be noted that our study population included adults that were able to provide self-reported AQ-10 answers. Therefore, it is estimated that this study population mostly represents adults with lower support needs. It is hypothesised that future inclusion of adults across a wider range of intellectually abilities, would result in similar or magnified findings compared to our study, since intellectual disability increases the risk for GI-disorders in adults with ASD (Bishop-Fitzpatrick and Rubenstein, 2019; Gilmore et al., 2021). It is also expected that investigating a study population including more adults with ASD, would result in larger significant findings regarding factors associated with GI-symptoms in these adults with ASD, because a larger sample size leads to more precision.

Strengths

The main strength of this study is the large sample size of a prospective general cohort, offering a wide range of basic, psychological, behavioural, and biological variables in more than 31,000 adults. The approximately 1% (n=309) of adults reporting an ASD-diagnosis in our study sample matches the worldwide prevalence of 1-2% (Dietz et al., 2020; Baio et al., 2018). This makes our study population a representative sample in terms of autism prevalence. Another asset to this study is the assessment of stress levels by perceived psychological stress using questionnaires and a laboratory approach by immunological blood markers. Furthermore, the combination of performing the same analyses

in both adults with ASD and adults with autistic traits, is relevant to include in research because of the prevalence of undiagnosed ASD-cases (Baron-Cohen et al., 2009) and the correlations between autistic traits and GI-symptoms (Amos et al., 2019; Williams and Gotham, 2021). A final strength of this study is the involvement of the autistic community in defining the research question, including relevant variables, and interpreting the results (through advice of autistic team-members).

Limitations

Since this study had a cross-sectional design, it was not possible to examine temporality. Another limitation of our study is the fact that data from the GI-questionnaire and the autism questionnaire were not available at the same moment in time. This resulted in a mean gap of 4 years between data about the ASD-diagnosis and AQ-10 scores, and psychological, behavioural, biological, and GI-data. Nonetheless, since ASD is considered as a life-long diagnosis, this time gap was not likely to interfere with our results in the ASD- and non-ASD-group. Broadbent et al. (2013) concluded that the AQ-10 test-retest reliability, with a time interval of 6 to 12 months, was satisfactory. As it is known that food selectivity and insufficient oral intake can affect the intestinal microbiome in children with ASD (Bandini et al., 2010; Murtaza et al., 2017), it is a limitation of our study that dietary variables were not included. Our study was limited to self-report regarding the presence of an ASD-diagnosis. However, this uncertainty was partly countered by a median AQ-10 sum-score of 6.0 in adults with ASD, compared to 2.0 in the adults without ASD. It should also be taken into account that GI-symptoms were based on self-report (ROME-III questions). However, Lefter et al. (2019) advised to use ROME-questionnaires to assess GI-problems in ASD. Since people were not eligible for inclusion in the Lifelines Cohort if they did not have the ability to fill in self-report surveys, our study sample does not represent those autistic adults with cognitive disabilities or other types of disabilities impacting self-report. Therefore, the results from our study cannot be generalised to all types of autistic adults, but are limited to autistic adults with the ability to fill in self-report surveys.

Implications

Both healthcare providers and autistic adults should be aware that psychological and behavioural factors are associated with GI-symptoms in autistic adults. It would be beneficial to people with ASD if this knowledge results in more integrated psychological, behavioural, and somatic care. Since we found that adults with autistic traits exhibit more psychological and behavioural risk factors, it could be useful to consider autistic traits in patients with poorly understood GI-complaints. After exclusion of a somatic cause of GI-problems, stress, perceived health, psychiatric comorbidity, and physical activity should

be evaluated by clinicians. Moreover, health education focusing on psychosomatic interactions could lead to better adherence of treatment or preventive measures. Future research should address the optimalisation of prevention and treatment of GI-symptoms in autistic adults. Finally, associations between GI-symptoms and increased leukocyte (subtype) counts in autistic adults should be investigated in more depth to clarify their value for clinical practice.

Conclusion

Our study demonstrates that not only adults with ASD, but also adults with higher levels of autistic traits are at increased risk for GI-symptoms. In addition, in both adults with ASD and adults with higher levels of autistic traits, GI-symptoms are strongly associated with higher stress levels, psychiatric comorbidity, and worse perceived health. In adults with the highest levels of autistic traits, GI-symptoms are also moderately associated with less physical activity. Together, these results suggest that assessment of GI-symptoms in adults with ASD or autistic traits might benefit from an integrated psychological and behavioural approach, next to the somatic assessment. Future research could focus on optimising clinical practice regarding prevention and treatment of GI-symptoms in autistic adults.

Acknowledgements

We wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centres delivering data to Lifelines, and all the study participants. We also thank the members of the project-team of the Dutch 'Academic Workplace for Autism' for contributing to this paper by sharing their insights into current problems in the autistic population. We thank dr. S. Böhringer for his support regarding the performed statistical analyses.

Funding

The Lifelines initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen, and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen). Our study was supported by a grant from the Netherlands Organization for Health Research and Development (NWO-ZonMw) [project number 639003101]. The authors declare not having any conflict of interest.

References

Allison, C., Auyeung, B., & Baron-Cohen, S. (2012). Toward brief "Red Flags" for autism screening: The Short Autism Spectrum Quotient and the Short Quantitative Checklist for Autism in toddlers in 1,000 cases and 3,000 controls [corrected]. Journal of the American Academy of Child and Adolescent Psychiatry, 51(2), 202–212.e7. https://doi.org/10.1016/j.jaac.2011.11.003

Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. BMC gastroenterology, 11, 22. https://doi.org/10.1186/1471-230X-11-22

Amos, G. A., Byrne, G., Chouinard, P. A., & Godber, T. (2019). Autism Traits, Sensory Over-Responsivity, Anxiety, and Stress: A Test of Explanatory Models. Journal of autism and developmental disorders, 49(1), 98–112. https://doi.org/10.1007/s10803-018-3695-6

Ashwood, K. L., Gillan, N., Horder, J., Hayward, H., Woodhouse, E., McEwen, F. S., Findon, J., Eklund, H., Spain, D., Wilson, C. E., Cadman, T., Young, S., Stoencheva, V., Murphy, C. M., Robertson, D., Charman, T., Bolton, P., Glaser, K., Asherson, P., Simonoff, E., & Murphy, D. G. (2016). Predicting the diagnosis of autism in adults using the Autism-Spectrum Quotient (AQ) questionnaire. Psychological medicine, 46(12), 2595–2604. https://doi.org/10.1017/S0033291716001082

Bandini, L. G., Anderson, S. E., Curtin, C., Cermak, S., Evans, E. W., Scampini, R., Maslin, M., & Must, A. (2010). Food selectivity in children with autism spectrum disorders and typically developing children. The Journal of pediatrics, 157(2), 259–264. https://doi.org/10.1016/j.jpeds.2010.02.013

Baron, M. G., Groden, J., Groden, G., & Lipsitt, L. P. (2006). Stress and coping in autism. Oxford University Press.

Baron-Cohen, S., Scott, F. J., Allison, C., Williams, J., Bolton, P., Matthews, F. E., & Brayne, C. (2009). Prevalence of autism-spectrum conditions: UK school-based population study. British journal of psychiatry, 194(6), 500–509. https://doi.org/10.1192/bjp.bp.108.059345

Bilski, J., Mazur-Bialy, A., Magierowski, M., Kwiecien, S., Wojcik, D., Ptak-Belowska, A., Surmiak, M., Targosz, A., Magierowska, K., & Brzozowski, T. (2018). Exploiting Significance of Physical Exercise in Prevention of Gastrointestinal Disorders. Current pharmaceutical design, 24(18), 1916–1925. https://doi.org/10.2174/1381612824666180522103759

Bishop-Fitzpatrick, L., Mazefsky, C. A., Minshew, N. J., & Eack, S. M. (2015). The relationship between stress and social functioning in adults with autism spectrum disorder and without intellectual disability. Autism research, 8(2), 164–173. https://doi.org/10.1002/aur.1433

Bishop-Fitzpatrick, L., & Rubenstein, E. (2019). The Physical and Mental Health of Middle Aged and Older Adults on the Autism Spectrum and the Impact of Intellectual Disability. Research in autism spectrum disorders, 63, 34–41. https://doi.org/10.1016/j.rasd.2019.01.001

Booth, T., Murray, A. L., McKenzie, K., Kuenssberg, R., O'Donnell, M., & Burnett, H. (2013). Brief report: an evaluation of the AQ-10 as a brief screening instrument for ASD in adults. Journal of autism and developmental disorders, 43(12), 2997–3000. https://doi.org/10.1007/s10803-013-1844-5

Broadbent, J., Galic, I., & Stokes, M. A. (2013). Validation of autism spectrum quotient adult version in an Australian sample. Autism research and treatment, 2013, 984205. https://doi.org/10.1155/2013/984205

Buie, T., Campbell, D. B., Fuchs, G. J., 3rd, Furuta, G. T., Levy, J., Vandewater, J., Whitaker, A. H., Atkins, D., Bauman, M. L., Beaudet, A. L., Carr, E. G., Gershon, M. D., Hyman, S. L., Jirapinyo, P., Jyonouchi, H., Kooros, K., Kushak, R., Levitt, P., Levy, S. E., Lewis, J. D., & Winter, H. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics, 125 Suppl 1, S1–S18. https://doi.org/10.1542/peds.2009-1878C

Bytzer, P., Howell, S., Leemon, M., Young, L. J., Jones, M. P., & Talley, N. J. (2001). Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population based study in 15 000 Australian adults. Gut, 49(1), 66–72. https://doi.org/10.1136/gut.49.1.66

Campbell, D. B., Buie, T. M., Winter, H., Bauman, M., Sutcliffe, J. S., Perrin, J. M., & Levitt, P. (2009). Distinct genetic risk based on association of MET in families with co-occurring autism and gastrointestinal conditions. Pediatrics, 123(3), 1018–1024. https://doi.org/10.1542/peds.2008-0819

Cacioppo, J. T., Tassinary, L. G., Berntson, G. (2007). The Handbook of Psychophysiology. 3rd edition. Cambridge University Press.

Chen G., & Haber P.S. (2021). Gastrointestinal Disorders Related to Alcohol and Other Drug Use. In: el-Guebaly N., Carrà G., Galanter M., Baldacchino A.M. (eds) Textbook of Addiction Treatment. Springer, Cham. https://doi.org/10.1007/978-3-030-36391-8_76

Chidambaram, S. B., Tuladhar, S., Bhat, A., Mahalakshmi, A. M., Ray, B., Essa, M. M., Bishir, M., Bolla, S. R., Nanjaiah, N. D., Guillemin, G. J., & Qoronfleh, M. W. (2020). Autism and Gut-Brain Axis: Role of Probiotics. Advances in neurobiology, 24, 587–600. https://doi.org/10.1007/978-3-030-30402-7_21

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. https://doi.org/10.1177/1362361315577517

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain, behavior, and immunity, 70, 61–75. https://doi.org/10.1016/j.bbi.2018.02.013

De Palma, G., Collins, S. M., Bercik, P., & Verdu, E. F. (2014). The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both?. The Journal of physiology, 592(14), 2989–2997. https://doi.org/10.1113/jphysiol.2014.273995

Dhabhar, F. S., Malarkey, W. B., Neri, E., & McEwen, B. S. (2012). Stress-induced redistribution of immune cells--from barracks to boulevards to battlefields: a tale of three hormones--Curt Richter Award winner. Psychoneuroendocrinology, 37(9), 1345–1368. https://doi.org/10.1016/j.psyneuen.2012.05.008

Dietz, P. M., Rose, C. E., McArthur, D., & Maenner, M. (2020). National and State Estimates of Adults with Autism Spectrum Disorder. Journal of autism and developmental disorders, 50(12), 4258–4266. https://doi.org/10.1007/s10803-020-04494-4

Dijkstra-de Neijs, L., Leenen, P. J. M., Hays, J. P., Van der Valk, E. S., Kraaij, R., Van Rossum, E. F. C., & Ester, W. A. (2020). Biological Consequences of Psychological Distress in Caregivers of Children with Autism Spectrum Disorder and its Potential Relevance to Other Chronic Diseases Including Cancer. Current Epidemiology Reports, 7, 139–148. https://doi.org/10.1007/s40471-020-00237-2

Emerenziani, S., Guarino, M., Trillo Asensio, L. M., Altomare, A., Ribolsi, M., Balestrieri, P., & Cicala, M. (2019). Role of Overweight and Obesity in Gastrointestinal Disease. Nutrients, 12(1), 111. https://doi.org/10.3390/nu12010111

Eslick G. D. (2012). Gastrointestinal symptoms and obesity: a meta-analysis. Obesity reviews, 13(5), 469–479. https://doi.org/10.1111/j.1467-789X.2011.00969.x

Ferguson, B. J., Dovgan, K., Severns, D., Martin, S., Marler, S., Gross Margolis, K., Bauman, M. L., Veenstra-VanderWeele, J., Sohl, K., & Beversdorf, D. Q. (2019). Lack of Associations Between Dietary Intake and Gastrointestinal Symptoms in Autism Spectrum Disorder. Frontiers in psychiatry, 10, 528. https://doi.org/10.3389/fpsyt.2019.00528

Ferguson, B. J., Marler, S., Altstein, L. L., Lee, E. B., Akers, J., Sohl, K., McLaughlin, A., Hartnett, K., Kille, B., Mazurek, M., Macklin, E. A., McDonnell, E., Barstow, M., Bauman, M. L., Margolis, K. G., Veenstra-VanderWeele, J., & Beversdorf, D. Q. (2017). Psychophysiological Associations with Gastrointestinal Symptomatology in Autism Spectrum Disorder. Autism research, 10(2), 276–288. https://doi.org/10.1002/aur.1646

Ferguson, B. J., Marler, S., Altstein, L. L., Lee, E. B., Mazurek, M. O., McLaughlin, A., Macklin, E. A., McDonnell, E., Davis, D. J., Belenchia, A. M., Gillespie, C. H., Peterson, C. A., Bauman, M. L., Margolis, K. G., Veenstra-VanderWeele, J., & Beversdorf, D. Q. (2016). Associations between cytokines, endocrine stress response, and gastrointestinal symptoms in autism spectrum disorder. Brain, behavior, and immunity, 58, 57–62. https://doi.org/10.1016/j.bbi.2016.05.009

Foxx-Orenstein A. E. (2010). Gastrointestinal symptoms and diseases related to obesity: an overview. Gastroenterology clinics of North America, 39(1), 23–37. https://doi.org/10.1016/j.gtc.2009.12.006

Gilmore, D., Harris, L., Longo, A., & Hand, B. N. (2021). Health status of Medicare-enrolled autistic older adults with and without co-occurring intellectual disability: An analysis of inpatient and institutional outpatient medical claims. Autism, 25(1), 266–274. https://doi.org/10.1177/1362361320955109

Green, S. A., & Ben-Sasson, A. (2010). Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: is there a causal relationship?. Journal of autism and developmental disorders, 40(12), 1495–1504. https://doi.org/10.1007/s10803-010-1007-x

Hand, B. N., Angell, A. M., Harris, L., & Carpenter, L. A. (2020). Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism, 24(3), 755–764. https://doi.org/10.1177/1362361319890793

Harris, H. A., Micali, N., Moll, H. A., van Berckelaer-Onnes, I., Hillegers, M., & Jansen, P. W. (2021). The role of food selectivity in the association between child autistic traits and constipation. The International journal of eating disorders, 54(6), 981–985. https://doi.org/10.1002/eat.23485

Hillier, A., Buckingham, A., & Schena, D., 2nd (2020). Physical Activity Among Adults With Autism: Participation, Attitudes, and Barriers. Perceptual and motor skills, 127(5), 874–890. https://doi.org/10.1177/0031512520927560

Hirvikoski, T., & Blomqvist, M. (2015). High self-perceived stress and poor coping in intellectually able adults with autism spectrum disorder. Autism, 19(6), 752–757. https://doi.org/10.1177/1362361314543530

Holingue, C., Newill, C., Lee, L. C., Pasricha, P. J., & Daniele Fallin, M. (2018). Gastrointestinal symptoms in autism spectrum disorder: A review of the literature on ascertainment and prevalence. Autism research, 11(1), 24–36. https://doi.org/10.1002/aur.1854

Hollins, S. L., & Hodgson, D. M. (2019). Stress, microbiota, and immunity. Current Opinion in Behavioral Sciences, 28, 66-71. https://doi.org/10.1016/j.cobeha.2019.01.015

Knutsson, A., & Bøggild, H. (2010). Gastrointestinal disorders among shift workers. Scandinavian journal of work, environment & health, 36(2), 85–95. https://doi.org/10.5271/sjweh.2897

Lai, M. C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. The Lancet Psychiatry, 2(11), 1013–1027. https://doi.org/10.1016/S2215-0366(15)00277-1

Lai, M. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. The Lancet, 383(9920), 896–910. https://doi.org/10.1016/S0140-6736(13)61539-1

Leader, G., Barrett, A., Ferrari, C., Casburn, M., Maher, L., Naughton, K., Arndt, S., & Mannion, A. (2021). Quality of life, gastrointestinal symptoms, sleep problems, social support, and social functioning in adults with autism spectrum disorder. Research in developmental disabilities, 112, 103915. https://doi.org/10.1016/j.ridd.2021.103915

Lee, C. G., Lee, J. K., Kang, Y. S., Shin, S., Kim, J. H., Lim, Y. J., Koh, M. S., Lee, J. H., & Kang, H. W. (2015). Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. The American journal of gastroenterology, 110(2), 310–319. https://doi.org/10.1038/ajg.2014.422

Lefter, R., Ciobica, A., Timofte, D., Stanciu, C., & Trifan, A. (2019). A Descriptive Review on the Prevalence of Gastrointestinal Disturbances and Their Multiple Associations in Autism Spectrum Disorder. Medicina, 56(1), 11. https://doi.org/10.3390/medicina56010011

Li, Y. J., Xie, X. N., Lei, X., Li, Y. M., & Lei, X. (2020). Global prevalence of obesity, overweight and underweight in children, adolescents and adults with autism spectrum disorder, attention-deficit hyperactivity disorder: A systematic review and meta-analysis. Obesity reviews, 21(12), e13123. https://doi.org/10.1111/obr.13123

Longstreth, G. F., Thompson, W. G., Chey, W. D., Houghton, L. A., Mearin, F., & Spiller, R. C. (2006). Functional bowel disorders. Gastroenterology, 130(5), 1480–1491. https://doi.org/10.1053/j.gastro.2005.11.061

Lundin, A., Kosidou, K., & Dalman, C. (2019). Measuring Autism Traits in the Adult General Population with the Brief Autism-Spectrum Quotient, AQ-10: Findings from the Stockholm Public Health Cohort. Journal of autism and developmental disorders, 49(2), 773–780. https://doi.org/10.1007/s10803-018-3749-9

Madra, M., Ringel, R., & Margolis, K. G. (2020). Gastrointestinal Issues and Autism Spectrum Disorder. Child and adolescent psychiatric clinics of North America, 29(3), 501–513. https://doi.org/10.1016/j.chc.2020.02.005

Mazurek, M. O., Vasa, R. A., Kalb, L. G., Kanne, S. M., Rosenberg, D., Keefer, A., Murray, D. S., Freedman, B., & Lowery, L. A. (2013). Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. Journal of abnormal child psychology, 41(1), 165–176. https://doi.org/10.1007/s10802-012-9668-x

McCoy, S. M., Jakicic, J. M., & Gibbs, B. B. (2016). Comparison of Obesity, Physical Activity, and Sedentary Behaviors Between Adolescents With Autism Spectrum Disorders and Without. Journal of autism and developmental disorders, 46(7), 2317–2326. https://doi.org/10.1007/s10803-016-2762-0

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. Pediatrics, 133(5), 872–883. https://doi.org/10.1542/peds.2013-3995

Memari, A. H., Panahi, N., Ranjbar, E., Moshayedi, P., Shafiei, M., Kordi, R., & Ziaee, V. (2015). Children with Autism Spectrum Disorder and Patterns of Participation in Daily Physical and Play Activities. Neurology research international, 2015, 531906. https://doi.org/10.1155/2015/531906

Moseley, R. L., Turner-Cobb, J. M., Spahr, C. M., Shields, G. S., & Slavich, G. M. (2021). Lifetime and perceived stress, social support, loneliness, and health in autistic adults. Health psychology: official journal of the Division of Health Psychology, American Psychological Association, 40(8), 556–568. https://doi.org/10.1037/hea0001108

Murtaza, N., Ó Cuív, P., & Morrison, M. (2017). Diet and the Microbiome. Gastroenterology clinics of North America, 46(1), 49–60. https://doi.org/10.1016/j.gtc.2016.09.005

Palsson, O. S., Whitehead, W. E., van Tilburg, M. A., Chang, L., Chey, W., Crowell, M. D., Keefer, L., Lembo, A. J., Parkman, H. P., Rao, S. S., Sperber, A., Spiegel, B., Tack, J., Vanner, S., Walker, L. S., Whorwell, P., & Yang, Y. (2016). Rome IV Diagnostic Questionnaires and Tables for Investigators and Clinicians. Gastroenterology, S0016-5085(16)00180-3. https://doi.org/10.1053/j.gastro.2016.02.014

Paré, P., Gray, J., Lam, S., Balshaw, R., Khorasheh, S., Barbeau, M., Kelly, S., & McBurney, C. R. (2006). Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. Clinical therapeutics, 28(10), 1726–1711. https://doi.org/10.1016/j.clinthera.2006.10.010

Rausch, C., van Zon, S., Liang, Y., Laflamme, L., Möller, J., de Rooij, S. E., & Bültmann, U. (2022). Geriatric Syndromes and Incident Chronic Health Conditions Among 9094 Older Community-Dwellers: Findings from the Lifelines Cohort Study. Journal of the American Medical Directors Association, 23(1), 54–59.e2. https://doi.org/10.1016/j.jamda.2021.02.030

Robison J. E. (2019). Autism prevalence and outcomes in older adults. Autism research, 12(3), 370–374. https://doi.org/10.1002/aur.2080

Scholtens, S., Smidt, N., Swertz, M. A., Bakker, S. J., Dotinga, A., Vonk, J. M., van Dijk, F., van Zon, S. K., Wijmenga, C., Wolffenbuttel, B. H., & Stolk, R. P. (2015). Cohort Profile: LifeLines, a three-generation cohort study and biobank. International journal of epidemiology, 44(4), 1172–1180. https://doi.org/10.1093/ije/dyu229

Sizoo, B. B., Horwitz, E. H., Teunisse, J. P., Kan, C. C., Vissers, C., Forceville, E., Van Voorst, A., & Geurts, H. M. (2015). Predictive validity of self-report questionnaires in the assessment of autism spectrum disorders in adults. Autism, 19(7), 842–849. https://doi.org/10.1177/1362361315589869

Stagg, S. D., & Belcher, H. (2019). Living with autism without knowing: receiving a diagnosis in later life. Health psychology and behavioral medicine, 7(1), 348–361. https://doi.org/10.1080/21642850.2019.1684920

Tafet, G. E., & Nemeroff, C. B. (2016). The Links Between Stress and Depression: Psychoneuroendocrinological, Genetic, and Environmental Interactions. The Journal of neuropsychiatry and clinical neurosciences, 28(2), 77–88. https://doi.org/10.1176/appi.neuropsych.15030053

Thompson, W. G., Drossman, D. A., Talley, N. (2006). Rome III diagnostic questionnaire for the adult functional GI disorders (including alarm questions) and scoring algorithm. Rome III: The Functional Gastrointestinal Disorders. 917-951.

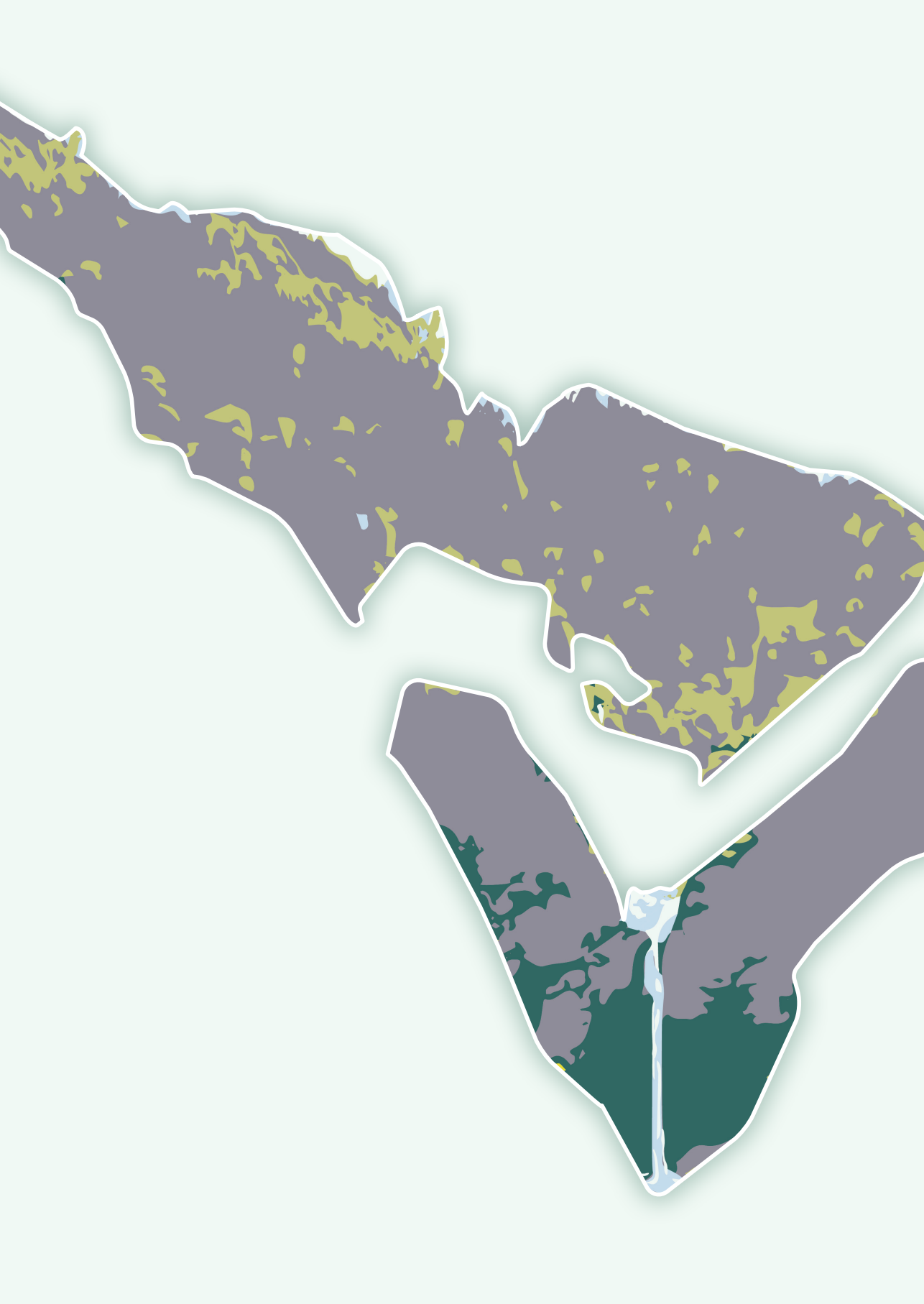
Tolchard, B., & Stuhlmiller, C. (2018). Chronic health and lifestyle problems for people diagnosed with autism in a student-led clinic. Advances in Autism, 4(2), 66-72. https://doi.org/10.1108/AIA-01-2018-0002

Vohra, R., Madhavan, S., & Sambamoorthi, U. (2017). Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism, 21(8), 995–1009. https://doi.org/10.1177/1362361316665222

Warrier, V., Greenberg, D. M., Weir, E., Buckingham, C., Smith, P., Lai, M. C., Allison, C., & Baron-Cohen, S. (2020). Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nature communications, 11(1), 3959. https://doi.org/10.1038/s41467-020-17794-1

Williams, Z. J., & Gotham, K. O. (2022). Current and lifetime somatic symptom burden among transition-aged autistic young adults. Autism research, 10.1002/aur.2671. https://doi.org/10.1002/aur.2671

Wouters, H., van Zeventer, I. A., van der Klauw, M. M., Wolffenbuttel, B., & Huls, G. (2020). Association Between Peripheral Blood Cell Count Abnormalities and Health-Related Quality of Life in the General Population. HemaSphere, 5(1), e503. https://doi.org/10.1097/HS9.0000000000000503



Chapter 4

Psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers: a cohort study

Eva Warreman, Susan Lloyd, Laura Nooteboom, Pieter Leenen, Mary Beth Terry, Wijbrand Hoek, Liesbeth van Rossum, Robert Vermeiren, Wietske Ester
eClinicalMedicine, 2023, 64
https://doi.org/10.1016/j.eclinm.2023.102211

Abstract

Background

People who give care to autistic individuals (autism-caregivers) experience higher levels of caregiver strain than people who provide care for individuals with other chronic conditions (non-autism-caregivers). This places them at higher risk for psychological, behavioural and physical health concerns. The aim of this study is to delineate psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers compared to non-autism-caregivers.

Methods

We included 3354 adult caregivers from the general population in the Netherlands participating in the second assessment (January, 1, 2014 – December, 31, 2017) of the Lifelines Cohort. In this cohort study, using multivariable regression adjusted for age, sex, and socioeconomic status, we analysed psychological (anxiety and depression based on a Mini International Neuropsychiatric Interview, and self-reported stress and perceived health), behavioural (questionnaire-assessed physical activity, alcohol use, and smoking), and physical aspects (body mass index, waist circumference, and leukocyte-counts) of caregiver strain in autism-caregivers (n=722) compared with non-autism-caregivers (n=2632).

Results

Autism-caregivers reported more stress (OR 3·61, 95% CI 2·60-4·99). Both anxiety (OR 1·85, 95% CI 1·37-2·49) and depressive disorders (OR 1·83, 95% CI 1·17-2·86) were more common in autism-caregivers than in non-autism-caregivers. Perceived health, physical activity, alcohol use, and smoking were not different between autism- and non-autism-caregivers. In autism-caregivers, lymphocyte- and monocyte-counts were lower than in non-autism-caregivers.

Conclusion

In this large cohort, autism-caregivers had worse psychological health than non-autism-caregivers. Moreover, autism-caregiving might be associated with an altered immune balance. These findings underline the higher caregiver strain in autism-caregivers compared to other caregivers. This calls for increased support to autism-caregivers. Lifelines has been funded by the Dutch government.

Research in context

Evidence before this study

A PubMed search including meta-analyses and (systematic) reviews from January 1, 2000, to May 31, 2023, using the search terms “caregiver/caregiving”, “autism/autistic”, “strain/health/distress/burden” mainly resulted in studies regarding parents of autistic children. Parents of autistic children seem to experience more stress and worse quality of life than other parents. Previous studies also found that there is a bidirectional relationship between strain in autism-caregivers and the child’s internalizing and externalizing behaviours.

Added value of this study

This study offers an integrated investigation of psychological, behavioural, and biological aspects of caregiver strain in a large sample of autism-caregivers, compared to other types of caregivers (non-autism-caregivers). The impact of autism-caregiving on different aspects of caregiver strain was investigated using both biomarkers and self-reported data. This integrated approach and the inclusion of both parental and non-parental autism-caregivers is a valuable addition to previous research, since previous studies assessed caregiver strain in autism-caregivers more fragmentarily and mainly in parental autism-caregivers.

Implications of the available evidence

Adding up the results of both previous research and the current study, it is evident that autism-caregivers are specifically at increased risk for adverse psychological caregiver strain. Moreover, the investigated psychological aspects of caregiver strain are not different between parental and non-parental autism-caregivers. In addition, autism-caregiving is related to an altered lymphocyte balance. Taken together, the available evidence calls for increased support to autism-caregivers. Therefore, future research focusing on implementation of interventions to prevent and reduce caregiver strain in both parental and non-parental autism-caregivers would be valuable.

Introduction

People who are caregiver for someone with a chronic condition can experience different objective and subjective aspects of caregiver strain, such as negative effects on finances, work, relationships, and psychological, behavioural and physical health (Brannan et al., 1997).

Caregiver burden is higher in people who provide care for autistic individuals (autism-caregivers) than in people who provide care for individuals with other chronic conditions (non-autism-caregivers) (Bayoumi et al., 2017). This might lead to a greater risk for various types of health problems among autism-caregivers compared to non-autism-caregivers, and even for higher mortality rates in some cases (Fairthorne et al., 2014; Van der Lubbe et al., 2024). Previous studies have identified several psychological, behavioural, and physical aspects of caregiver strain in general, but not specifically for autism-caregivers (Ruiz-Robledillo & Moya-Albiol et al., 2013). To improve autism-caregivers' health and well-being, more insight into psychological, behavioural, and physical aspects of their health is needed (Adelman et al, 2014; Van der Lubbe et al., 2024).

Stress is an important psychological aspect of caregiver strain. The observed greater mortality risk for autism-caregivers might be related to higher stress levels, as autism-caregivers experience on average more caregiver stress than non-autism-caregivers (Fairthorne et al., 2014; Hayes & Watson, 2013). Moreover, there is a relationship, which can intensify through bidirectional feedback, between stress levels in parents of autistic children (parental autism-caregivers) and internalizing and externalizing behaviours in these children (Zaidman-Zait et al., 2014). However, we hypothesise that these increased stress-levels are not only present in parental autism-caregivers, but also in adults who are caregiver for another autistic family member or friend (non-parental autism-caregivers), because being a lifelong non-parental autism-caregiver might also be more stressful than being a non-parental non-autism-caregiver. Another relevant psychological aspect in caregiver strain is self-perceived health, as caregivers have reported worse health than non-caregivers (Hartley et al., 2021). Moreover, anxiety and depression are highly prevalent in parental autism-caregivers, which seems to be mediated by parenting stress, and thus important to examine in non-parental autism-caregivers as well (Rezendes & Scarpa, 2011; Scherer et al., 2019).

Behavioural aspects like smoking, alcohol use, and physical activity are important when assessing caregiver strain, because these are lifestyle risk factors for non-communicable diseases. Moreover, smoking and alcohol consumption can be part of a coping mechanism for caregiver stress. Parents of autistic children seem to be more frequently users of alcohol and tobacco compared to the general population (Wade et al., 2014). To our knowledge,

smoking and alcohol use have only been investigated in parental autism-caregivers, and not in both parental and non-parental autism-caregivers (Wade et al., 2014). Furthermore, the prevalence of smoking, alcohol use, and physical activity in (both parental and non-parental) autism-caregivers compared to non-autism-caregivers is still unknown.

Lastly, physical aspects of caregiver strain can be assessed with physiological markers related to caregiver stress, including immune components responding to hypothalamic-pituitary-adrenal (HPA) axis activity, such as leukocyte- and -subtype counts. However, with regard to HPA axis activity in autism-caregivers, previous research focused on salivary cortisol, which revealed altered cortisol levels in parental autism-caregivers compared to parental non-autism-caregivers (Padden et al., 2019). In addition, body mass index (BMI) and waist circumference should be taken into account, because of their association with for example cardiovascular and cancer risk (Janssen et al., 2002). Only BMI has been previously described in parental autism-caregivers, but their BMI was not different than in parental non-autism-caregivers (Li et al., 2018).

In summary, a better understanding of autism-caregivers strain is needed, because of our first hypothesis regarding increased health risks in autism-caregivers compared to non-autism-caregivers. Therefore, the first aim of this study is to compare the above-mentioned psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers and non-autism-caregivers. Moreover, we hypothesise that autism-caregiving is associated with higher caregiver strain than non-autism-caregiving, irrespective of being a parent. However, to our knowledge, caregiver strain has not previously been compared between parental and non-parental autism-caregivers. Therefore, to investigate this second hypothesis, we also aim to compare the above-mentioned psychological, behavioural, and physical aspects of caregiver strain between parental autism-caregivers and non-parental autism-caregivers, and between parental autism-caregivers and parental non-autism-caregivers.

Methods

Study population

All data used in this study were extracted from the Lifelines Cohort database. The Lifelines protocol was approved by the UMCG Medical ethical committee under number 2007/152. Lifelines is a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviours of 167,729 persons living in the North of the Netherlands in a unique three-generation design. These participants were included through general practitioners, which resulted in a general population sample. Lifelines employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioural, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics (Scholtens et al., 2014). Baseline assessment was performed from 2007 until 2013, and the second assessment took place between January, 1st, 2014 and December, 31st, 2017 (Figure 1). In 2019, 109,352 participants received an autism and caregiver questionnaire (AUTQ). In order to evaluate potential selection bias, we executed a non-response analysis to map characteristics of the 71,428 Lifelines participants that did receive the AUTQ, but did not submit this questionnaire (and could therefore not be included in our study, see Figure 2). This non-response analysis showed that these 71,428 non-eligible Lifelines participants were younger in age and consisted of more men compared to the 37,924 participants who did submit this AUTQ questionnaire.

In this cohort study, we included 3354 participants who reported being an informal unpaid caregiver to someone close prior to 2015 (since the second Lifelines assessment started in 2014), and who were age 18 years or older during the physical visit of the second Lifelines assessment (Figure 2). In this way, the caregiving began prior to the outcome measurement of caregiver strain. Of the 3354 included caregivers (Figure 2), 722 were autism-caregiver and 2632 were non-autism-caregiver. These autism-caregivers consisted of 511 parental autism-caregivers (71·9%). In the group of non-autism-caregivers, there were 350 parental non-autism-caregivers (13·3%). Parental caregivers were adults who gave care to their son or daughter (in law). Non-parental caregivers were adults who gave care to their partner, mother (in law), father (in law), brother, sister, friend, acquaintance, or neighbour.

Measures

Caregiving
The AUTQ assessed whether or not participants were informal caregivers, and if so, for how long they have been a caregiver, what type of condition their care-receivers had and what type of relative/acquaintance their care-receiver was. Informal caregiving was defined as giving unpaid care to someone close with long-term limitations and/or health problems. 'Someone close' was described as a partner, a relative (including a child), a friend, or someone else close to you. Volunteer work was not included in our definition of caregiving.

Psychological aspects of caregiver strain

Chronic stress
Self-reported chronic stress was investigated with the Long-term Difficulties Inventory (LDI) (Rosmalen et al., 2012). LDI sum-scores were calculated to compare stress levels between groups. The LDI sum-scores ranged from 0-19 and were divided in four categories (0, 1-2, 3-4, ≥5) for unordered polytomous analyses.

Perceived health
Perceived health was assessed with a question from the RAND-36-Item Health Survey about general health, in which participants answered on a 5-point Likert scale how they would rate their health generally speaking: poor, mediocre, good, very good, excellent (Hays & Morales, 2009).

Anxiety and depressive disorder
The presence of an anxiety or depressive disorder was determined in a face-to-face Mini International Neuropsychiatric Interview (MINI), based on the DSM-IV-TR (Sheehan et al., 1998). Anxiety was defined as the presence of any current anxiety disorder: panic disorder, agoraphobia, social phobia, or generalized anxiety disorder. Depression included the presence of any current depressive disorder: major depressive disorder or dysthymia.

Behavioural aspects of caregiver strain

Physical activity
Physical activity was measured using the following question from the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH): 'Adding everything up, on how many days per week on average are you involved in cycling, doing odd jobs, gardening, sport, or other strenuous activities for at least 30 minutes?' (Wendel-Vos et al., 2003). This variable was analysed binary, using a cut-off point of ≥5 days a week of performing at least 30 minutes of physical activity (≥150 minutes/week).

Smoking
Participants were categorized as a smoker if they answered the following question with 'yes': "Do you smoke now or have you smoked in the past month?".

Alcohol use
Alcohol use was assessed with a question from the Flower Food Frequency questionnaire: 'During the past month, how many glasses of alcoholic drinks did you drink per day on average?' (Brouwer-Brolsma et al., 2021). An average alcohol intake of more than two glasses per day (heavy drinking) was taken as cut-off point in analyses.

Physical aspects of caregiver strain

Body mass index
Height and weight (for calculation of BMI) were measured by trained Lifelines personnel during a physical visit of the second assessment. Moreover, overweight (BMI 25-29·99 kg/m^2) and obesity (BMI≥30 kg/m^2) were investigated.

Waist circumference
Waist circumference was also measured by trained Lifelines personnel during a physical visit of the second assessment. Waist circumference was analysed as a continuous variable. Besides, a waist circumference above the threshold for metabolic syndrome (≥88 cm in women, ≥102 cm in men) was used as a cut-off point in analyses (Alberti et al., 2009).

Leukocytes and subtypes
Blood samples were drawn during a physical visit of the second assessment. Leukocyte- and -subtype counts were analysed as measures of (low-grade) inflammation, regulated by HPA axis activity. The investigated leukocyte-subtypes included neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Lastly, the neutrophil-to-lymphocyte ratio was analysed by dividing the neutrophil count to the lymphocyte count.

Covariates
AQ-10
The short version of the Autism Spectrum Quotient (AQ-10) was used to quantify the degree of autistic traits in caregivers (Allison et al., 2012).

Employment
Self-reported employment status and educational attainment were used in analyses as measures of socioeconomic status. Participants were categorized as being employed if they currently had paid work for one or more hours per week.

Education
Educational attainment was categorised in four groups: low (no education, primary, lower or preparatory vocational education, or lower general secondary education), middle (intermediate vocational education or apprenticeship, higher general secondary education, or pre-university secondary education), high (higher vocational education or university), or other.

Statistical analysis

IBM SPSS Statistics version 25 was used for all data analyses. We executed descriptive statistics to compare age, sex, educational attainment, employment, ethnicity, number of people in the household, the type of person they were caregiver for, and the AQ-10 sum-score between autism-caregivers and non-autism-caregivers, between parental autism-caregivers and non-parental autism-caregivers, and between parental autism-caregivers and parental non-autism-caregivers. For these comparisons of demographics, we used Student *t* tests or Mann-Whitney U tests for continuous variables, and Chi-square tests for categorical variables (Table 1). Next, we conducted separate multivariable multinomial, logistic, or linear regression models to examine the association between caregiver type (autism-caregiver vs non-autism caregiver) and each of the above-mentioned psychological, behavioural, and physical aspects of caregiver-strain as outcomes (Table 2). Stress and perceived health were analysed with unordered multinomial regression analyses. Binary outcomes, including anxiety, depression, physical

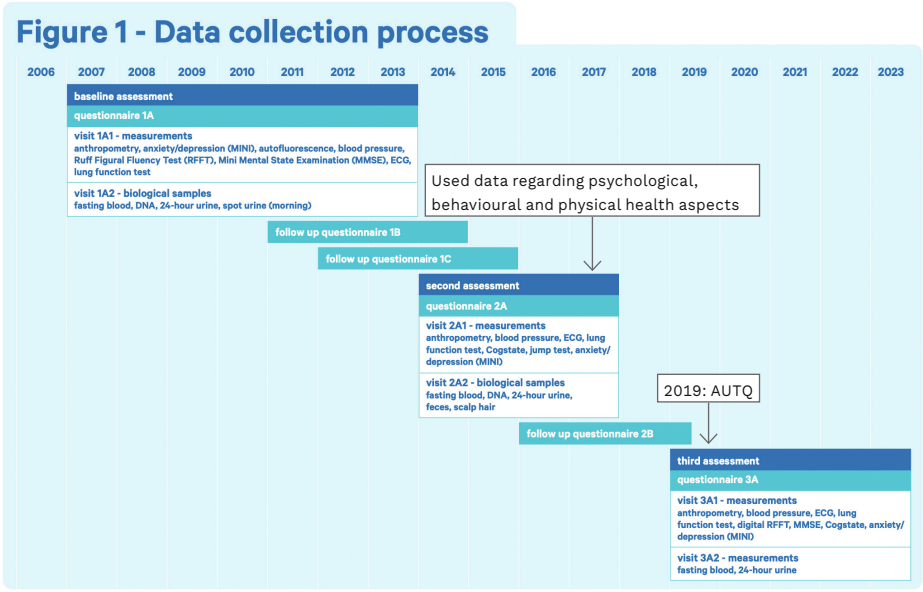
activity, smoking, alcohol use, overweight, obesity, and waist circumference above the threshold were analysed using logistic regression analyses. BMI, waist circumference, leukocytes, and leukocyte-subtypes were analysed with quantile regression. Because of missing data in the covariates of employment and educational attainment (see all missing data in Supplementary Table 1), we performed step-by-step analyses: model 1 adjusted only for age and sex; model 2 adjusted for age, sex, and employment; model 3 adjusted for age, sex, employment, and educational attainment. Lastly, we performed the same multivariable regression analyses in the subgroups, with (1) being a parental or non-parental autism-caregiver as independent variable, and (2) being a parental autism-caregiver or parental non-autism-caregiver as independent variable (Table 3). Since the results remained similar between model 1, 2, and 3 in the main analyses (Table 2), the parental subgroup analyses were performed with model 3: adjusted for age, sex, employment, and educational attainment. In these parental subgroup-analyses, the lowest two categories of perceived health (poor and mediocre) were combined due to small response in the “poor” category.

As supplementary analyses, Spearman correlation tests were performed to investigate the correlations between the psychological and physical aspects of caregiver strain: see Supplementary Table 2.

Role of the funding source

The funding source had no role in the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit this paper for publication.

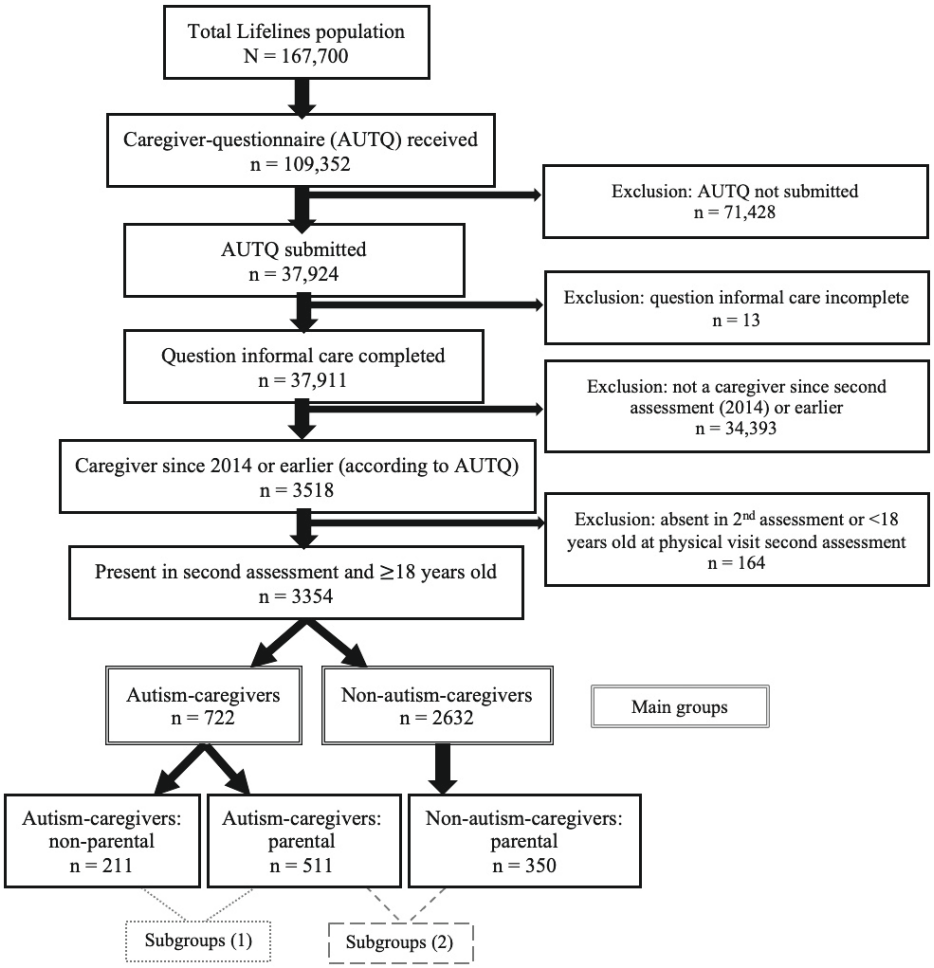
Figure 1. Data collection process *



AUTQ = autism and caregiver questionnaire

* Downloaded from: https://www.lifelines.nl/researcher/data-and-biobank

Figure 2. Flow diagram of study population



AUTQ = autism and caregiver questionnaire

Results

Basic characteristics
The basic characteristic of the 722 autism-caregivers and 2632 non-autism-caregivers are summarised in Table 1. On average, the autism-caregivers were three years younger than the non-autism-caregivers (50·8 versus 53·8 years old). The autism-caregivers consisted of more females (75%) than the non-autism-caregivers (68%). The majority of the autism-caregivers were parental caregivers (71·9%), while most non-autism-caregivers (61·1%) took care of their mother and/or father (in law). Educational attainment was higher in autism-caregivers than in non-autism-caregivers. Importantly, autistic traits as measured by the AQ-10 sum-scores were not different between autism-caregivers and non-autism-caregivers.

Psychological aspects of caregiver strain
In Table 2, the psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers compared to non-autism-caregivers are displayed. In this results section, outcomes from model 3 are summarised. Reported chronic stress was higher in autism-caregivers than in non-autism-caregivers (stress ≥5: odds ratio (OR) 3·6, 95% confidence interval (CI) 2·60-4·99). Perceived health was not different between autism-caregivers and non-autism-caregivers. Moreover, the prevalence of an anxiety disorder was higher in autism-caregivers than in non-autism-caregivers (12·2% versus 6·9%; OR 1·85, 95% CI 1·37-2·49), as well as the prevalence of a depressive disorder (6·0% versus 2·8%; OR 1·83, 95% CI 1·17-2·86).

Behavioural aspects of caregiver strain
The prevalence of being physically active during ≥150 minutes per week (OR 1·12, 95% CI 0·93-1·35), the prevalence of smoking (OR 0·97, 95% CI 0·73-1·31), and alcohol use of more than two glasses per day (OR 0·99, 95% CI 0·73-1·34) were not different between autism-caregivers and non-autism-caregivers.

Physical aspects of caregiver strain
The mean BMI, mean waist circumference, prevalence of overweight, and prevalence of obesity were not different between autism-caregivers and non-autism-caregivers (see Table 2: p-values ≥0·05). With regard to the total leukocyte- and -subtype counts, lymphocyte and monocyte levels were lower in autism-caregivers than in non-autism-caregivers (lymphocytes: ß -0·08, p=0·016; monocytes: ß -0·02, p=0·014).

Parental autism-caregivers

The basic characteristics of the parental autism-caregivers are summarized in Table 1. The parental autism-caregivers had a lower mean age and consisted of more females than the non-parental autism-caregivers and parental non-autism-caregivers. Furthermore, less parental autism-caregivers had low education attainment and more were employed than the parental non-autism-caregivers. Education and employment were not different between parental and non-parental autism-caregivers.

With respect to the subgroups within autism-caregivers, almost all investigated psychological, behavioural and physical aspects of caregiver strain were not different between the 511 parental autism-caregivers and the 211 non-parental autism-caregivers (column (1) in Table 3: p-values ≥0·05). Only the percentage of smokers was higher in parental autism-caregivers than in non-parental autism-caregivers (13·5% versus 7·6%; OR 2·36, 95% CI 1·19-4·70). When comparing the parental subgroups (column (2) in Table 3), the 511 parental autism-caregivers had higher stress levels (stress ≥5: OR 3·10, 95% CI 1·86-5·17), a higher prevalence of anxiety disorders (12·7% versus 6·9%; OR 1·87, 95% CI 1·09-3·25), and higher monocyte levels (ß -0·03, p=0·031) than the 350 parental non-autism-caregivers. Perceived health, the prevalence of a depressive disorder, and the investigated behavioural and other physical aspects of caregiver strain were not different between the parental autism-caregivers and parental non-autism-caregivers (column (2) in Table 3: p-values ≥0·05).

Table 1. Basic characteristics in autism-caregivers compared to non-autism-caregivers

	Autism-caregivers n=722	Non-autism-caregivers n=2632	p-value [a]	Autism-caregivers: parental n=511	Autism-caregivers: non-parental n=211	p-value [a]	Non-autism-caregivers: parental n=350	p-value [b]
Age (mean, SD) [c]	50·8 (9·1)	53·8 (9·0)	<0·001	50·0 (8·2)	52·6 (10·8)	<0·001	53·6 (9·4)	<0·001
Female sex (N, %)	541 (74·9)	1794 (68·2)	<0·001	395 (77·3)	146 (69·2)	0·022	247 (70·6)	0·026
Educational attainment								
Low (N, %)	104 (14·4)	577 (21·9)	<0·001	73 (14·3)	31 (14·7)	0·987	84 (24·0)	0·003
Medium (N, %)	260 (36·0)	879 (33·4)		188 (36·8)	72 (34·1)		112 (32·0)	
High (N, %)	211 (29·2)	735 (27·9)		143 (28·0)	68 (32·2)		111 (31·7)	
Employment (N, %)	491 (68·0)	1777 (67·5)	0·098	356 (69·7)	135 (64·0)	0·063	223 (63·7)	<0·001
Ethnicity [d]								
Eastern or Western European (N, %)	659 (91·3)	2463 (93·6)	0·038	457 (89·4)	202 (95·7)	0·236	326 (93·1)	0·057
Mediterranean or Arabic (N, %)	<10 (<1·4)	<10 (<0·4)		<10 (<2·0)	<10 (<4·7)		<10 (<2·9)	
Asian (N, %)	<10 (<1·4)	<10 (<0·4)		<10 (<2·0)	<10 (<4·7)		<10 (<2·9)	
Other (N, %)	10 (1·4)	12 (0·5)		<10 (<2·0)	<10 (<4·7)		<10 (<2·9)	
Number of people in household (median, IQR) [e]	3 (2-4)	2 (2-3)	0·000	4 (2-4)	2 (2-3)	<0·001	3 (2-4)	<0·001
Caregiver of…								
Partner (N, %)	69 (9·6)	424 (16·1)	<0·001	31 (6·1)	38 (18·0)	<0·001	16 (4·6)	0·343
Mother and/or father (in law) (N, %)	156 (21·6)	1607 (61·1)	<0·001	99 (19·4)	57 (27·0)	0·023	83 (23·7)	0·125
Son and/or daughter (in law) (N, %)	511 (70·8)	350 (13·3)	<0·001	511 (100)	<10 (<4·7)	<0·001	350 (100)	-
Brother and/or sister (N, %)	84 (11·6)	207 (7·9)	0·001	11 (2·2)	73 (34·6)	<0·001	<10 (<2·9)	0·650
Friend or acquaintance (N, %)	38 (5·3)	162 (6·2)	0·370	11 (2·2)	27 (12·8)	<0·001	<10 (<2·9)	0·878
Neighbour (N, %)	10 (1·4)	98 (3·7)	0·002	<10 (<2·0)	<10 (<4·7)	0·451	<10 (<2·9)	0·744
Other (N, %)	81 (11·2)	232 (8·8)	0·049	12 (2·3)	69 (32·7)	<0·001	12 (3·4)	0·3444
AQ-10 sum score (median, IQR)	2 (1-4)	2 (1-3)	0·676	2 (1-4)	2 (1-3)	0·134	2 (1-3)	0·082

a. Univariable analyses in which continuous variables were analysed with Student *t* tests or Mann-Whitney U tests, and categorical variables with Chi-square tests. b. Parental non-autism-caregivers (n=350) compared to parental autism-caregivers (n=511) using univariable analyses in which continuous variables were analysed with Student *t* tests or Mann-Whitney U tests, and categorical variables with Chi-square tests. c. SD = standard deviation. d. Assessed with the following multiple-choice question: 'Which of the following populations do you consider yourself belonging to?' e. IQR = interquartile range

Table 2. Psychological, behavioural, and physical aspects of caregiver strain: autism-caregivers versus non-autism-caregivers

	Autism-caregivers n=722	Non-autism-caregivers n=2632	Being an autism-caregiver as independent variable, adjusted for age and sex (model 1) [a]	Being an autism-caregiver as independent variable, adjusted for age, sex, and employment (model 2) [a]	Being an autism-caregiver as independent variable, adjusted for age, sex, employment, and educational attainment (model 3) [a]
Psychological					
Stress [b]					
0 (N, %)	91 (12·6)	660 (25·1)	Reference	Reference	Reference
1-2 (N, %)	232 (32·1)	970 (36·9)	OR 1·60 (95% CI 1·22-2·08), p<0·001	OR 1·62 (95% CI 1·24-2·12), p<0·001	OR 1·58 (95% CI 1·18-2·11), p=0·002
3-4 (N, %)	157 (21·7)	531 (20·2)	OR 1·86 (95% CI 1·39-2·49), p<0·001	OR 1·88 (95% CI 1·41-2·53), p<0·001	OR 1·91 (95% CI 1·40-2·62), p<0·001
≥ 5 (N, %)	169 (23·4)	291 (11·1)	OR 3·50 (95% CI 2·59-4·74), p<0·001	OR 3·54 (95% CI 2·61-4·80), p<0·001	OR 3·61 (95% CI 2·60-4·99), p<0·001
Perceived health [c]					
Poor (N, %)	<10 (1·4)	<10 (0·4)	Reference	Reference	Reference
Mediocre (N, %)	102 (14·1)	257 (9·8)	OR 0·56 (95% CI 0·19-1·64), p=0·294	OR 0·58 (95% CI 0·20-1·72), p=0·324	OR 0·59 (95% CI 0·18-1·96), p=0.390
Good (N, %)	346 (47·9)	1356 (51·5)	OR 0·38 (95% CI 0·13-1·08), p=0·069	OR 0·39 (95% CI 0·14-1·14), p=0·086	OR 0·40 (95% CI 0·12-1·29), p=0·124
Very good (N, %)	149 (20·6)	616 (23·4)	OR 0·37 (95% CI 0·13-1·06), p=0·063	OR 0·38 (95% CI 0·13-1·12), p=0·079	OR 0·36 (95% CI 0·11-1·17), p=0·089
Excellent (N, %)	48 (6·6)	218 (8·3)	OR 0·33 (0·11-0·99), p=0·049	OR 0·34 (95% CI 0·11-1·03), p=0·057	OR 0·32 (95% CI 0·10-1·09), p=0·069
Anxiety disorder (N, %)	88 (12·2)	181 (6·9)	OR 1·72 (95% CI 1·30-2·27), p<0·001	OR 1·82 (95% CI 1·35-2·44), p<0·001	OR 1·85 (95% CI 1·37-2·49), p<0·001
Depressive disorder (N, %)	43 (6·0)	74 (2·8)	OR 1·97 (95% CI 1·33-2·93), p<0·001	OR 1·87 (95% CI 1·21-2·91), p=0·005	OR 1·83 (95% CI 1·17-2·86), p=0·008
Behavioural					
Physical activity ≥ 150 minutes/ week) (N, %) [d]	348 (48·2)	1247 (47·4)	OR 1·17 (95% CI 0·98-1·39), p=0·086	OR 1·17 (95% CI 0·98-1·39), p=0·089	OR 1·12 (95% CI 0·93-1·35), p=0·251

Smoking (currently or in past month) (N, %)	85 (11·8)	313 (11·9)	OR 0·96 (95% CI 0·74-1·25), p=0·769	OR 0·98 (95% CI 0·75-1·30), p=0·907	OR 0·97 (95% CI 0·73-1·31), p=0·854
Alcohol use (>2 glasses/day) (N, %)	86 (11·9)	362 (13·8)	OR 0·91 (95% CI 0·68-1·19), p=0·469	OR 0·94 (95% CI 0·71-1·25), p=0·687	OR 0·99 (95% CI 0·73-1·34), p=0·924
Physical					
Body mass index (median, IQR)	25·7 (23·3-29·2)	25·8 (23·5-28·7)	ß 0·05 (95% CI -0·35-0·45), p=0·806	ß 0·11 (95% CI -0·31-0·53), p=0·606	ß 0·05 (95% CI -0·39-0·48), p=0·832
Overweight (N, %)	265 (36·7)	1111 (42·2)	OR 0·85 (95% CI 0·71-1·01), p=0·063	OR 0·84 (95% CI 0·70-1·00), p=0·051	OR 0·83 (95% CI 0·68-1·00), p=0·055
Obesity (N, %)	146 (20·2)	450 (17·1)	OR 1·18 (95% CI 0·96-1·36), p=0·124	OR 1·24 (95% CI 0·99-1·55), p=0·056	OR 1·26 (95% CI 0·99-1·59), p=0·057
Waist circumference (median, IQR)	90·0 (81·0-99·0)	90·0 (82·5-99·0)	ß -0·14 (95% CI -1·31-1·02), p=0·812	ß -0·07 (95% CI -1·30-1·16), p=0·911	ß 0·22 (95% CI -1·07-1·51), p=0·739
≥ threshold (N, %) [e]	323 (44·7)	1129 (42·9)	OR 1·08 (95% CI 0·91-1·28), p=0·374	OR 1·10 (95% CI 0·92-1·32), p=0·293	OR 1·10 (95% CI 0·91-1·33), p=0·339
Leukocytes (10^E9/L) (median, IQR)	5·80 (4·90-6·90)	5·80 (5·00-6·90)	ß -0·06 (95% CI -0·21-0·08), p=0·380	ß -0·05 (95% CI -0·20-0·10), p=0·503	ß -0·08 (95% CI -0·24-0·08), p=0·335
Neutrophils (10^E9/L) (median, IQR)	3·15 (2·53-3·99)	3·07 (2·47-3·87)	ß 0·02 (95% CI -0·09-0·13), p=0·708	ß 0·04 (95% CI -0·08-0·15), p=0·555	ß 0·01 (95% CI -0·12-0·14), p=0·862
Lymphocytes (10^E9/L) (median, IQR)	1·89 (1·56-2·22)	1·93 (1·60-2·36)	ß -0·07 (95% CI -0·13- -0·01), p=0·019	ß -0·07 (95% CI -0·13- -0·01), p=0·022	ß -0·08 (95% CI -0·15- -0·02), p=0·016
Monocytes (10^E9/L) (median, IQR)	0·45 (0·38-0·55)	0·47 (0·40-0·58)	ß -0·02 (95% CI -0·03- -0·001), p=0·034	ß -0·02 (95% CI -0·04- -0·01), p=0·010	ß -0·02 (95% CI -0·04- -0·004), p=0·014
Eosinophils (10^E9/L) (median, IQR)	0·16 (0·10-0·24)	0·16 (0·11-0·24)	ß 0·00 (95% CI -0·01-0·01), p=1·000	ß 0·00 (95% CI -0·01-0·01), p=1·000	ß -0·00 (95% CI -0·01-0·01), p=0·940
Basophils (10^E9/L) (median, IQR)	0·04 (0·03-0·06)	0·05 (0·03-0·06)	ß -0·01 (95% CI -0·01- -0·01), p=0·000	ß -0·000 (95% CI -0·002-0·002), p=1·000	ß -0·000 (95% CI -0·004-0·004), p=1·000
Neutrophil-to-lymphocyte ratio (median, IQR)	1·63 (1·31-2·16)	1·60 (1·25-2·05)	ß -0·01 (95% CI -0·08-0·06), p=0·779	ß -0·004 (95% CI -0·073-0·066), p=0·921	ß 0·02 (95% CI -0·05-0·10), p=0·593

SD = standard deviation. IQR = interquartile range. OR = odds ratio. 95% CI = 95% confidence interval. a. Multivariable logistic, linear, or unordered polytomous regression with a psychological, behavioural, and physical aspects of caregiver strain as dependent variable and being an autism-caregiver or non-autism-caregiver as independent variable. b. A higher score in the Long-term Difficulties Inventory resembles more perceived stress. c. A lower score resembles worse perceived health. d. Based on the Short Questionnaire to Assess Health-enhancing physical activity. e. Waist circumference above threshold for metabolic syndrome: ≥ 88 cm in women, ≥ 102 cm in men.

Table 3. Subgroup analyses: Psychological, behavioural, and physical aspects of caregiver strain in (1) autism-caregivers: parental versus non-parental, and (2) parental caregivers: parental autism-caregivers versus parental non-autism-caregivers

	Autism-caregivers: parental n=511	**Autism-caregivers: non-parental n=211**	(1) Being a parental or non-parental autism-caregiver as independent variable, adjusted for age, sex, employment, and educational attainment (model 3) [a]	**Non-autism-caregivers: parental n=350**	(2) Being a parental autism-caregiver or parental non-autism-caregiver as independent variable, adjusted for age, sex, employment, and educational attainment (model 3) [a]
Psychological					
Stress [b]					
0 (N, %)	61 (11·9)	30 (14·2)	Reference	95 (27·1)	Reference
1-2 (N, %)	162 (31·7)	70 (33·2)	OR 0·74 (95% CI 0·40-1·36), p=0·328	122 (34·9)	OR 1·52 (95% CI 0·98-2·37), p=0·063
3-4 (N, %)	104 (20·4)	53 (25·1)	OR 0·61 (95% CI 0·32-1·16), p=0·133	66 (18·9)	OR 1·95 (95% CI 1·19-3·20), p=0·008
≥ 5 (N, %)	130 (25·4)	39 (18·5)	OR 1·03 (95% CI 0·53-1·99), p=0·938	50 (14·3)	OR 3·10 (95% CI 1·86-5·17), p<0·001
Perceived health [c]					
Poor or mediocre (N, %)	77 (15·1)	31 (14·7)	Reference	40 (11·4)	Reference
Good (N, %)	243 (47·6)	103 (48·8)	OR 0·92 (95% CI 0·55-1·53), p=0·734	188 (53.7)	OR 0·64 (95% CI 0·40-1·01), p=0·056
Very good (N, %)	109 (21·3)	40 (19·0)	OR 1·27 (95% CI 0·69-2·34), p=0·446	78 (22·3)	OR 0·71 (95% CI 0·42-1·20), p=0·205
Excellent (N, %)	30 (5·9)	18 (8·5)	OR 0·88 (95% CI 0·39-1·97), p=0·756	28 (8·0)	OR 0·60 (95% CI 0·30-1·20), p=0·147
Anxiety disorder (N, %)	65 (12·7)	23 (10·9)	OR 1·08 (95% CI 0·62-1·88)	24 (6·9)	OR 1·87 (95% CI 1·09-3·25)
Depressive disorder (N, %)	30 (5·9)	13 (6·2)	OR 0·83 (95% CI 0·39-1·79)	12 (3·4)	OR 1·75 (95% CI 0·80-3·20)
Behavioural					
Physical activity ≥ 150 minutes/ week) (N, %) [d]	242 (47·4)	106 (50·2)	OR 0·90 (95% CI 0·62-1·30), p=0·560	170 (48·6)	OR 1·07 (95% CI 0·79-1·46), p=0·653

Smoking (currently or in past month) (N, %)	69 (13·5)	16 (7·6)	OR 2·36 (95% CI 1·19-4·70)	44 (12·6)	OR 1·08 (95% CI 0·69-1·70)
Alcohol use (>2 glasses/day) (N, %)	65 (12·7)	21 (10·0)	OR 1·51 (95% CI 0·80-2·88)	39 (11·1)	OR 1·17 (95% CI 0·71-1·92)
Physical					
Body mass index (median, IQR)	25·8 (23·2-29·0)	25·6 (23·5-29·8)	ß -0·10 (95% CI -1·06-0·86), p=0·833	26·2 (23·6-29·0)	ß -0·51 (95% CI -1·31-0·28), p=0·205
Overweight (N, %)	197 (38·6)	68 (32·2)	OR 1·47 (95% CI 0·99-2·17)	151 (43·1)	OR 0·90 (95% CI 0·66-1·23)
Obesity (N, %)	100 (19·6)	46 (21·8)	OR 0·72 (95% CI 0·46-1·12)	67 (19·1)	OR 0·93 (95% CI 0·63-1·38)
Waist circumference (median, IQR)	89·5 (81·0-98·0)	90·0 (82·0-100·0)	ß 0·06 (95% CI -2·82-2·94), p=0·965	91·0 (84·0-99·6)	ß -2·00 (95% CI -4·19-0·19), p=0·073
≥ threshold (N, %) [e]	234 (45·8)	89 (42·2)	OR 1·13 (95% CI 0·78-1·65)	162 (46·3)	OR 0·97 (95% CI 0·71-1·33)
Leukocytes (10^E9/L) (median, IQR)	5·90 (5·00-6·05)	5·65 (4·80-6·80)	ß 0·10 (95% CI -0·24-0·45), p=0·559	5·90 (5·00-6·90)	ß -0·14 (95% CI -0·43-0·15), p=0·330
Neutrophils (10^E9/L) (median, IQR)	3·22 (2·63-4·01)	3·04 (2·35-3·93)	ß 0·12 (95% CI -0·13-0·38), p=0·339	3·16 (2·54-4·01)	ß 0·01 (95% CI -0·22-0·23), p=0·965
Lymphocytes (10^E9/L) (median, IQR)	1·89 (1·56-2·20)	1·93 (1·55-2·27)	ß -0·08 (95% CI -0·19-0·04), p=0·185	1·90 (1·54-2·35)	ß -0·03 (95% CI -0·13-0·07), p=0·553
Monocytes (10^E9/L) (median, IQR)	0·46 (0·38-0·55)	0·45 (0·37-0·56)	ß -0·000 (95% CI -0·029-0·027), p=0·953	0·48 (0·39-0·57)	ß -0·03 (95% CI -0·05- -0·002), p=0·031
Eosinophils (10^E9/L) (median, IQR)	0·17 (0·11-0·24)	0·15 (0·10-0·24)	ß 0·000 (95% CI -0·023-0·023), p=1·000	0·16 (0·11-0·23)	ß 0·004 (95% CI -0·01-0·02), p=0·607
Basophils (10^E9/L) (median, IQR)	0·05 (0·03-0·06)	0·04 (0·03-0·06)	ß 0·003 (95% CI -0·001-0·008), p=0·117	0·05 (0·03-0·06)	ß 0·000 (95% CI -0·004-0·004), p=1·000
Neutrophil-to-lymphocyte ratio (median, IQR)	1·68 (1·35-2·18)	1·51 (1·24-2·11)	ß 0·10 (95% CI -0·05-0·26), p=0·181	1·69 (1·35-2·13)	ß -0·01 (95% CI -0·14-0·11), p=0·831

SD = standard deviation. IQR = interquartile range. OR = odds ratio. 95% CI = 95% confidence interval. [a.] Multivariable logistic, linear, or unordered polytomous regression with a psychological, behavioural, and physical aspects of caregiver strain as dependent variable and being an autism-caregiver or non-autism-caregiver as independent variable. [b.] A higher score in the Long-term Difficulties Inventory resembles more perceived stress. [c.] A lower score resembles worse perceived health. [d.] Based on the Short Questionnaire to Assess Health-enhancing physical activity. [e.] Waist circumference above threshold for metabolic syndrome: ≥ 88 cm in women, ≥ 102 cm in men.

Discussion

The need to gain more insight into multiple psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers is evident because of their increased caregiver strain, since this seems to be associated with adverse health outcomes, and since parental autism-caregiver strain can impact children's internalizing and externalizing behaviour (Hayes & Watson, 2013; Zaidman-Zait et al., 2014). In this study, we observed that being an autism-caregiver is associated with chronic stress, anxiety disorders, depressive disorders, and lower lymphocyte-counts.

Our finding that chronic stress was higher in autism-caregivers than in non-autism-caregivers, as well as in parental autism-caregivers compared to parental non-autism-caregivers, supports the conclusion that autism-caregivers are at greater risk for chronic stress than caregivers for people with other conditions. This is consistent with results from previous studies (Hayes & Watson, 2013; Zaidman-Zait et al., 2014). The autism-caregivers in our study reported worse perceived health, but the differences were not statistically significantly different compared to non-autism-caregivers. However, previous research has reported worse perceived health in parents of autistic children than in parents of typically developing children (Adelman et al., 2014). Thus, self-reported health should still be assessed in future studies as measure of caregiver strain in autism-caregivers (Ruiz-Robledillo & Moya-Albiol, 2013). In our study, the prevalence of both an anxiety disorder and a depressive disorder were higher in autism-caregivers than in non-autism-caregivers. This finding is partly in line with a recent meta-analysis, which concluded that parents of autistic children have elevated levels of depressive symptoms compared to controls, but levels of anxiety symptoms were not different (Scherer et al., 2019). However, the included studies in this meta-analysis used self-reported depression and anxiety symptoms assessed by questionnaire, while in our study, the presence of a depressive or anxiety disorder was assessed with a face-to-face Mini International Neuropsychiatric Interview. Also, another previous study showed that parents of autistic children reported higher levels of depression and anxiety than parents of children without a chronic condition (Hamlyn-Wright et al., 2007). Thus, our study results, support the notion that autism-caregivers are at greater risk for both depression and anxiety than non-autism-caregivers, since there are still mixed findings in the field.

It should also be noted that some autistic traits, like sensory over-responsivity, are associated with stress and anxiety (Amos et al., 2019). So, one can debate that the increased risk for psychological adverse outcomes is related to autistic traits in autism-caregivers. However, in our study population, autism-caregivers did not have a higher AQ-10 sum-score than non-autism-caregivers. Thus, our findings do not support the hypothesis that the

increased psychological caregiver strain in autism-caregivers is only due to their autistic traits.

It should be noted that the subgroup analysis, comparing parental autism-caregivers with non-parental autism-caregivers, is not a classical subgroup analysis using tests of interaction, but is interpreted qualitatively. Nonetheless, the findings of these subgroup analyses show that the investigated psychological aspects of caregiver strain are not different between these parental and non-parental autism-caregivers.

Based on previous research, we hypothesise that this increased psychological caregiver strain in autism-caregivers could be related to lifelong uncertainties regarding the expected life outcomes of the care-receiver, partly related to the increased risk for psychiatric and somatic comorbities in autistic people (Bally et al., 2018). Secondly, societal stigmas concerning autism might play a role, possibly leading to social isolation of both the autism-caregiver and autistic care-receiver.[7] These underlying pathways that may contribute to higher psychological caregiver strain in autism-caregivers should be subject of future research.

Our study did not display a difference in physical activity between autism-caregivers and non-autism-caregivers, while previous research showed varying results (Lovell et al., 2021; Horne et al., 2021). It should be taken into account that caregivers could experience barriers to being physically active, for example because of a lack of time (Horne et al., 2021). In our study, the prevalence of alcohol use of more than two glasses per day in autism-caregivers was not different from non-autism-caregivers. Previous studies observed more alcohol use in parents of autistic children than in controls (Wade et al., 2014; Lovell et al., 2021). Because of the differences in investigated study populations, more research into alcohol use in autism-caregivers is needed. The prevalence of smoking in autism-caregivers in our study (11·8%) was not different compared to non-autism-caregivers, but the smoking prevalence we observed in autism-caregivers is in line with previous research (Wade et al., 2014). For the subgroup of parental autism-caregivers, smoking cessation interventions should especially be considered, since they smoked more than the non-parental autism-caregivers in our study.

Waist circumference and BMI were not different between autism-caregivers and non-autism-caregivers, nor between parental autism-caregivers and parental non-autism-caregivers. In previous research investigating parental autism-caregivers, BMI was also not different compared to parental non-autism-caregivers (Li et al., 2018). However, it should be noted that the prevalence of obesity in the autism-caregivers in our study was 20%, which is considerably higher than the prevalence of 14% in the Dutch general population and in line with a recent study into obesity in parental autism-caregivers (Van der Lubbe et al., 2024). Thus, more research into obesity in (parental and non-parental)

autism-caregivers is needed, since previous studies only investigated parental autism-caregivers.

In our study population, lower lymphocyte and monocyte-counts were observed in autism-caregivers than in non-autism-caregivers. In previous research, caregiver stress has been associated with several immunological markers, such as altered levels of interleukin-6, nuclear factor-κB, and T-cells (Hänsel et al., 2010; Prather et al., 2018). In a study including high-stress mothers of autistic children, altered percentages of T-cell subpopulations were detected in these autism-caregivers compared to low-stress mothers of neurotypical children (Prather et al., 2018). Taken together, increased stress levels experienced by autism-caregivers could be related to immunological alterations, including altered leukocyte and monocyte levels, which could hypothetically be explained by the relation between chronic stress and disturbances in the HPA axis. To clarify, there is an association between chronic stress (psychological well-being) and leukocyte-counts in the peripheral blood, mediated through altered gene expression of myeloid cells (Cole SW, 2019). Thus, the immunological alterations in our autism-caregivers endorse that the higher stress levels in autism-caregivers than in non-autism-caregivers might not only self-perceived, but could also be reflected in biological measures linked to the HPA axis.

The main strength of this study is the large prospective study cohort, in which we investigated caregiver strain including biomarkers and other clinical measurements, and not merely relying on self-reported health. Accordingly, we assessed stress levels using both self-report questionnaires and a laboratory approach including immunological blood markers. To our knowledge, the overview of relevant psychological, behavioural, and biological aspects of caregiver strain in a large caregiver-population that we offer in this study is a significant contribution to previous research in the field.

We were limited, however, in the way and time the various measurements were assessed in the Lifelines cohort (Figure 1). The caregiver questionnaire (AUTQ) was submitted in 2019, while the psychological, behavioural, and physical aspects were assessed in the time frame of 2014-2017, leading to a time gap of 2-5 years. However, we only included participants who reported to be caregiver since 2014 or earlier, to ensure the caregiving exposure began prior to the measurement of aspects of caregiver strain. Due to the study design, it is important to note that direct causality between being an autism-caregiver and the psychological, behavioural, and physical outcomes cannot be proved. Thus, for clinical practice, our study results offer insights into associations between autism-caregiving and psychological, behavioural, and physical aspects of caregiver strain, but to unravel underlying causal pathways, further research is needed.

The worse psychological aspects of caregiver strain and altered immune balance we found in autism-caregivers compared with non-autism-caregivers imply that autism-caregivers are at higher risk for adverse chronic health outcomes. Implementation of (preventive) interventions focusing on improvement of autism-caregivers' health should be the objective of future studies. It is important that not only parents of autistic children (parental autism-caregivers) are being included in future preventive caregiver strain interventions, but also non-parental autism-caregivers, since the parental and non-parental autism-caregivers in our study experienced similar psychological caregiver strain. Moreover, future research including older caregivers who are giving care to their autistic child throughout their child's lifetime, could be valuable in order to investigate the long-term associations between being an autism-caregiver and adverse health outcomes. This is especially relevant for autism-caregivers, since autism is a life-long condition, which often requires life-long informal care.

Autism-caregivers are characterised by higher levels of psychological stress and a higher prevalence of anxiety and depressive disorders compared to non-autism-caregivers. In addition, autism-caregiving is related to an altered lymphocyte balance, which could hypothetically be related to increased stress. The results of our subgroup analyses regarding parental versus non-parental autism-caregivers show that these subgroups are rather similar regarding caregiver strain. Taken together, reduction of their stress, anxiety and depression in autism-caregivers is needed. Interventions aiming at improvement of autism-caregivers' health and reduction of their caregiver strain could be focus of future research, and eventually might contribute to reduction of their increased morbidity and mortality risk.

Contributors

Conceptualization of this paper was done by EBW, SEL, LAN, MBT, RJMV, and WAE. Literature search was conducted by EBW. EBW and SEL had access to the direct data and verified the underlying data. LAN, PJML, MBT, HWH, EFCR, RRJMV, and WAE had access to the data summary and analyses output for review and comment. The statistical analyses were performed by EBW and SEL, with supervision of MBT and WAE. The original draft was written by EBW with review and editing by EBW, SEL, LAN, PJML, MBT, HWH, EFCR, RRJMV, and WAE.

Data sharing statement

All data collected for the study, including individual (pseudonymized) participant data and a data dictionary defining each field in the set, are available via the Lifelines Research Office (https://www.lifelines.nl/researcher/how-to-apply/). Access to this dataset and other available data and samples from the Lifelines cohort can be requested by scientists working in the field of “healthy ageing”. Access will be granted after evaluation of an application form describing the research proposal (including a data selection) and a signed Data and Material Transfer Agreement. Data will be released in a secure environment.

Declaration of interests

The authors declare not having any conflict of interest.

Acknowledgements

We wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centres delivering data to Lifelines, and all the study participants. The Lifelines initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Centre Groningen, and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen).

Supplementary table 1. Missing data in covariates and outcome measures

	Autism-caregivers n=722	Non-autism-caregivers n=2632
Covariates		
Age, missing (N, %)	0 (0)	0 (0)
Female sex, missing (N, %)	0 (0)	0 (0)
Educational attainment, missing (N, %)	147 (20·4)	441 (16·8)
Employment, missing (N, %)	72 (10·0)	174 (6·6)
Outcome measures		
Stress, missing (N, %)	73 (10·1)	180 (6·8)
Perceived health, missing (N, %)	71 (9·8)	176 (6·7)
Anxiety disorder, missing (N, %)	159 (22·0)	580 (22·0)
Depressive disorder, missing (N, %)	159 (22·0)	580 (22·0)
Physical activity, missing (N, %)	75 (10·4)	184 (7·0)
Smoking, missing (N, %)	118 (16·3)	306 (11·6)
Alcohol use, missing (N, %)	332 (46·0)	1065 (40·5)
Body mass index, missing (N, %)	0 (0)	0 (0)
Overweight, missing (N, %)	0 (0)	0 (0)
Obesity, missing (N, %)	0 (0)	0 (0)
Waist circumference, missing (N, %)	0 (0)	0 (0)
≥ threshold, missing (N, %)	0 (0)	0 (0)
Leukocytes, missing (N, %)	22 (3·0)	88 (3·3)
Neutrophils, missing (N, %)	22 (3·0)	88 (3·3)
Lymphocytes, missing (N, %)	22 (3·0)	88 (3·3)
Monocytes, missing (N, %)	22 (3·0)	88 (3·3)
Eosinophils, missing (N, %)	22 (3·0)	88 (3·3)
Basophils, missing (N, %)	22 (3·0)	88 (3·3)
Neutrophil-to-lymphocyte ratio, missing (N, %)	22 (3·0)	88 (3·3)

Supplementary table 2. Spearman correlations between psychological and physical measures in total study population

	Stress	Perceived health	Anxiety disorder	Depressive disorder
Body mass index	CC 0·005, p=0·780	CC -0·185, p<0·001 *	CC 0·007, p=0·711	CC 0·032, p=0·105
Waist circumference	CC -0·042, p=0.018 *	CC -0·178, p<0·001 *	CC 0·007, p=0·703	CC 0·025, p=0·202
Leukocytes	CC 0·060, p=0·001 *	CC -0·116, p<0·001 *	CC 0·024, p=0·233	CC 0·026, p=0·183
Neutrophils	CC 0·084, p<0·001 *	CC -0·107, p<0·001 *	CC 0·036, p=0·066	CC 0·021, p=0·297
Lymphocytes	CC 0·007, p=0·684	CC -0·074, p<0·001 *	CC -0·015, p=0·434	CC 0·020, p=0·316
Monocytes	CC -0·030, p=0·100	CC -0·056, p=0·002 *	CC -0·011, p=0·564	CC 0·023, p=0·237
Eosinophils	CC -0·009, p=0·638	CC -0·056, p=0·002 *	CC 0·005, p=0·794	CC 0·010, p=0·602
Basophils	CC 0·019, p=0·295	CC -0·027, p=0·144	CC 0·004, p=0·824	CC 0·002, p=0·929
Neutrophil-to-lymphocyte ratio	CC 0·066, p<0·001 *	CC -0·032, p=0·078	CC 0·043, p=0·030 *	CC 0·001, p=0·979

CC = correlation coefficient
Statistically significant correlation coefficients are marked: *.

References

Adelman, R. D., Tmanova, L. L., Delgado, D., Dion, S., & Lachs, M. S. (2014). Caregiver burden: a clinical review. JAMA, 311(10), 1052–1060. https://doi.org/10.1001/jama.2014.304

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., Smith, S. C., Jr, International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, & International Association for the Study of Obesity (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Allison, C., Auyeung, B., & Baron-Cohen, S. (2012). Toward brief "Red Flags" for autism screening: The Short Autism Spectrum Quotient and the Short Quantitative Checklist for Autism in toddlers in 1,000 cases and 3,000 controls [corrected]. Journal of the American Academy of Child and Adolescent Psychiatry, 51(2), 202–212.e7. https://doi.org/10.1016/j.jaac.2011.11.003

Amos, G. A., Byrne, G., Chouinard, P. A., & Godber, T. (2019). Autism Traits, Sensory Over-Responsivity, Anxiety, and Stress: A Test of Explanatory Models. Journal of autism and developmental disorders, 49(1), 98–112. https://doi.org/10.1007/s10803-018-3695-6

Bally, J. M. G., Smith, N. R., Holtslander, L., Duncan, V., Hodgson-Viden, H., Mpofu, C., & Zimmer, M. (2018). A Metasynthesis: Uncovering What Is Known About the Experiences of Families With Children Who Have Life-limiting and Life-threatening Illnesses. Journal of pediatric nursing, 38, 88–98. https://doi.org/10.1016/j.pedn.2017.11.004

Bayoumi, M. M., Ezzat, O., Samarkandi, O. (2017). Quality of Life and Subjective Burden on Family Caregiver of Children with Autism. American Journal of Nursing Science, 6, 33-39. https://doi.org/10.11648/j.ajns.20170601.15

Brannan, A. M., Heflinger, C. A., Bickman, L. (1997). The Caregiver Strain Questionnaire: Measuring the Impact on the Family of Living with a Child with Serious Emotional Disturbance. Journal of Emotional and Behavioral Disorders, 5, 212-222. https://doi.org/10.1177/106342669700500404

Brouwer-Brolsma, E. M., Perenboom, C., Sluik, D., van de Wiel, A., Geelen, A., Feskens, E. J., & de Vries, J. H. (2022). Development and external validation of the 'Flower-FFQ': a FFQ designed for the Lifelines Cohort Study. Public health nutrition, 25(2), 225–236. https://doi.org/10.1017/S1368980021002111

Cole S. W. (2019). The Conserved Transcriptional Response to Adversity. Current opinion in behavioral sciences, 28, 31–37. https://doi.org/10.1016/j.cobeha.2019.01.008

Fairthorne, J., Hammond, G., Bourke, J., Jacoby, P., & Leonard, H. (2014). Early mortality and primary causes of death in mothers of children with intellectual disability or autism spectrum disorder: a retrospective cohort study. PloS one, 9(12), e113430. https://doi.org/10.1371/journal.pone.0113430

Hamlyn-Wright, S., Draghi-Lorenz, R., & Ellis, J. (2007). Locus of control fails to mediate between stress and anxiety and depression in parents of children with a developmental disorder. Autism, 11(6), 489–501. https://doi.org/10.1177/1362361307083258

Hänsel, A., Hong, S., Cámara, R. J., & von Känel, R. (2010). Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neuroscience and biobehavioral reviews, 35(1), 115–121. https://doi.org/10.1016/j.neubiorev.2009.12.012

Hartley, J., Bluebond-Langner, M., Candy, B., Downie, J., & Henderson, E. M. (2021). The Physical Health of Caregivers of Children With Life-Limiting Conditions: A Systematic Review. Pediatrics, 148(2), e2020014423. https://doi.org/10.1542/peds.2020-014423

Hayes, S. A., & Watson, S. L. (2013). The impact of parenting stress: a meta-analysis of studies comparing the experience of parenting stress in parents of children with and without autism spectrum disorder. Journal of autism and developmental disorders, 43(3), 629–642. https://doi.org/10.1007/s10803-012-1604-y

Hays, R. D., & Morales, L. S. (2001). The RAND-36 measure of health-related quality of life. Annals of medicine, 33(5), 350–357. https://doi.org/10.3109/07853890109002089

Horne, J., Kentzer, N., Smith, L., Trott, M., & Vseteckova, J. (2021). A Systematic Review on the Prevalence of Physical Activity, and Barriers and Facilitators to Physical Activity, in Informal Carers in the United Kingdom. Journal of physical activity & health, 18(2), 212–218. https://doi.org/10.1123/jpah.2020-0526

Janssen, I., Katzmarzyk, P. T., & Ross, R. (2002). Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Archives of internal medicine, 162(18), 2074–2079. https://doi.org/10.1001/archinte.162.18.2074

Li, X. S., Pinto-Martin, J. A., Thompson, A., Chittams, J., & Kral, T. V. E. (2018). Weight status, diet quality, perceived stress, and functional health of caregivers of children with autism spectrum disorder. Journal for specialists in pediatric nursing, 23(1), 10.1111/jspn.12205. https://doi.org/10.1111/jspn.12205

Lovell, B., Elder, G. J., & Wetherell, M. A. (2021). Sleep disturbances and physical health problems in caregivers of children with ASD. Research in developmental disabilities, 113, 103932. https://doi.org/10.1016/j.ridd.2021.103932

Padden, C., Concialdi-McGlynn, C., & Lydon, S. (2019). Psychophysiological measures of stress in caregivers of individuals with autism spectrum disorder: a systematic review. Developmental neurorehabilitation, 22(3), 149–163. https://doi.org/10.1080/17518423.2018.1460769

Prather, A. A., Epel, E. S., Portela Parra, E., Coccia, M., Puterman, E., Aiello, A. E., & Dhabhar, F. S. (2018). Associations between chronic caregiving stress and T cell markers implicated in immunosenescence. Brain, behavior, and immunity, 73, 546–549. https://doi.org/10.1016/j.bbi.2018.06.019

Rezendes, D. L., & Scarpa, A. (2011). Associations between Parental Anxiety/Depression and Child Behavior Problems Related to Autism Spectrum Disorders: The Roles of Parenting Stress and Parenting Self-Efficacy. Autism research and treatment, 2011, 395190. https://doi.org/10.1155/2011/395190

Rosmalen, J. G., Bos, E. H., & de Jonge, P. (2012). Validation of the Long-term Difficulties Inventory (LDI) and the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-based cohort studies. Psychological medicine, 42(12), 2599–2608. https://doi.org/10.1017/S0033291712000608

Ruiz-Robledillo, N., & Moya-Albiol, L. (2013). Self-reported health and cortisol awakening response in parents of people with asperger syndrome: the role of trait anger and anxiety, coping and burden. Psychology & health, 28(11), 1246–1264. https://doi.org/10.1080/08870446.2013.800517

Scherer, N., Verhey, I., & Kuper, H. (2019). Depression and anxiety in parents of children with intellectual and developmental disabilities: A systematic review and meta-analysis. PloS one, 14(7), e0219888. https://doi.org/10.1371/journal.pone.0219888

Scholtens, S., Smidt, N., Swertz, M. A., Bakker, S. J., Dotinga, A., Vonk, J. M., van Dijk, F., van Zon, S. K., Wijmenga, C., Wolffenbuttel, B. H., & Stolk, R. P. (2015). Cohort Profile: LifeLines, a three-generation cohort study and biobank. International journal of epidemiology, 44(4), 1172–1180. https://doi.org/10.1093/ije/dyu229

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry, 59 Suppl 20, 22–57.

Van der Lubbe, A., Swaab, H., Vermeiren, R. R. J. M., & Ester, W. A. (2024). Stress, Eating Behavior and Adverse Health in Parents of Young Children with Autism Spectrum Disorder. Journal of autism and developmental disorders, 54(2), 662–672. https://doi.org/10.1007/s10803-022-05825-3

Wade, J. L., Cox, N. B., Reeve, R. E., & Hull, M. (2014). Brief report: impact of child problem behaviors and parental broad autism phenotype traits on substance use among parents of children with ASD. Journal of autism and developmental disorders, 44(10), 2621–2627. https://doi.org/10.1007/s10803-014-2132-8

Wendel-Vos, G. C., Schuit, A. J., Saris, W. H., & Kromhout, D. (2003). Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. Journal of clinical epidemiology, 56(12), 1163–1169. https://doi.org/10.1016/s0895-4356(03)00220-8

Zaidman-Zait, A., Mirenda, P., Duku, E., Szatmari, P., Georgiades, S., Volden, J., Zwaigenbaum, L., Vaillancourt, T., Bryson, S., Smith, I., Fombonne, E., Roberts, W., Waddell, C., Thompson, A., & Pathways in ASD Study Team (2014). Examination of bidirectional relationships between parent stress and two types of problem behavior in children with autism spectrum disorder. Journal of autism and developmental disorders, 44(8), 1908–1917. https://doi.org/10.1007/s10803-014-2064-3

Chapter 5

How do primary care providers and autistic adults want to improve their primary care? – a Delphi-study

Eva Warreman, Wietske Ester, Hilde Geurts,
Robert Vermeiren, Laura Nooteboom
Autism, 2024, 28(2), 449-460
https://doi.org/10.1177/13623613231172865

Abstract

Background

Autistic adults often experience health problems and a range of healthcare barriers. Therefore, the aim of this study was to evaluate barriers and explore how primary care providers (PCPs) and autistic adults want to improve their primary healthcare.

Methods

Semi-structured interviews with three autistic adults, two parents of autistic children and six care providers, were performed to evaluate barriers in Dutch healthcare. Next, in a three-round Delphi-study, 21 autistic adults and 20 PCPs rated barriers in primary healthcare and assessed recommendations based on usefulness and feasibility.

Results

In the thematically analysed interviews, 20 barriers in Dutch healthcare for autistic people were identified. In the Delphi-study, the PCPs rated the negative impact of most barriers lower than the autistic adults. The Delphi-study resulted in 22 recommendations to improve primary healthcare for autistic adults, focused on: PCPs (i.e., education in collaboration with autistic people), autistic adults (i.e., improvement of preparation for GP-appointments), and organization of general practice (i.e., enhancement of continuity in care).

Conclusion

In conclusion, PCPs seem to assess healthcare barriers as less impactful than autistic adults. With use of the Delphi-method, useful and feasible recommendations to improve primary healthcare for autistic adults were identified, based on the needs of autistic adults and PCPs.

Lay abstract

Autistic adults often encounter different types of healthcare barriers. Because autistic adults also have an increased risk for health problems, the aim of this study was to evaluate barriers and to explore how primary care providers (PCPs) and autistic adults want to improve their primary healthcare.

In this co-created study, semi-structured interviews with three autistic adults, two parents of autistic children and six care providers were performed to evaluate barriers in Dutch healthcare. Next, in the survey-study (using the Delphi-method including controlled feedback in three consecutive questionnaires), 21 autistic adults and 20 PCPs rated the impact of barriers, and the usefulness and feasibility of recommendations to improve primary healthcare.

In the interviews, 20 barriers in Dutch healthcare for autistic people were found. In the survey-study, the PCPs rated the negative impact of most barriers lower than the autistic adults. This survey-study resulted in 22 recommendations to improve primary healthcare focused on: PCPs (including education in collaboration with autistic people), autistic adults (including improvement of preparation for GP-appointments), and organization of general practice (including improvement of continuity in care).

In conclusion, PCPs seem to view healthcare barriers as less impactful than autistic adults. In this co-created study, recommendations to improve primary healthcare for autistic adults were identified, based on the needs of autistic adults and PCPs. These recommendations provide a basis for PCPs, autistic adults and their support network to start conversations about for example strategies to improve PCPs' knowledge, autistic adults' preparation for a GP-appointment, and organisation of primary care.

Introduction

Early mortality alongside an increased prevalence of somatic and psychiatric conditions in autistic adults are pressing problems that ask for urgent improvement of healthcare for autistic adults (Croen et al., 2015; Hand et al., 2020; Hirvikoski et al., 2016; Hwang et al., 2019; Schendel et al., 2016). These health inequities are associated with disparities in access to healthcare, which can result in delayed and insufficient care, higher rates of hospitalization, increased financial costs, and premature mortality (Bowles et al., 2002; Lindly et al., 2019; Long et al., 2002; Vecchio et al., 2018). Impaired access to healthcare can be caused by different barriers (Mason et al., 2019). Reducing these barriers in primary healthcare for autistic adults is key, since providing (access to) appropriate healthcare is a main task of general practitioners (GPs) (Mazurek et al., 2020). Despite this need to improve autistic adults' primary healthcare, there is a lack of recommendations about how to reduce barriers in general practice, from the perspectives of both primary care providers (PCPs) and autistic adults (Gilmore et al., 2022; Walsh et al., 2021).

To understand what type of recommendations could improve primary healthcare, it is crucial to have an impression of barriers that PCPs and autistic adults face in general practice (Doherty et al., 2020; Mason et al., 2019; Walsh et al., 2020b). Hence, the 'Barriers to Healthcare Checklist', an instrument to assess barriers for autistic people in different types of healthcare, and a comparable caregiver-report tool have already been developed (Raymaker et al., 2017; Walsh et al., 2020a). Overall, barriers can be divided into four categories: being related to 1) the autistic person, 2) the PCP, 3) the healthcare system, or 4) the social environment (Nicolaidis et al., 2015; Walsh et al., 2020b).

In previous research, various strategies have been suggested to improve primary healthcare for autistic people, such as adjusting lighting in an exam room, minimizing time in the waiting room, providing the PCP with a list of a patient's needs, and education of PCPs (Stein Duker et al., 2019; Taylor et al., 2022; Warfield et al., 2015). Furthermore, to improve autistic people's communication about their healthcare needs, for example The Academic Autism Spectrum Partnership in Research and Education (AASPIRE) Healthcare toolkit (Nicolaidis et al., 2016) and different versions of an 'Autism passport' have been developed (e.g., from Autism Anglia, the British National Autistic Society, and the Dutch *Spectrumvisie* (Agterberg S., 2018)). In a recent review about interventions improving healthcare access or experiences for autistic people, it was reported that the majority of interventions focused on autistic people and mostly consisted of skills training. Another large part of interventions was provider-focused, mainly comprising education. Organization-focused interventions were less frequently investigated (Walsh et al., 2021). Thus,

recommendations to improve primary healthcare for autistic adults should focus on all these three domains: PCPs, autistic adults, and the healthcare organization.

It should be noted that the knowledge about barriers and recommendations to improve primary care for autistic adults is based on studies performed in the USA and UK (Doherty et al., 2020; Mason et al., 2019; Walsh et al., 2020b). This limits the generalizability of these barriers and recommendations for improvement, as pathways of funding through insurances and availability of resources can vary between countries and healthcare systems (Faber et al., 2012; Ridic et al., 2012). Moreover, in the Netherlands, the GP is a gatekeeper for referrals from primary care to specialised secondary care (Faber et al., 2012). A team of PCPs in a Dutch GP-office mainly consists of a GP, a general practice nurse (GPN) focused on somatic care, and/or a primary care mental health worker (PCMHW, in Dutch: 'POH-GGZ'). In the Netherlands, these PCMHWs most often have a formal education in psychology (university level) or in nursing focused on psychiatric care (based on vocational education). However, the composition of the types of PCPs employed in a GP-office and the educational levels of these different PCPs also vary between countries (Groenewegen et al., 2015). Therefore, it is needed to specifically explore what type of barriers and recommendations for improvement are relevant in primary care for autistic adults in the Netherlands.

All in all, considering the increased risk of co-occurring conditions and mortality for autistic adults, and the healthcare barriers they experience, improving primary healthcare for autistic adults is a necessity (Raymaker et al., 2017; Walsh et al., 2021). However, recommendations to reduce these barriers and improve primary healthcare for autistic adults specifically in the Netherlands, based on both the needs of Dutch PCPs and autistic adults themselves, are limited, considering the differences in previously studied healthcare systems. Therefore, we identified barriers in Dutch primary care for autistic adults. Subsequently, our main objective was to explore how Dutch PCPs and autistic adults want to improve their primary healthcare; what recommendations do they agree on regarding usefulness and feasibility.

Methods

Study design

Autistic community involvement
This study was initiated by a project-team of the Dutch Academic Workplace Autism (*Academische Werkplaats Autisme)*, which is a collaborative effort of organizations of autistic people, clinicians, and academic institutions, aiming to improve the lives of autistic people based on co-created academic research. The project-team for this study consisted of three healthcare providers, four researchers, and three members with lived experience (i.e., two autistic adults and a parent of an autistic child). These project-team members shared their insights into current healthcare barriers and suggestions for reduction of these barriers, which contributed to the development of the research questions and formulation of the Delphi survey-questions.

Study design
The total study design is summarised in Figure 1. After a project-team brainstorm and an orientating literature review, 11 semi-structured interviews were performed with primary, secondary and tertiary care providers, and (parents of) autistic people. Based on the outcomes of these interviews and the expertise of the project-team members, it was determined that the consecutive Delphi-study should focus on primary healthcare. Since PCPs and autistic people approach the investigated barriers and recommendations from other perspectives (being a care-provider versus a care-receiver), the Delphi-method was used to increase consensus between these two Delphi-panels regarding the usefulness and feasibility of barriers and recommendations. The Delphi-method is specifically suitable for this purpose of creating credible evidence-based recommendations for a healthcare setting, since the Delphi-method results in a smaller range of responses and in more expert consensus (Taylor et al., 2020). Our study protocol was approved by the institutional review board of the Leiden University Medical Center (reference number: N21.043).

Participants

Interviews
For the semi-structured interviews, two groups were recruited: 1) people who receive care (n=5) and 2) care providers (n=6). Adults, with a minimum age of 18 years old, with a self-reported autism spectrum disorder (ASD) diagnosis or with an autistic child were included in the first group. In the second group, care providers working with autistic patients in primary, secondary, or tertiary care were eligible for inclusion. Purposive sampling was used to include a diverse

sample of participants (Moser and Korstjens, 2018). Diversity was evaluated based on age, gender, educational attainment, and type of care provider.

Delphi-study
The Delphi-panels also consisted of two groups: 1) autistic adults and 2) PCPs. We aimed to include approximately 20 participants in each group, taking possible drop-out into account (Niederberger and Spranger, 2020; Taylor et al., 2020). Criteria for inclusion in the first group were: a minimum age of 18 years old, the self-reported presence of an ASD-diagnosis, the ability to independently fill in digital questionnaires, and the ability to answer the questionnaires with a broader perspective on the autistic population (for example based on experience as an autism-advocate or peer-support worker). In the second group, GPs, GPNs, and PCMHWs, with some experience with autistic people in their work in primary care, were eligible for inclusion. Participants were recruited via the network of the project-team members. Purposive sampling was used to include diverse panels (based on age and gender).

Data collection and analysis

Interviews
The list of interview-topics was developed based on literature reviews (Mason et al., 2019; Morris et al., 2019; Walsh et al., 2020b) and input of the project-team members collected in the preparatory brainstorm-session. With signed informed consent of the participants, the interviews were audio-recorded and transcribed verbatim by the main researcher (EW).

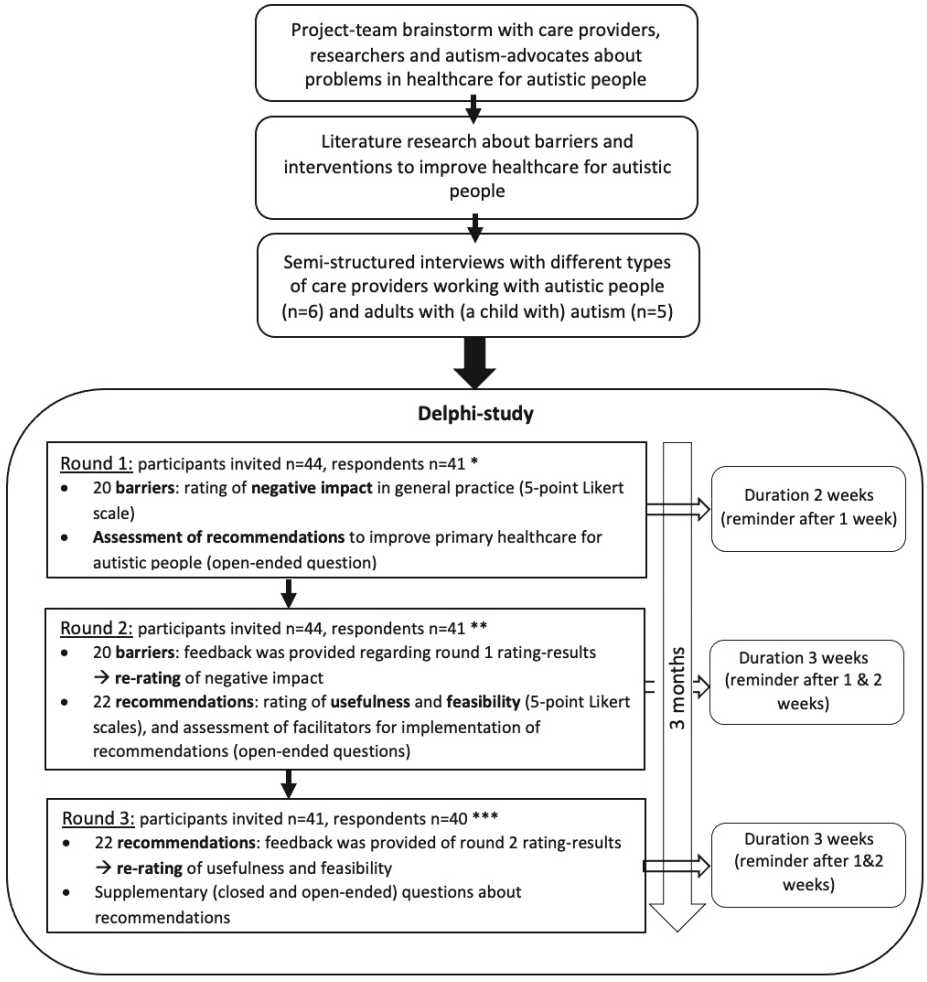
Transcripts of the interview audio-recordings were uploaded to the software-program ATLAS.ti (ATLAS.ti Scientific Software Development GmbH, version 9). A thematic analysis was performed with a predetermined code-tree (Mason et al., 2019; Morris et al., 2019; Walsh et al., 2020b). If other relevant themes were encountered, these were openly coded. Central themes were summarized in three main categories: barriers related to PCPs, to autistic people (and their support system), and to healthcare organization.

Delphi-study
The Delphi-study was performed with digital questionnaires using Castor EDC software (Castor EDC, 2019). The content and formulation of questions in the surveys were developed in cooperation with the autistic project-team members. An outline of the main questions in each of the three Delphi-rounds is displayed in Figure 1. The list of 20 barriers, first assessed in round 1, was created based on the interview-outcomes, input from the autistic project-team members, and literature reviews (Mason et al., 2019; Walsh et al., 2020b; Morris et al., 2019). In round 2, participants re-rated the barriers that did not reach consensus in

round 1. The set of recommendations (first assessed in round 2), was generated out of the participants' input in open-ended questions in round 1 and the expertise from project-team members. In round 3, recommendations were also re-rated. In all re-rating questions, the participants were provided with feedback about results from the previous round: participant's own answers and group-results. Based on the outcomes of round 2, additional closed and open-ended questions were incorporated in round 3, aiming for a more detailed understanding of the rating of recommendations.

Consensus in a category (namely: negative impact or priority) of a barrier was reached if ≥70% of all participants placed it in one of the three main answer options (very low / low, medium, or high / very high). Open-ended questions from all three rounds were thematically also analysed in ATLAS.ti, with categorization in themes based on the recommendations and their usefulness and feasibility.

Figure 1. Study design



** 21 autistic adults and 20 PCPs; ** The same respondents as in round 1; *** 20 autistic adults and 20 PCPs*

Results

Participants

Interviews

The five interviewed individuals in the autism-group (two autistic men, one autistic woman, two mothers of an autistic child) were 28 to 56 years old. One of the autistic men also had a learning disability. The six interviewed care providers (four men, two women) were a psychiatrist, GP, psychotherapist, physician specialised in care for people with a learning disability, primary care mental health worker (PCMHW), and physician from a rehabilitation centre.

Delphi-study

In total, 21 autistic adults and 20 PCPs participated in the Delphi-study (see Table 1). Most PCPs were female (n=18) and middle-aged (15 PCPs were 41-64 years old). The group of autistic participants consisted of more men (n=8 versus n=2) and were younger than the group of PCPs.

Interviews

As a result of the interviews, 27 barriers in healthcare for autistic people were identified and categorized into three main themes, barriers related to: care providers, autistic people (and their support network), and healthcare organization. These 27 barriers were reduced (with consent of the project-team) to 20 barriers, which were assessed in the Delphi-study (Table 2). This reduction was executed by combining some of the more detailed barriers into broader categories.

Delphi-study: barriers

The total group of Delphi-participants reached consensus about the (very) high negative impact of nine of the 20 barriers: highlighted in bold in Table 2. None of the other 11 barriers were rated as having a (very) low negative impact. Overall, compared with the autistic participants, PCPs rated the negative impact of most barriers relatively lower. The most prominent difference between the two panels was that only 10% of PCPs rated the negative impact of stigmatizing views of PCPs as (very) high, compared with 78% of autistic participants.

Delphi-study: recommendations

A set of 22 recommendations[1-22] to improve primary healthcare for autistic adults was formulated; for the results of the total group of Delphi-participants, see Table 3 (in which recommendations were numbered[1-22] and highlighted in bold if consensus was reached), and for the results of the subgroups of autistic participants and PCPs, see Table 4. Overall, the majority of the total group of Delphi-participants rated all recommendations as relatively useful, except for

a flyer about stigmatization[7]. The feasibility of the total set of recommendations was divided into two main groups: most feasible[1-3,5,7,9,11,12,14-17] and less feasible[4,6,8,10,13,18-22] (see Figure 2), based on the results of the total group of Delphi-participants. In the section below, we take a closer look into the recommendations based on a thematic analysis of the Delphi-questionnaires.

A. Recommendations focusing on PCPs

Education of PCPs (through online information on a website[1], e-learning[1], with a training of a care provider with autism-expertise[2], through videos[3] or guest lectures[4] of autism-advocates) was assessed as very useful by the majority of the Delphi-participants. Another recommendation entailed integration of this education into existing meetings in the GP-office[5]. Autistic participants often commented that education will be more effective if a diverse team of autistic people with lived experience is involved in the development of educational programmes. Education could for example provide information about autism spectrum disorders, healthcare barriers autistic people face, and health problems and somatic symptoms related to autism. PCPs mentioned that the feasibility of educational interventions will be higher if accreditation is added, which makes it more appealing to partake in a training or e-learning.

The feasibility of a communication skills training[8] was evaluated less highly than most other recommendations. Participants mentioned the complexity of such a training and doubted PCPs' motivation to voluntarily participate. The idea of letting a PCP be an intern (for a day) at an autism-care facility[6], to increase experience with autistic people, was assessed as least feasible because of a lack of time. In both groups, but particularly in autistic participants, a flyer about stigmatization[7] was the only recommendation that was rated with relatively low usefulness. Autistic participants mainly doubted if this flyer could really change PCPs' behaviour towards autistic adults.

B. Recommendations focusing on autistic adults

In this category, active involvement of the autistic person's support system[11] was assessed with (very) high usefulness and relatively high feasibility. Next, education for autistic adults, using e-health about recognizing (psycho) somatic complaints[9], was not considered as most useful, but the feasibility was evaluated as (very) high. Autistic participants doubted if education with e-health could actually improve body awareness and recognition of physical complaints, because the ability the apply generalised information to yourself can be impaired in autistic people. Lastly, a preparational questionnaire about physical complaints to fill in before the GP-appointment[10] was assessed as (very) useful by both groups. However, this preparational questionnaire was seen as less feasible, mainly by PCPs, because of the expected difficulty to develop a questionnaire covering all types of physical complaints.

C. Recommendations focusing on the organization of general practice
Both groups considered planning appointments with the same PCPs[17] as the most useful recommendation (across all categories), because predictability and consistency in care is very important for autistic adults. Moreover, the feasibility of this recommendation was assessed as (very) high. The recommendation concerning an online overview of different types of autism-aid[14] was also attributed with (very) high usefulness and feasibility by the total group of Delphi-participants. Specifically, to provide individualised care, PCPs need to know to who and how to refer a patient, based on regional information about available services. The recommendation regarding the availability of online information[15] (such as pictures on the website of the GP-office about the employees, waiting room, and doctor's office) was rated as (very) useful and (very) feasible, according to the total group of Delphi-participants. PCPs did comment that maintaining an up-to-date website about employees could be challenging, because of the often rapidly changing composition of teams in a GP-office. Planning more time per GP-appointment[16] was also assessed with (very) high usefulness and relatively high feasibility. This recommendation could be useful if an autistic person for example needs more time to process information. Its feasibility depends on the ability to claim a longer consultation through healthcare insurance.

The recommendations in category C that the majority of Delphi-participants perceived as (very) useful, but were assessed with relatively lower feasibility, were: conversation with a PCP about personal/practical implications of an autism-diagnosis[13], regulate/adjust stimuli in the GP-office[18], support of autistic adults by peer support workers[19] or by GPNs/PCMHWs[20], collaborative evaluations of autism-cases by the PCPs working in the GP-office[21], and consultation between the GP and psychiatric care providers with autism-expertise[22]. Suggested facilitators to improve the feasibility of each recommendation respectively included: planning a separate appointment with a PCP about personal healthcare barriers[13], considering to plan appointments outside rush-hours at the GP-office to reduce an overload of stimuli[18], informing PCPs about autistic peer support workers and where to find them[19], educating GPNs/PCMHWs about autism[20], adding these autism-case-evaluations to existing complex-case evaluations[21], and expanding consultation to regional autism-networks, instead of only consulting psychiatric facilities[22].
Lastly, the recommendation with the relatively lowest usefulness in this category, was the use of a pop-up in the digital patient-file about the presence of an autism-diagnosis and/or autistic traits[12]. Autistic Delphi-participants commented that this pop-up could be stigmatizing and that its usefulness depends on PCPs' knowledge about autism. On the other hand, PCPs mentioned that this type of pop-ups are often closed before the content is read, because there are already too many pop-ups in patient-files.

Table 1. Delphi-study participants' characteristics: autistic adults and primary care providers (PCPs)

	Autistic adults n = 21		**PCPs** n = 20		**Total group** N = 41	
Gender	n	(%)	n	(%)	n	(%)
Male	8	(38)	2	(10)	10	(24)
Female	13	(62)	18	(90)	31	(76)
Other	0	(0)	0	(0)	0	(0)
Age						
20-30 years	0	(0)	1	(5)	1	(2)
31-40 years	10	(48)	3	(15)	13	(32)
41-50 years	4	(19)	8	(40)	12	(29)
51-64 years	4	(19)	7	(35)	11	(27)
65+ years	3	(14)	1	(5)	4	(10)
Country of birth						
The Netherlands	20	(95)	20	(100)	40	(98)
Outside the Netherlands	1	(5)	0	(0)	1	(2)
Parents' country of birth						
The Netherlands	20	(95)	20	(100)	40	(98)
Outside the Netherlands	1	(5)	0	(0)	1	(2)
GP / GPN / PCMHW / autistic peer support worker						
General practitioner (GP)	0	(0)	9	(45)	9	(22)
General practice nurse (GPN)	0	(0)	3	(15)	3	(7)
Primary care mental health worker (PCMHW)	0	(0)	8	(40)	8	(20)
Peer-support worker or autism-advocate	21	(100)	0	(0)	21	(51)
Duration of career as a GP (N, %)						
1-5 years	-	-	1	(5)	-	-
6-10 years	-	-	3	(15)	-	-
11-20 years	-	-	3	(15)	-	-
21+ years	-	-	2	(10)	-	-
Not applicable, because I am not a GP	-	-	11	(55)	-	-
Type of nurses working in your own GP-office						
No GPN or PCMHW	-	-	0	(0)	-	-
Only GPN(s)	-	-	0	(0)	-	-
Only PCMHW(s)	-	-	1	(5)	-	-
GPN(s) and PCMHW(s)	-	-	18	(90)	-	-
Not applicable, because I retired during this study	-	-	1	(5)	-	-

Table 2. Barriers: negative impact according to autistic adults, primary care providers (PCPs), and the total group of Delphi-participants *

Barriers	Negative impact **								
	Low / very low			*Medium*			*High / very high*		
	Autistic adults	PCPs	Total group	Autistic adults	PCPs	Total group	Autistic adults	PCPs	Total group
Related to PCPs									
Knowledge about autism	0%	0%	0%	16%	25%	21%	84%	70%	**77%**
Experience with autism	0%	5%	3%	21%	35%	28%	79%	55%	67%
Stigmatizing views about autism	11%	15%	13%	11%	60%	36%	78%	10%	44%
Skills/awareness to individualise care	0%	15%	8%	5%	15%	10%	90%	65%	**78%**
Personal interest in autism	11%	15%	13%	63%	55%	59%	26%	25%	26%
Related to autistic adults									
Knowledge about physical complaints	26%	5%	15%	47%	55%	51%	16%	30%	23%
Rigidity / ability to adjust	5%	5%	5%	21%	20%	21%	68%	75%	**72%**
Sensory regulation of stimuli	5%	5%	5%	21%	45%	33%	74%	50%	62%
Ability to cope with stress/ emotions	5%	5%	5%	11%	40%	26%	84%	55%	69%
Recognizing physical complaints	5%	0%	3%	0%	15%	8%	85%	65%	**75%**
Processing of information	5%	5%	5%	10%	25%	18%	75%	65%	**70%**
Communication skills	0%	5%	3%	10%	30%	21%	90%	65%	**77%**
Executive and coordination skills	0%	0%	0%	26%	30%	28%	74%	65%	69%
Feeling of being misunderstood	5%	0%	3%	21%	25%	23%	74%	70%	**72%**
Behavioural problems	26%	5%	15%	26%	50%	39%	42%	40%	41%
Adequate support system	0%	10%	5%	37%	20%	28%	58%	65%	62%
Related to organization of general practice									
Time during appointment with GP	5%	0%	3%	11%	30%	21%	84%	70%	**77%**
Ability to refer to autism-aid	5%	0%	3%	37%	50%	44%	53%	40%	46%
Continuity of care from PCPs	0%	5%	3%	10%	15%	13%	75%	80%	**78%**
Collaboration with other care providers	0%	5%	3%	21%	30%	26%	63%	60%	62%

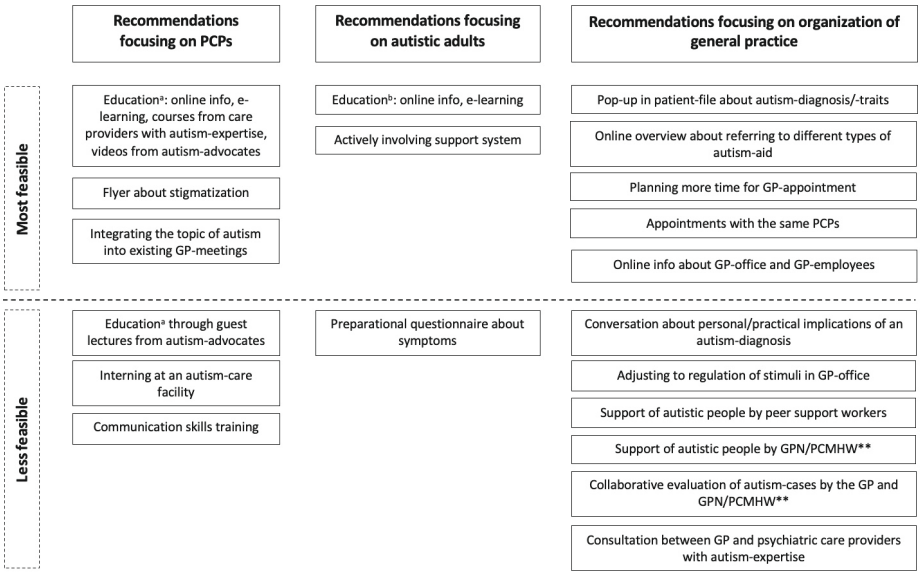
* Results from round 1 if consensus was reached in round 1, and results from round 2 if consensus was not reached in round 1. Percentages in bold highlight the barriers about which consensus (≥ 70%) was reached in total group of Delphi-participants (C). ** Participants could also answer 'I do not know / recognize this barrier'. Therefore, the percentages shown of the 3 categories (none/almost none, a little bit, much/very much) per group (A, B, and C) in this table do not always add up to 100%.

Table 3. Recommendations: usefulness and feasibility, according to the total group of Delphi-participants *

Recommendations	Usefulness			Feasibility		
	Low / very low	*Medium*	*High / very high*	*Low / very low*	*Medium*	*High / very high*
Focusing on primary care providers (PCPs)						
Education ...						
1. ... with online info or e-learning	3%	34%	63%	5%	21%	**74%**
2. ... provided by care providers with autism-expertise	3%	10%	**87%**	0%	46%	54%
3. ... with videos of autism-advocates	3%	22%	**75%**	5%	25%	**70%**
4. ... with guest lectures of autism-advocates	6%	17%	**77%**	15%	38%	48%
5. ... by integrating the topic of autism into existing meetings in the GP-office	5%	25%	**70%**	5%	26%	68%
6. Interning at an autism-care facility	13%	23%	65%	**71%**	19%	0%
7. Flyer about stigmatization	23%	48%	30%	0%	31%	69%
8. Communication training	6%	24%	**71%**	13%	**70%**	18%
Focusing on autistic adults						
9. Education with e-health	3%	40%	58%	3%	25%	**73%**
10. Preparational questionnaire	0%	20%	**80%**	5%	31%	64%
11. Actively involving support system	8%	14%	**78%**	0%	33%	68%
Focusing on organization of general practice						
12. Pop-up in patient-file about autism-diagnosis/-traits	18%	28%	54%	8%	26%	67%
13. Conversation about personal/practical implications of an autism-diagnosis	15%	13%	**72%**	33%	35%	33%
14. Online overview of autism-aid	6%	24%	**71%**	3%	9%	**88%**
15. Online info about GP-office/-PCPs	3%	23%	**75%**	8%	18%	**75%**
16. Planning more time for GP-appointment	0%	18%	**82%**	5%	28%	68%
17. Appointments with the same PCPs	0%	3%	**97%**	11%	17%	**72%**
18. Adjusting to regulation of stimuli	5%	38%	58%	21%	50%	29%
19. Support of autistic adults by peer support workers	3%	25%	**73%**	43%	40%	18%
20. Support of autistic adults by GPN/PCMHW **	5%	30%	65%	20%	58%	23%
21. Collaborative evaluation of autism-cases by GP and GPN/PCMHW	3%	20%	**78%**	18%	33%	50%
22. Consultation between GP and psychiatric care providers with autism-expertise	8%	22%	**70%**	39%	31%	31%

* Results from round 2 if consensus was reached in round 2, and results from round 3 if consensus was not reached in round 2. Percentages were calculated based on the number of participants that filled in the answer option (N.B. low / very low, medium, or high / very high) divided by the total number of participants that answered the specific question. Percentages in bold highlight the recommendations about which consensus (≥ 70%) was reached in the total group of Delphi-participants. The corresponding results of the subgroups of autistic adults and primary care providers can be found in Table 4. ** GPN = general practice nurse; PCMHW = primary care mental health worker

Figure 2. Summary of recommendations to improve primary healthcare, based on both the needs of autistic adults and primary care providers *



* In the total group of Delphi-participants, almost all recommendations (except for a flyer about stigmatization) scored relatively high on usefulness. Therefore, this figure only shows a differentiation in feasibility. ** GPN = general practice nurse; PCMHW = primary care mental health worker. [a.] Education about autism, autism-related health problems and autism-related somatic symptoms. [b.] Education about autism-related health problems and physical complaints.

Table 4. Recommendations: usefulness and feasibility, according to the subgroups of autistic adults (AA) and primary care providers (PCPs)

Recommendations	Usefulness						Feasibility					
	Low / very low		*Medium*		*High / very high*		*Low / very low*		*Medium*		*High / very high*	
	AA	PCPs	AA	PCPs	AA	PCPs	AA	PCPs	AA	PCPs	AA	PCPs
Focusing on primary care providers (PCPs)												
Education ...												
1. ... with online info or e-learning	6%	0%	41%	27%	53%	73%	10%	0%	10%	32%	80%	68%
2. ... provided by care providers with autism-expertise	5%	0%	14%	6%	81%	94%	0%	0%	37%	55%	63%	45%
3. ... with videos of autism-advocates	6%	0%	17%	28%	78%	72%	5%	5%	10%	40%	85%	55%
4. ... with guest lectures of autism-advocates	11%	0%	11%	24%	78%	77%	5%	25%	35%	40%	60%	35%
5. ... by integrating the topic of autism into existing meetings in the GP-office	5%	5%	20%	30%	75%	65%	0%	10%	28%	25%	72%	65%
6. Interning at an autism-care facility	20%	5%	25%	20%	55%	75%	72%	85%	28%	15%	0%	0%
7. Flyer about stigmatization	30%	15%	40%	55%	30%	30%	0%	0%	16%	45%	84%	55%
8. Communication training	12%	0%	12%	35%	77%	65%	5%	20%	75%	65%	20%	15%
Focusing on autistic adults												
9. Education with e-health	5%	0%	40%	40%	55%	60%	0%	5%	25%	25%	75%	70%
10. Preparational questionnaire	0%	0%	20%	20%	80%	80%	10%	0%	20%	42%	70%	58%
11. Actively involving support system	16%	0%	11%	17%	74%	83%	0%	0%	25%	40%	75%	60%
Focusing on organization of general practice												
12. Pop-up in patient-file about autism-diagnosis/-traits	25%	11%	30%	26%	45%	63%	11%	5%	21%	30%	68%	65%
13. Conversation about personal/ practical implications of an autism-diagnosis	26%	5%	11%	15%	63%	80%	35%	30%	30%	40%	35%	30%
14. Online overview of autism-aid	12%	0%	24%	24%	65%	77%	0%	6%	6%	12%	94%	82%
15. Online info about GP-office/-PCPs	0%	5%	20%	25%	80%	70%	5%	10%	10%	25%	85%	65%
16. Planning more time for GP-appointment	0%	0%	26%	11%	74%	90%	5%	5%	25%	30%	70%	65%
17. Appointments with the same PCPs	0%	0%	5%	0%	95%	100%	6%	17%	28%	6%	67%	78%
18. Adjusting to regulation of stimuli	5%	5%	35%	40%	60%	55%	16%	26%	53%	47%	32%	26%
19. Support of autistic people by peer support workers	5%	0%	15%	35%	80%	65%	35%	50%	40%	40%	25%	10%
20. Support of autistic people by GPN/ PCMHW **	10%	0%	10%	50%	80%	50%	10%	30%	60%	55%	30%	15%
21. Collaborative evaluation of autism-cases by GP and GPN/PCMHW	0%	5%	20%	20%	80%	75%	10%	25%	35%	30%	55%	45%
22. Consultation between GP and psychiatric care providers with autism-expertise	5%	11%	26%	17%	68%	72%	32%	45%	21%	40%	47%	15%

* Results from round 2 if consensus was reached in round 2, and results from round 3 if consensus was not reached in round 2. Percentages per group (autistic adults: n=21; PCPs: n=20) were calculated based on the number of participants in the respective group that filled in the answer option (N.B. low / very low, medium, or high / very high) divided by the total number of participants that answered the specific question in that group. ** GPN = general practice nurse; PCMHW = primary care mental health worker

Discussion

The need to improve healthcare for autistic adults is evident because of the multiple barriers autistic adults and their PCPs often face in accessing and providing healthcare. In the current study, we explored how PCPs and autistic adults want to improve their primary healthcare. First, 20 barriers in Dutch primary healthcare were investigated; all these 20 barriers were assessed with a medium to (very) high negative impact in general practice by the majority of Delphi-participants. However, PCPs rated the negative impact of most barriers relatively lower than the autistic participants. This discrepancy emphasises the need to better recognize and decrease these barriers in primary care, as PCPs might not always be able to adequately assess the impact of barriers in primary care for autistic adults. Next, we conceptualised recommendations to improve primary healthcare for autistic adults, based on the perspectives of autistic adults and PCPs. All recommendations (except for the flyer about stigmatization) were assessed as relatively useful. Since the feasibility results were more divergent, all recommendations were divided into two categories: most feasible and relatively less feasible for implementation.

The identified recommendations regarding PCPs mainly involved education. In previous literature, mostly online educational interventions to increase PCPs' knowledge about autism have been suggested as well (Nicolaidis et al., 2015; Walsh et al., 2021). The results from our study add that it should be considered to complement educational courses with input from a diverse group of autistic people with lived experience, so they can illustrate the healthcare barriers they face. A facilitator for educational interventions is the inclusion of accreditation, since this could make it more appealing for PCPs to partake in a course or an e-learning.

An informational flyer about stigmatization was assessed as less useful, partly because of the uncertainty in autistic participants about if this flyer could actually result in changes of PCPs' behaviour/communication towards autistic adults. However, the need for interventions to reduce stigma (Mason et al., 2019; Nicolaidis et al., 2015) was emphasised by the striking discrepancy we found between autistic participants' and primary PCPs' perceptions of the negative impact of the barrier involving PCPs' stigmatizing views. Moreover, this disagreement between the autistic participants and PCPs regarding the negative impact of stigmas, asks for more research into the presence and different types of stigmatic beliefs among PCPs, and into the possible negative and positive impact of these stigmas on primary care for autistic adults.

Previous research regarding interventions focusing on autistic people mostly included behavioural interventions (Walsh et al., 2021). However, in our study, the recommendations focusing on autistic adults were directed at enhancing their own knowledge about how their body works, to more actively involve their

support system, and to improve their preparation for a GP-appointment. The latter recommendation is supported by the British online AASPIRE Healthcare toolkit (Nicolaidis et al., 2016; toolkit available at: http://autismandhealth.org) and a recently developed pre-appointment health check (Taylor et al., 2022), since this toolkit and health check are partly aimed to improve an autistic person's preparation for a (primary) healthcare appointment.

With regard to the third category of recommendations focusing on organizational aspects of general practice, previous studies about general healthcare or primary care reported some comparable recommendations. These are for example the availability of a list of local supportive services, enhancement of the interior of the GP-office (e.g., by adjusting the light in the waiting room and reducing waiting times), consistency in care, clarification of the autistic person's needs and personal implications of the autism-diagnosis, and improvement of collaboration between different care providers (Taylor et al., 2022; Walsh et al., 2021; Warfield et al., 2015). Thus, our study supports these recommendations, which would therefore be useful and feasible for implementation in both the Netherlands as in other countries. In this category of recommendations focusing on organizational aspects, our study adds some recommendations to previous literature regarding the implementation of more support by primary practice nurses (GPN/PCMHW) and by autistic peer support workers. It should be noted that the implementation of support by practice nurses could vary between countries, as the level/type of education and responsibilities/tasks of practice nurses are different in each healthcare system. Lastly, while the concept of peer support by autistic individuals is not new, future implementation of autistic peer support workers in primary care also depends on the possibilities of developments in the healthcare system in a country, since this asks for training programs, reforms in primary care, and financial support (Shea et al., 2024).

Strengths and limitations

The main strength of this study is the inclusion of a large Delphi-panel consisting of 20 PCPs and 21 autistic adults, in order to establish recommendations based on the perspectives and needs of both stakeholders. Also, de drop-out in our Delphi-study was very low, which magnifies the validity of the Delphi-method. Moreover, our study design was co-created with autistic project-team members with lived experience, which increases the relevance of our study (Fletcher-Watson et al., 2019). Furthermore, a thorough step-by-step study design (including qualitative methods), enforced by regular project-team feedback-rounds, was executed.

We aimed to include diverse panels of Delphi-participants, but we experienced difficulties to recruit participants with different ethnic and cultural backgrounds. This limits our study in the extent that the results

cannot be generalized to autistic adults of all types of background, while this is important in the fight against racism in autism research and practice (Jones et al., 2020). Also, our study results can only be related to the primary care for autistic adults, as we purposively only included adults in the Delphi-study. This adult study population was chosen because we hypothesised that barriers and recommendations for improvement of primary care could be very different for autistic children and their parents. The latter would ask for separate research into recommendations to improve Dutch primary care for autistic children. It should also be noted that the Delphi-participants had to be able to independently complete the questionnaires. Therefore, our study results cannot be generalized to autistic adults with higher levels of support needs. Another limitation of our study design was the lack of more detailed information regarding the participating PCPs' familiarity with autistic people, while it was an inclusion criterium to have some experience with autistic patients. In future research, it could be attempted to include autistic PCPs, because it would be interesting to investigate if autistic PCPs for example experience less or other barriers in the care for autistic adults. Furthermore, we explored how PCPs and autistic adults want to improve their primary care, but we did not investigate the practical implementation of our recommendations. Thus, from our study, no conclusions can be drawn regarding the effectiveness of implementation in general practice.

Implications

Most barriers we investigated, were assessed with relatively lower negative impact on primary healthcare for autistic adults by PCPs than by autistic participants in our Delphi-study. It could be hypothesised that a better understanding among PCPs regarding the possible impact of barriers in primary care for autistic adults, might contribute to both earlier recognition and more effective implementation of recommendations to improve primary care. Thus, this first finding suggests that education for PCPs about the impact of these barriers could be relevant. The recommendations assessed in this study provide a basis for PCPs, autistic adults and their support/social network to start conversations about their needs in providing, accessing and improving healthcare; recommendations in different categories can guide future implementation in general practice. A next step for future studies is to investigate the effectiveness of our recommendations implemented in general practice. Furthermore, several recommendations investigated in our study point in the direction of the use of both autism-advocates (autistic individuals with lived experience) to improve education for PCPs and autistic peer support workers to help other autistic adults navigate through primary care. However, since these recommendations were assessed as relatively less feasible, the implementation of these recommendations involving autistic peer support workers should be

investigated in more depth. Lastly, our study only focused on improvement of primary care for autistic adults, but the recommendations we investigated might also be applicable for improvement of care for other types of adults experiencing comparable barriers in primary care. For example, the individualization of care based on personal traits or barriers, the implementations of peer support workers, the active involvement of the social network, or the enhancement of collaboration between different types of care providers could all possibly be recommendations that might be helpful for improvement of primary care for adults without autism experiencing comparable barriers.

Conclusion

Autistic adults have an increased risk for co-occurring conditions and for mortality, while also facing impaired access to healthcare due to different types of barriers. Surprisingly, PCPs seem to view most healthcare barriers we investigated as less impactful than autistic adults. All in all, this Delphi-study resulted in 22 recommendations to improve primary healthcare for autistic adults, based on the perspectives of both autistic adults and PCPs, and related to PCPs, autistic adults, and the organization of general practice. For example, these recommendations can be used as guidance to increase PCPs' knowledge, enhance autistic adults' preparation for a GP-appointment, personalise healthcare for adults with autism, and improve organisational aspects of primary healthcare for autistic adults. Future research into the outcomes of implementation of our recommendations in general practice is needed.

Acknowledgments

We wish to acknowledge all interview- and Delphi-participants for sharing their experiences and perspectives. We also thank all members of our project-team from the Dutch 'Academic Workplace for Autism'. We are especially grateful for the autistic team members with lived experience, who shared their insights into current barriers in healthcare for the autistic population and contributed to adequate formulation of the Delphi-survey questions.

Funding

Our study was supported by a grant from the Netherlands Organization for Health Research and Development (NWO-ZonMw) [project number 639003101]. The authors declare not having any conflict of interest.

References

Agterberg S. & Spectrumvisie, 2018. Autismepaspoort. Available at: https://autismepaspoort.nl

Bowles, K. H., Naylor, M. D., & Foust, J. B. (2002). Patient characteristics at hospital discharge and a comparison of home care referral decisions. Journal of the American Geriatrics Society, 50(2), 336-342. https://doi.org/10.1046/j.1532-5415.2002.50067.x

Castor EDC. (2019). Castor Electronic Data Capture. Available at: https://castoredc.com.

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. https://doi.org/10.1177/1362361315577517

Doherty, A. J., Atherton, H., Boland, P., Hastings, R., Hives, L., Hood, K., James-Jenkinson, L., Leavey, R., Randell, E., Reed, J., Taggart, L., Wilson, N., & Chauhan, U. (2020). Barriers and facilitators to primary health care for people with intellectual disabilities and/or autism: an integrative review. British Journal of General Practice open, 4(3), bjgpopen20X101030. https://doi.org/10.3399/bjgpopen20X101030

Faber, M. J., Burgers, J. S., & Westert, G. P. (2012). A sustainable primary care system: lessons from the Netherlands. The Journal of ambulatory care management, 35(3), 174–181. https://doi.org/10.1097/JAC.0b013e31823e83a4

Fletcher-Watson, S., Adams, J., Brook, K., Charman, T., Crane, L., Cusack, J., Leekam, S., Milton, D., Parr, J. R., & Pellicano, E. (2019). Making the future together: Shaping autism research through meaningful participation. Autism, 23(4), 943–953. https://doi.org/10.1177/1362361318786721

Gilmore, D., Krantz, M., Weaver, L., & Hand, B. N. (2022). Healthcare service use patterns among autistic adults: A systematic review with narrative synthesis. Autism, 26(2), 317–331. https://doi.org/10.1177/13623613211060906

Groenewegen, P., Heinemann, S., Greß, S., & Schäfer, W. (2015). Primary care practice composition in 34 countries. Health policy, 119(12), 1576–1583. https://doi.org/10.1016/j.healthpol.2015.08.005

Schendel, D. E., Overgaard, M., Christensen, J., Hjort, L., Jørgensen, M., Vestergaard, M., & Parner, E. T. (2016). Association of Psychiatric and Neurologic Comorbidity With Mortality Among Persons With Autism Spectrum Disorder in a Danish Population. JAMA pediatrics, 170(3), 243–250. https://doi.org/10.1001/jamapediatrics.2015.3935

Stein Duker, L. I., Sadie Kim, H. K., Pomponio, A., Mosqueda, L., & Pfeiffer, B. (2019). Examining Primary Care Health Encounters for Adults With Autism Spectrum Disorder. The American journal of occupational therapy, 73(5), 7305185030p1–7305185030p11. https://doi.org/10.5014/ajot.2019.037226

Hand, B. N., Angell, A. M., Harris, L., & Carpenter, L. A. (2020). Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism, 24(3), 755–764. https://doi.org/10.1177/1362361319890793

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. The British journal of psychiatry, 208(3), 232–238. https://doi.org/10.1192/bjp.bp.114.160192

Hwang, Y., Srasuebkul, P., Foley, K. R., Arnold, S., & Trollor, J. N. (2019). Mortality and cause of death of Australians on the autism spectrum. Autism research, 12(5), 806–815. https://doi.org/10.1002/aur.2086

Jones, D. R., Nicolaidis, C., Ellwood, L. J., Garcia, A., Johnson, K. R., Lopez, K., & Waisman, T. C. (2020). An Expert Discussion on Structural Racism in Autism Research and Practice. Autism in Adulthood, 2(4). https://doi.org/10.1089/aut.2020.29015.drj

Lindly, O. J., Zuckerman, K. E., & Kuhlthau, K. A. (2019). Healthcare access and services use among US children with autism spectrum disorder. Autism, 23(6), 1419–1430. https://doi.org/10.1177/1362361318815237

Long, S. K., Coughlin, T. A., & Kendall, S. J. (2002). Access to care among disabled adults on Medicaid. Health care financing review, 23(4), 159–173.

Mason, D., Ingham, B., Urbanowicz, A., Michael, C., Birtles, H., Woodbury-Smith, M., Brown, T., James, I., Scarlett, C., Nicolaidis, C., & Parr, J. R. (2019). A Systematic Review of What Barriers and Facilitators Prevent and Enable Physical Healthcare Services Access for Autistic Adults. Journal of autism and developmental disorders, 49(8), 3387–3400. https://doi.org/10.1007/s10803-019-04049-2

Mazurek, M. O., Harkins, C., Menezes, M., Chan, J., Parker, R. A., Kuhlthau, K., & Sohl, K. (2020). Primary Care Providers' Perceived Barriers and Needs for Support in Caring for Children with Autism. The Journal of pediatrics, 221, 240–245.e1. https://doi.org/10.1016/j.jpeds.2020.01.014

Morris, R., Greenblatt, A., & Saini, M. (2019). Healthcare Providers' Experiences with Autism: A Scoping Review. Journal of autism and developmental disorders, 49(6), 2374–2388. https://doi.org/10.1007/s10803-019-03912-6

Moser, A., & Korstjens, I. (2018). Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. The European journal of general practice, 24(1), 9–18. https://doi.org/10.1080/13814788.2017.1375091

Nicolaidis, C., Raymaker, D. M., Ashkenazy, E., McDonald, K. E., Dern, S., Baggs, A. E., Kapp, S. K., Weiner, M., & Boisclair, W. C. (2015). "Respect the way I need to communicate with you": Healthcare experiences of adults on the autism spectrum. Autism, 19(7), 824–831. https://doi.org/10.1177/1362361315576221

Nicolaidis, C., Raymaker, D., McDonald, K., Kapp, S., Weiner, M., Ashkenazy, E., Gerrity, M., Kripke, C., Platt, L., & Baggs, A. (2016). The Development and Evaluation of an Online Healthcare Toolkit for Autistic Adults and their Primary Care Providers. Journal of general internal medicine, 31(10), 1180–1189. https://doi.org/10.1007/s11606-016-3763-6

Niederberger, M., & Spranger, J. (2020). Delphi Technique in Health Sciences: A Map. Frontiers in public health, 8, 457. https://doi.org/10.3389/fpubh.2020.00457

Raymaker, D. M., McDonald, K. E., Ashkenazy, E., Gerrity, M., Baggs, A. M., Kripke, C., Hourston, S., & Nicolaidis, C. (2017). Barriers to healthcare: Instrument development and comparison between autistic adults and adults with and without other disabilities. Autism, 21(8), 972–984. https://doi.org/10.1177/1362361316661261

Ridic, G., Gleason, S., & Ridic, O. (2012). Comparisons of health care systems in the United States, Germany and Canada. Materia socio-medica, 24(2), 112–120. https://doi.org/10.5455/msm.2012.24.112-120

Shea, L. L., Wong, M. Y., Song, W., Kaplan, K., Uppal, D., & Salzer, M. S. (2024). Autistic-Delivered Peer Support: A Feasibility Study. Journal of autism and developmental disorders, 54(2), 409–422. https://doi.org/10.1007/s10803-022-05816-4

Taylor E. (2020). We Agree, Don't We? The Delphi Method for Health Environments Research. HERD, 13(1), 11–23. https://doi.org/10.1177/1937586719887709

Taylor, H., Ingham, B., Mason, D., Finch, T., Wilson, C., Scarlett, C., Moss, S., Buckley, C., Urbanowicz, A., Raymaker, D., Seiboth, C., Lees, R., Garland, D., Osbourne, M., Lennox, N., Cooper, S. A., Nicolaidis, C., & Parr, J. R. (2023). Co-design of an NHS primary care health check for autistic adults. Autism, 27(4), 1079–1091. https://doi.org/10.1177/13623613221132921

Vecchio, N., Davies, D., & Rohde, N. (2018). The effect of inadequate access to healthcare services on emergency room visits. A comparison between physical and mental health conditions. PloS one, 13(8), e0202559. https://doi.org/10.1371/journal.pone.0202559

Walsh, C., Lydon, S., Hehir, A., & O'Connor, P. (2020a). Development and evaluation of a novel caregiver-report tool to assess barriers to physical healthcare for people on the autism spectrum. Research in autism spectrum disorders, 79, 101680. https://doi.org/10.1016/j.rasd.2020.101680

Walsh, C., Lydon, S., O'Dowd, E., & O'Connor, P. (2020b). Barriers to Healthcare for Persons with Autism: A Systematic Review of the Literature and Development of A Taxonomy. Developmental Neurorehabilitation, 23:7, 413-430. https://doi.org/10.1080/17518423.2020.1716868

Walsh, C., O'Connor, P., Walsh, E., & Lydon, S. (2021). A Systematic Review of Interventions to Improve Healthcare Experiences and Access in Autism. Review Journal of Autism and Developmental Disorders. https://doi.org/10.1007/s40489-021-00279-2

Warfield, M. E., Crossman, M. K., Delahaye, J., Der Weerd, E., & Kuhlthau, K. A. (2015). Physician Perspectives on Providing Primary Medical Care to Adults with Autism Spectrum Disorders (ASD). Journal of autism and developmental disorders, 45(7), 2209–2217. https://doi.org/10.1007/s10803-015-2386-9

Chapter 6
General discussion

Improvement of the health of autistic adults and autism-caregivers is an urgent matter. However, only a small proportion of the research into autistic adults is dedicated to their physical health. Nevertheless, it is evident that autistic adults' health should be improved, considering their increased mortality risk (Mason et al., 2022). Literature regarding biopsychosocial aspects of caregiver strain in autism-caregivers is also scarce, while their caregiver burden seems to be higher than in other types of caregivers (Bayoumi et al., 2017). This dissertation contributes to the gap in knowledge concerning the mental and physical health(care) of autistic adults and autism-caregivers. Hence, we conducted quantitative research to investigate metabolic syndrome in adults with autistic traits (Chapter 2), gastrointestinal symptoms in autistic adults (Chapter 3), and biopsychosocial aspects of caregiver strain in autism-caregivers (Chapter 4). Furthermore, autistic people often report unmet healthcare needs and barriers in (access to) healthcare, which ask for improvement of their primary care (Mazurek et al., 2020). Therefore, we performed a mixed-method study to explore how primary care providers (PCPs) and autistic adults suggest to improve their primary care (Chapter 5). This general discussion first offers a summary of the main findings of these four studies. Next, methodological considerations, including study limitations, are reviewed. Lastly, implications of these study results for clinicians, policy, future research, autistic adults, and autism-caregivers are formulated.

Summary

In Chapter 2, we aimed to compare the prevalence of metabolic syndrome, as a measure of cardiovascular risk, and associated biopsychosocial factors between adults with higher and lower levels of autistic traits. In this study, all analysed data from 17,705 included adults came from the Lifelines Cohort, a database covering a general population sample in the Northern Netherlands. The statistical analyses showed that metabolic syndrome is more prevalent in women with higher levels of autistic traits (10.0%) than in women with lower levels of autistic traits (7.5%). In men with higher levels of autistic traits, this is not the case. In these investigated male and female adults with relatively high levels of autistic traits, the presence of metabolic syndrome is associated with lower perceived health, less physical activity, and altered leukocyte levels.

Also based on quantitative results from the Lifelines database, Chapter 3 explored psychological, behavioural, and biological factors associated with gastrointestinal symptoms in adults with an autism diagnosis and in adults with autistic traits. This study displayed that adults with autism (n=309) have a higher risk for gastrointestinal symptoms (including constipation, diarrhoea,

heartburn, abdominal pain/discomfort) than adults without autism (n=30,876); the prevalence of one or more gastrointestinal symptom(s) was 1.7 times higher in adults with autism than in adults without autism. An additional insight concerned the 1.3 times higher prevalence of gastrointestinal symptoms in adults with higher levels of autistic traits (n=7783) compared to adults with lower levels of autistic traits (n=7783). Next, multivariable logistic regression showed that psychological factors, including anxiety, depression, stress, and perceived health, were associated with the presence of gastrointestinal symptoms in both adults with autism and adults with higher levels of autistic traits. More specifically, a higher stress score and lower self-perceived health were associated with a higher risk for gastrointestinal symptoms. Next, being less physically active was associated with the presence of gastrointestinal symptoms in adults with higher levels of autistic traits. Furthermore, leukocyte, neutrophil, and lymphocyte counts were positively associated with the presence of gastrointestinal symptoms in adults with higher levels of autistic traits. In summary, both adults with autism and adults with higher levels of autistic traits have an increased risk for gastrointestinal symptoms, which is associated with anxiety, depression, more stress, and worse perceived health.

Our third Lifelines study, with the aim of comparing biopsychosocial aspects of caregiver strain between autism-caregivers (n=722) and non-autism-caregivers (n=2632), was presented in Chapter 4. We found that autism-caregivers have an approximately twofold higher risk for anxiety and depressive disorders compared to non-autism-caregivers. In addition, autism-caregivers reported higher chronic psychological stress levels than non-autism-autism-caregivers. It should be noted that within the group of autism-caregivers, the investigated psychological aspects of caregiver strain were not different between parental and non-parental autism-caregivers. This indicates that not only the parents of autistic children but also the non-parental autism-caregivers experience high psychological strain. Regarding the investigated inflammatory blood markers potentially related to chronic exposure to stress, both lymphocyte and monocyte counts were lower in autism-caregivers than in non-autism-caregivers. Leukocyte responses are part of the gut-brain axis, which can be affected by psychological stress. Thus, autism-caregivers are at higher risk for psychological burden than non-autism-caregivers, which was not associated with just being a parent.

In Chapter 5, the aim of the Delphi-study was to explore how primary care for autistic people could be improved according to Dutch PCPs and autistic adults. In order to reach this main goal, the Delphi-study first increased insight into the barriers specifically experienced in Dutch primary care for people with autism. Selection of the investigated barriers was based on previous literature, 11 initial semi-structured interviews with autistic adults and healthcare providers, and the input of our project team members. These barriers are related to

healthcare providers, autistic people, and the organization of general practice. The Delphi-study showed that the 20 investigated barriers were recognized by both the participants with autism and the primary care providers. Markedly, the autistic participants assessed the negative impact of most barriers relatively higher than the primary care providers. Next, a set of 22 recommendations for improvement of primary care for autistic people, focusing on healthcare providers, autistic people, and the organization of general practice, were all assessed as very useful by PCPs and autistic adults. Based on the assessment of feasibility, these 22 recommendations were categorized into less or more feasible. Examples of useful and feasible recommendations for improvement are education for PCPs, enhancement of autistic adults' preparation for a GP-appointment, and planning more time for a GP-consultation.

Methodological considerations

General considerations

In this dissertation, both quantitative measures, semi-structured interviews, and a Delphi-study were conducted to explore biopsychosocial factors and healthcare barriers relevant for improvement of the health and care for autistic adults. To incorporate the perspectives of autistic people, we consulted several autistic adults during the conceptualization of our study designs and interpretation of study results, as participatory research is encouraged (Poulsen et al., 2022). However, since our collaboration did not come without difficulties experienced by both the researchers and autistic project team members, it is advised for future researchers and autistic people to be thoroughly informed about participatory research (Fletcher-Watson et al., 2019; Pickard et al., 2022). Moreover, from our project team experiences, we learned that it is vital to clarify all team members' roles, competencies, expectations, and responsibilities up-front. This could increase internal collaboration and maximize all team members' input.

Next, it is important to note that autistic adults with an intellectual disability were not represented in the studies of this dissertation. Also, selection bias regarding autistic people working together with researchers in participatory research should be taken into consideration. In participatory research, most of the time, verbally strong or high-functioning people with autism are joining participatory research, which could lead to a biased perspective. In addition, in both the Lifelines studies and Delphi-study the cultural and ethnic diversity of participants was low. Lifelines is a cohort in the Northern Netherlands, which resulted in the inclusion of mainly adults with an Eastern or Western European background. Therefore, our Lifelines results cannot be generalized to autistic adults with other backgrounds than Eastern or Western European, possibly having different genetics, socioeconomic status, or lifestyles. In the Delphi-study, we aimed to include participants with different ethnic and cultural

backgrounds. However, this was very difficult, despite the use of the AWA's widespread network, and we were not able to get in contact with a lot of adults with autism with varying ethnic or cultural backgrounds.

Lifelines studies

The main strength of the quantitative studies in this dissertation entails the analysis of data based on both physical measurements (weight, length, waist circumference, immunological variables), self-report (stress, perceived health), and semi-structured interviews (MINI: anxiety and depression) in adults with autistic traits and autism-caregivers from the large general population sample, the Lifelines Cohort. In our Lifelines Study concerning the autism-caregivers, we were able to use the prospective design of the Lifelines Cohort by investigating biopsychosocial aspects of caregiver strain in a period after the start of being a caregiver. However, when using retrospectively collected data, not all variables of interest are available. For example, in our study regarding gastrointestinal symptoms, it could have been valuable also to take dietary habits into account, as these could be different in autistic people, considering restrictive or selective patterns.

The statistical associations reported in the quantitative Lifelines studies in this dissertation do not prove causality between the investigated biopsychosocial factors and outcome measures (N.B. metabolic syndrome, gastrointestinal symptoms, autism-caregiver-strain). Therefore, these results might not lead to the direct implementation of clinical interventions since such interventions should first be developed and analysed on effectiveness.

The studies in this dissertation are limited to the inclusion of participants based on a self-reported autism diagnosis. However, 99.1% of the Lifelines participants who reported to have autism also added the year of diagnosis. This increases the validity of these self-reported autism diagnoses. Also, in our Lifelines studies, the self-reported autism diagnoses were complemented with AQ-10 data. One can debate autistic people's self-report skills, which could be affected by their reflective abilities. However, in autistic adults, self-report skills, specifically regarding autistic traits, have not been investigated yet. The predictive value of the AQ-10 with respect to having an autism diagnosis has been investigated. However, in the Lifelines studies in this dissertation, the aim of using the AQ-10 was not to predict an autism diagnosis, but to roughly quantify the degree of autistic traits in a large general population sample.

Delphi-study

The main strength of the Delphi-method is the inclusion of a panel consisting of both autistic adults and PCPs, in order to reach higher levels of consensus, using controlled feedback (Niederberger & Spranger, 2020). This method leads to concrete study outcomes and corresponding recommendations for general

practice. Furthermore, the Delphi-method gives all participants an equal anonymous voice, which might not be the case in, for example, focus groups (Taylor, 2020). Moreover, we prepared this Delphi-study with both an orientating literature search, semi-structured interviews, and input from autistic people with lived experience. This resulted in a substantiated list of 20 barriers investigated in the Delphi-study. For our Delphi-study, it was chosen to perform digital surveys, instead of physical Delphi-rounds, as this was a more feasible study design during the COVID-19 pandemic. One can debate if other types of study designs would have been suitable as well. For example, a quantitative survey study using a larger sample of respondents might include more different types of autistic adults and PCPs. Considering that specifically the autism spectrum has a wide range, selection bias of high-functioning autistic people could be the case in our Delphi-panel. However, to reduce selection bias in our Delphi-study, we aimed to include autistic adults with experience in speaking on behalf of a broader range of people on the autism spectrum. These participants were selected using our project team members' professional network. Lastly, for example, a study design using concept mapping could also have been useful for our research question. In concept mapping, a group brainstorm on topic statements is followed by individual ratings of these statements. Next, multivariate analyses of these ratings result in a visually presented concept map, which is then interpreted by the group of participants (Rosas & Kane, 2011). For our Delphi research question, concept mapping could have added more insight into how our participants interpreted the rating results of the barriers and recommendations, possibly leading to more in-depth implementation suggestions for general practice.

Implications

This dissertation resulted in several implications for clinicians, policy, future research, autistic adults, and autism-caregivers, which will be described below and summarized in Figure 1. These implications mainly concern future steps leading to the improvement of healthcare for adults with autism and autism-caregivers, as the reduction of their health risks is urgent. Many of these future steps could possibly be catalysed by more integrated psychiatric and somatic care for autistic adults and their caregivers. Such steps meet the aims of the Dutch Integrated Care Agreement (Integraal Zorgakkoord, version 1.0, September, 2022), the Dutch Health Advisory Board (Gezondheidsraad, Integrale zorg voor mensen met lichamelijke en psychische aandoeningen, 27 May 2020), and the Integrated Health Services Department of the World Health Organization (https://www.who.int/teams/integrated-health-services/about).

Implications for clinicians

The hypothesis that underlying autistic traits are associated with an increased risk for metabolic syndrome and gastrointestinal symptoms is firstly supported by the finding that women from the general population with higher levels of autistic traits have an increased risk for metabolic syndrome. Secondly, this hypothesis is supported by the finding that adults with higher levels of autistic traits experience gastrointestinal symptoms more often. This means that clinicians, such as general practitioners and psychiatrists, should be aware of this higher risk when they see people who have autistic traits, but do not have an autism diagnosis (yet). This awareness could help clinicians with earlier recognition of cardiovascular risk factors or gastrointestinal symptoms in individual adult patients with autistic traits, possibly leading to the reduction of chronic diseases.

Increased knowledge and awareness are helpful steps towards improved health for autistic adults, as also supported by the participants from our Delphi-study. For example, healthcare providers could be educated about the increased health risks in adults with autistic traits, associated biopsychosocial factors, and barriers and recommendations for improvement of primary care. This education could be developed for PCPs, but also for medical students, psychiatrists, and residents in general practice and psychiatry. Moreover, accredited courses for medical specialists or other specialists, organized by healthcare providers with autism expertise and autistic people with lived experience can be helpful.

The above-mentioned topics for education could also be an important subject of patient-doctor conversations, contributing to a mutual understanding. However, it is known that most patients also want to receive appropriate referrals and diagnostics for their symptoms, besides being informed about underlying biopsychosocial mechanisms. These steps are important for timely diagnosis or exclusion of medical conditions and for the patient's feeling of being taken seriously (Federatie Medisch Specialisten, Richtlijn SOLK en somatoforme stoornissen). The latter, the feeling of being misunderstood, was a barrier that three-quarters of the autistic adults in our Delphi-study experienced as having a very negative impact on their primary care. Possibly, stigmatization or communication barriers might be interrelated with the feeling of being misunderstood and with insufficient diagnostic step-by-step workups.

Furthermore, clinical guidelines, for example including psychiatric autism spectrum disorder guidelines and gastrointestinal or cardiovascular risk management guidelines, should be enriched with our study results and those of previous studies (e.g., Micai et al., 2023) concerning somatic comorbidities and related biopsychosocial factors in autistic people. In the Netherlands, one can also think of a general practice guideline on autism, because current Dutch general practice guidelines (*Nederlands Huisartsen Genootschap (NHG)*

richtlijnen) include ADHD, anxiety, depression, but not autism. Moreover, a revision of Chapter 4 of the Dutch *GGZ Standaard Autisme,* regarding diagnostics and psychological and somatic monitoring of people with autism, is necessary (available on https://https//www.ggzstandaarden.nl/zorgstandaarden/autisme).

Despite the fact that the associations demonstrated between various factors of the biopsychosocial model and metabolic syndrome and gastrointestinal symptoms do not imply causality, these associations can be an important starting point for tailored interventions. One could think of specifically incorporating interventions for the reduction of stress, anxiety, and depression in healthcare for adults with autistic traits. Information regarding the relationships between these psychological aspects in autism could for example be integrated into standard psychoeducation modules for people who are diagnosed with autism.

Many people with autism have a caregiver in everyday life. As autism is a life-long condition, these autism-caregivers often provide long-term care for their child, family member, or acquaintance. Furthermore, caregiver-strain is related to increased mortality (Fairthorne et al., 2014; Schulz & Beach, 1999). Clinicians should also be aware that being an autism-caregiver is associated with higher stress levels, more anxiety, and depression compared to being another type of informal caregiver. So, autism-caregivers should not be overlooked, as their psychological caregiver strain is increased as well. Timely assessment of caregiver-strain and specifically reduction of stress, anxiety, and depression in autism-caregivers is indicated. Both psychiatrists and general practitioners should question the families of autistic people more about their experienced caregiver strain.

Lastly, our Delphi-study specifically investigated recommendations for improvement of primary care. Thus, it is advised that PCPs discuss the presence of healthcare barriers with colleagues and with autistic patients. Next, PCPs have the responsibility to assess which specific improvements are feasible in their own clinical practice, as experienced barriers could possibly vary between individual healthcare providers. Based on our Delphi-study, it is not possible to directly generalize the investigated recommendations to other types of healthcare for autistic adults. However, it is imaginable that some of the barriers and related recommendations to reduce these barriers can also be applicable in other types of healthcare for autistic people, rather than just in primary care. Thus, clinicians from other medical specialties could possibly learn from these study outcomes as well. For example, education about autism could be helpful for other types of healthcare providers who treat people with autism relatively often, such as neurologists, physiotherapists, dentists, surgeons, or internal medicine specialists. However, the latter might ask for more qualitative research aiming to translate our study outcomes to other

types of clinical settings, making these results more relatable and easier to implement in different clinical practices.

Implications for policy

The results of this dissertation suggest that policymakers should facilitate more integrated psychiatric and somatic care for autistic adults and their caregivers, which is in line with the biopsychosocial model (Deter et al., 2018). This psychiatric and somatic integrated care could for example be a collaboration between hospital-specialists, mental care providers, and PCPs (Leue et al., 2020). Moreover, somatic monitoring of autistic adults in out- or inpatient psychiatric clinics could be helpful. This was for example done in the 'Monitoring Outcomes of Psychiatric Pharmacotherapy (MOPHAR)' study, in which metabolic syndrome was detected in an outpatient bipolar population (Simoons et al., 2019). However, at what scale (locally or nationally) and which other medical specialties should be involved to facilitate widely-available integrated psychiatric and somatic care for autistic adults and their caregivers, should still be defined. Future policy changes on integrated care should also lead to revisions of clinical guidelines, such as Chapter 8 of the Dutch *GGZ Standaard Autisme* regarding Organization of care (available at https://https//www.ggzstandaarden.nl/zorgstandaarden/autisme).

It can be advocated that integrated psychiatric and somatic care should not only be incorporated for autistic people, but for the broader population of psychiatric patients, having an increased risk for different somatic comorbidities. An example of a national Dutch initiative is the combined lifestyle intervention program (*gecombineerde leefstijlinterventie*, *GLI*). In this program, people with obesity are coached to improve their lifestyle guided by both medical specialists and primary care providers. The development of more locally integrated psychiatric and somatic care in the Netherlands fits within the Dutch Integrated Care Agreement published in 2022 and created by the Dutch government, Dutch mental healthcare, and the Dutch Federation of Medical Specialists (*Integraal Zorgakkoord*, version 1.0, September, 2022). Nota Bene, one of the statements in this Dutch Integrated Care Agreement involves the improvement of appropriate care for people with higher health risks by constructing more integrated care.

Lastly, several recommendations that resulted from our Delphi-study implicate changes in organization of general practice, which could possibly result in more autism-friendly practices (Johnson et al., 2020). For example, in Dutch general practice, it has already been made possible to use double consultation times for people with autism, as this will be covered by insurance policies. All in all, the knowledge gained in this dissertation contributes to a better understanding of the neurodiverse population. As a consequence, policymakers should invest in both stigma-reducing national campaigns and

in the widespread development of neurodiverse-accommodating logistics and design of healthcare. However, in order to also facilitate adequate integrated psychiatric and somatic care, such changes are also needed in other types of healthcare for autistic people.

Implications for future research

A first lead for future research could be to investigate which specific autistic traits seem to be most associated with the increased health risks in adults with autistic traits. It could for example be useful to investigate associations between specific traits or clusters of autistic traits and physical health problems using the AQ-10 in adults from the general population and in adults with autism. This could delineate underlying pathways and identify subgroups of adults with autistic traits (also in the general population) who are more at risk for certain physical symptoms. Next, longitudinal research exploring causal pathways needs to be performed to gain a better understanding of the relationship between autism and increased health risks. Additionally, it could be relevant for example to investigate the cardiovascular risk in autistic adults with intellectual disabilities and with different types of ethnic backgrounds, as cardiovascular risk could be affected by both variables. All in all, those outcomes could be helpful knowledge for revisions of clinical guidelines regarding for example more person-centred primary care, psychiatric care, and cardiovascular risk management.

Furthermore, this dissertation asks for future research with a similar biopsychosocial approach investigating other types of stress-/lifestyle-related chronic physical conditions in adults with autistic traits. For example, it raises questions about cancer risk in adults with autistic traits and associated biopsychosocial factors. In future research, these biopsychosocial factors could also be complemented with more contextual (e.g., life events) and environmental factors (e.g., living circumstances, local resources). Moreover, we investigated immunological markers in autistic adults and adults with autistic traits. This asks for more research into the presence and effects of chronic low-grade inflammatory status in autistic adults, since the innate immune memory plays an important role in the development of atherosclerotic cardiovascular disease (Bahrar et al., 2024).

Alongside the above-mentioned research aims focusing on a better understanding of somatic risk profiles in adults with autistic traits, future research should focus more on the effective implementation of integrated clinical guidelines, and on the organizational steps that need to be taken to facilitate integrated and somatic care. The latter is relevant as organizational changes often cost time and money, which can become available with supporting research outcomes. Lastly, considering the different needs of autistic people and the barriers they experience in healthcare, it should be investigated if the

current national cardiovascular risk management programs are effective and tailored enough for the autistic population.

Implications for autistic adults and autism-caregivers

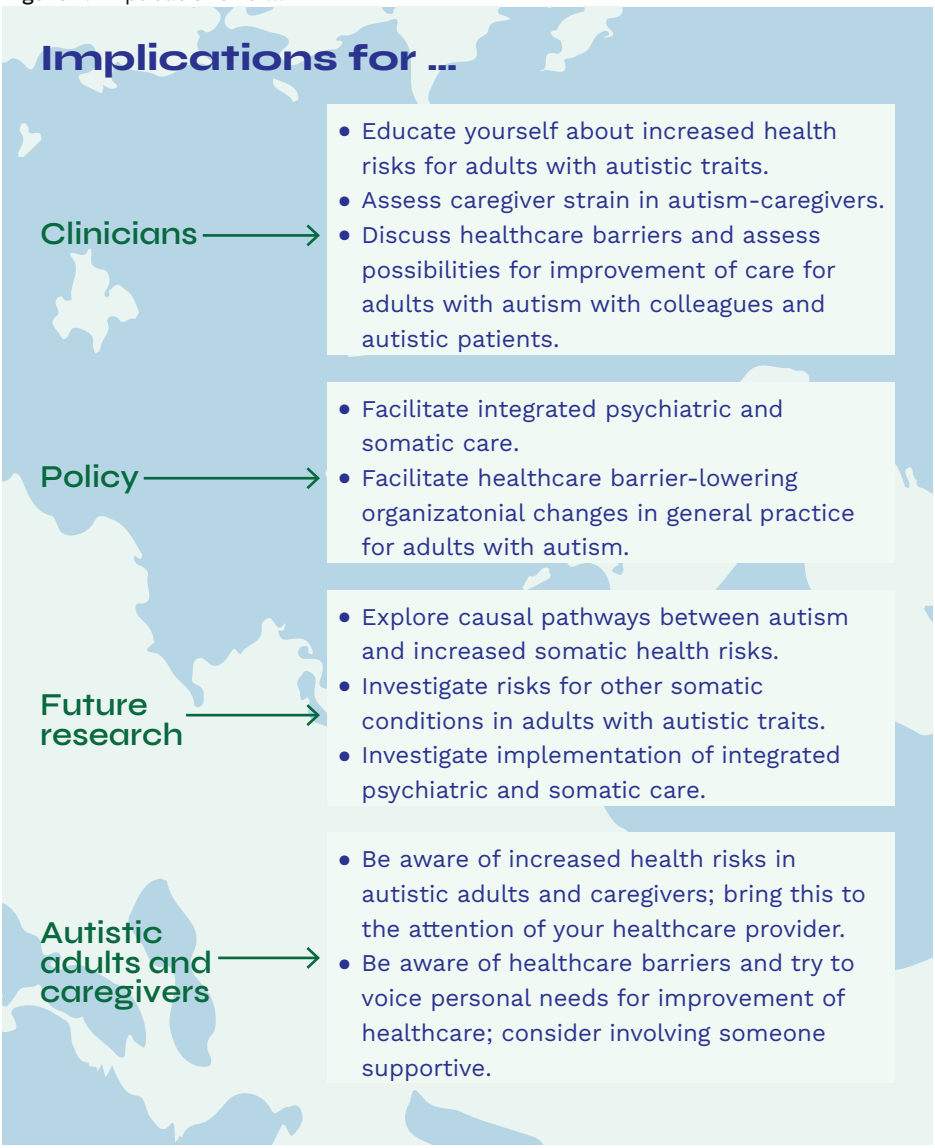
Both our Lifelines studies and our Delphi-study implicate that autistic adults and autism-caregivers need improved healthcare to prevent somatic symptoms, chronic diseases, and caregiver strain. Knowledge of these increased health risks should be accessible for autistic adult and autism-caregivers through for example (online) factsheets/flyers or informative websites. Our AWA project-team, for example, published a factsheet summarizing the outcomes of our Lifelines study regarding gastrointestinal symptoms (see Appendices). This type of factsheet could be used to educate both autistic adults, autism-caregivers, and healthcare providers. Autistic adults who are willing and able to, could take action in their own hands and notify their healthcare providers (PCPs, psychiatrists, etc.) about the increased health risks in autistic adults, to enhance prevention or early recognition of for example gastrointestinal symptoms and metabolic syndrome. However, educating healthcare providers is not the responsibility of autistic adults themselves, particularly because not all autistic adults are capable to adequately verbalise their rights and needs. Hence, based on our Delphi-study, it is advised to consider involving someone from the social support system when autistic people experience barriers in healthcare. In the end, clinicians and policymakers are primarily the parties that should prioritize the improvement of the health and healthcare for autistic adults with more effective prevention and treatment of comorbidities.

Despite that improvement of primary care should mostly come from PCPs and policymakers, it is important that autistic adults themselves are aware of possible healthcare barriers as well. Awareness of these barriers might empower some autistic adults to discuss these barriers with their PCPs. To spread knowledge and awareness, our AWA project team created a summarizing flyer in Dutch about the Delphi-study outcomes regarding barriers and recommendations for improvement of primary care (see Appendices).

Lastly, the results in this dissertation regarding autism-caregiver strain might increase the personal validation of experiencing chronic stress, anxiety, or depression for autism-caregivers in daily life. Validation is important in being able to cope with these psychological aspects of caregiver-strain, as it may result in a feeling of being understood. The outcomes of this dissertation might also give autism-caregivers the opportunity to take their own health more into account, considering the strain that comes with taking care for someone with autism. However, currently, there still is a gap between scientific results, such as the outcomes in this dissertation, and the daily lives of autism-caregivers. Thus, a first step should involve the dissemination of scientific results combined with lived experiences. This could be achieved in collaboration with

for example peer support platforms, bringing autism-caregivers together (e.g., in the Netherlands: https://www.mamavita.nl/).

Figure 1. Implications for...



Conclusion

Taken together, this dissertation is a call to place the health of adults with autistic traits and autism-caregivers higher on the agenda of clinicians, researchers, policymakers, and autistic adults and autism-caregivers themselves. Primarily, clinicians should be educated about the increased health risks in autistic adults and autism-caregivers, in order to be able to prevent or recognize these comorbidities timely. This is relevant because of the higher prevalence of both metabolic syndrome and gastrointestinal symptoms in adults from the general population with higher levels of autistic traits, as shown in this dissertation. The associations we found between biopsychosocial factors and respectively metabolic syndrome and gastrointestinal symptoms ask for more psychiatric and somatic integrated care for autistic adults. With this, a hypothetically chronic hyper-stimulation of the HPA-axis through increased chronic stress and immunological alterations in autistic adults should be considered for more in-depth research. Since it is evident that autistic adults have an increased risk for physical health problems and mortality, future research could use the associations we found between the biopsychosocial model and autistic traits to develop preventive interventions specifically targeted for adults with autism (or higher levels of autistic traits). To make sure future preventive measures and the treatment of physical health problems are effective for this target population to improve their health, barriers in the healthcare for autistic people should be reduced. Therefore, this dissertation also offers recommendations for improvement of primary care, the gatekeeper of adequate healthcare for autistic adults.

References

Bahrar, H., Bekkering, S., Stienstra, R., Netea, M. G., & Riksen, N. P. (2024). Innate immune memory in cardiometabolic disease. Cardiovascular research, 119(18), 2774–2786. https://doi.org/10.1093/cvr/cvad030

Bayoumi M, Ezzat O, & Samarkandi O. (2017). Quality of Life and Subjective Burden on Family Caregiver of Children with Autism. American Journal of Nursing Science, 6, 33-39. https://doi.org/10.11648/j.ajns.20170601.15

Deter, H. C., Kruse, J., & Zipfel, S. (2018). History, aims and present structure of psychosomatic medicine in Germany. BioPsychoSocial medicine, 12, 1. https://doi.org/10.1186/s13030-017-0120-x

Fairthorne, J., Hammond, G., Bourke, J., Jacoby, P., & Leonard, H. (2014). Early mortality and primary causes of death in mothers of children with intellectual disability or autism spectrum disorder: a retrospective cohort study. PloS one, 9(12), e113430. https://doi.org/10.1371/journal.pone.0113430

Fletcher-Watson, S., Adams, J., Brook, K., Charman, T., Crane, L., Cusack, J., Leekam, S., Milton, D., Parr, J. R., & Pellicano, E. (2019). Making the future together: Shaping autism research through meaningful participation. Autism, 23(4), 943–953. https://doi.org/10.1177/1362361318786721

Gezondheidsraad, (2020). Integrale zorg voor mensen met lichamelijke en psychische aandoeningen. Nr. 2020/07, Den Haag, 27 May 2020.

Integraal Zorgakkoord, version 1.0, September, 2022. https://www.rijksoverheid.nl/documenten/rapporten/2022/09/16/integraal-zorgakkoord-samen-werken-aan-gezonde-zorg

Johnson, M., Doherty, M., & Shaw, S. C. (2022). Overcoming barriers to autistic health care: towards autism-friendly practices. The British journal of general practice, 72(719), 255–256. https://doi.org/10.3399/bjgp22X719513

Leue, C., van Schijndel, M.A., Keszthelyi D., van Koeveringe G., Ponds R.W., Kathol R.G., Rutten B.P. (2020). The multi-disciplinary arena of psychosomatic medicine – Time for a transitional network approach. The European Journal of Psychiatry, 34(2), 63-73.

Mason, D., Ingham, B., Urbanowicz, A., Michael, C., Birtles, H., Woodbury-Smith, M., Brown, T., James, I., Scarlett, C., Nicolaidis, C., & Parr, J. R. (2019). A Systematic Review of What Barriers and Facilitators Prevent and Enable Physical Healthcare Services Access for Autistic Adults. Journal of autism and developmental disorders, 49(8), 3387–3400. https://doi.org/10.1007/s10803-019-04049-2

Mazurek, M. O., Harkins, C., Menezes, M., Chan, J., Parker, R. A., Kuhlthau, K., & Sohl, K. (2020). Primary care providers' perceived barriers and needs for support in caring for children with autism. The Journal of Pediatrics, 221, 240. e1–245.e1. https://doi.org/10.1016/j.jpeds.2020.01.014

Micai, M., Fatta, L. M., Gila, L., Caruso, A., Salvitti, T., Fulceri, F., Ciaramella, A., D'Amico, R., Del Giovane, C., Bertelli, M., Romano, G., Schünemann, H. J., & Scattoni, M. L. (2023). Prevalence of co-occurring conditions in children and adults with autism spectrum disorder: A systematic review and meta-analysis. Neuroscience and biobehavioral reviews, 155, 105436. https://doi.org/10.1016/j.neubiorev.2023.105436

Niederberger, M., & Spranger, J. (2020). Delphi Technique in Health Sciences: A Map. Frontiers in public health, 8, 457. https://doi.org/10.3389/fpubh.2020.00457

Pickard, H., Pellicano, E., den Houting, J., & Crane, L. (2022). Participatory autism research: Early career and established researchers' views and experiences. Autism, 26(1), 75–87. https://doi.org/10.1177/13623613211019594

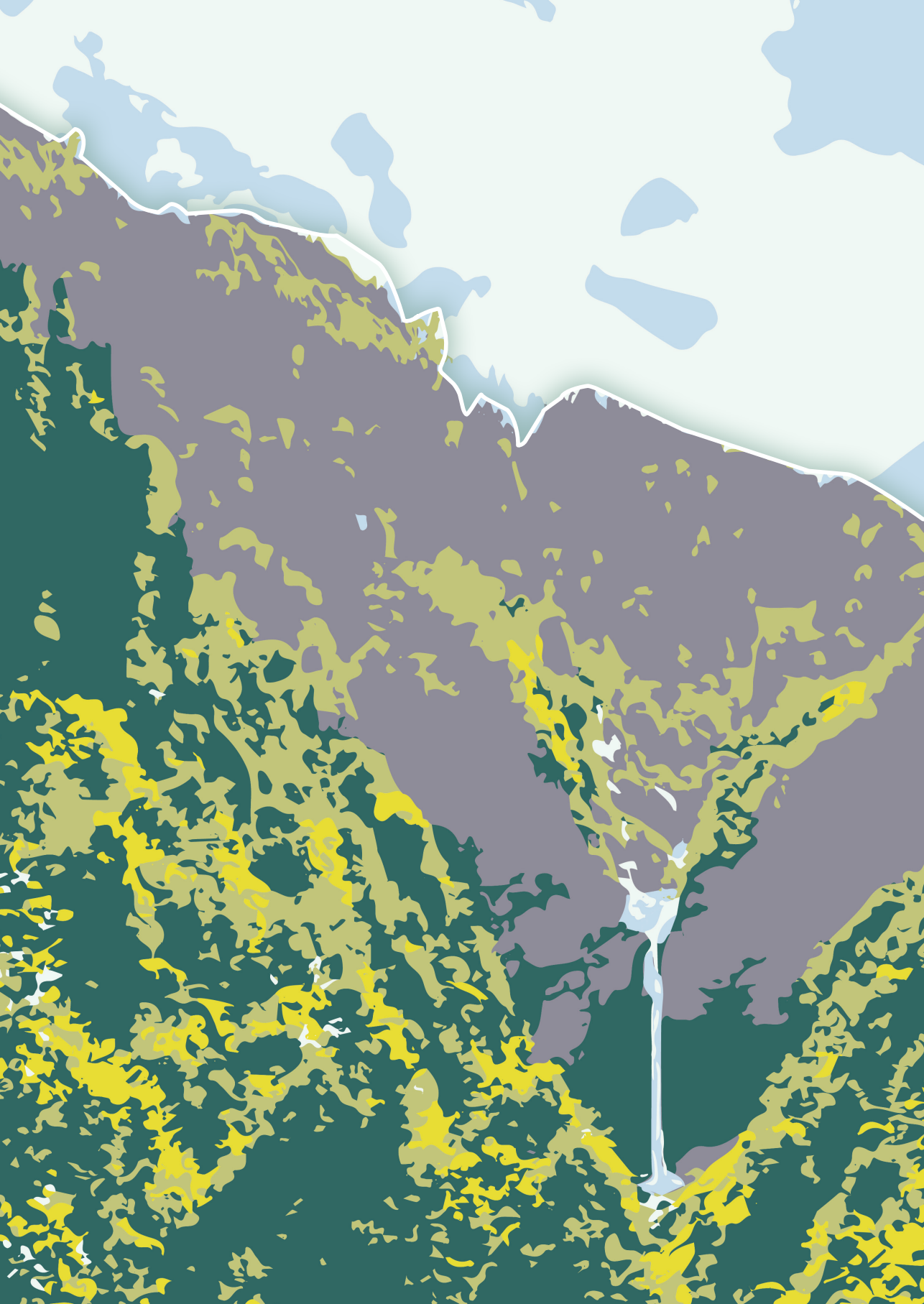
Poulsen, R., Brownlow, C., Lawson, W., & Pellicano, E. (2022). Meaningful research for autistic people? Ask autistics!. Autism, 26(1), 3–5. https://doi.org/10.1177/13623613211064421

Rosas, S. R., & Kane, M. (2012). Quality and rigor of the concept mapping methodology: a pooled study analysis. Evaluation and program planning, 35(2), 236–245. https://doi.org/10.1016/j.evalprogplan.2011.10.003

Schulz, R., & Beach, S. R. (1999). Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA, 282(23), 2215–2219. https://doi.org/10.1001/jama.282.23.2215

Simoons, M., Mulder, H., Doornbos, B., Raats, P. C. C., Bruggeman, R., Cath, D. C., Schoevers, R. A., Ruhé, H. G., & van Roon, E. N. (2019). Metabolic Syndrome at an Outpatient Clinic for Bipolar Disorders: A Case for Systematic Somatic Monitoring. Psychiatric services, 70(2), 143–146. https://doi.org/10.1176/appi.ps.201800121

Taylor E. (2020). We Agree, Don't We? The Delphi Method for Health Environments Research. HERD, 13(1), 11–23. https://doi.org/10.1177/1937586719887709



Chapter 7

Nederlandse samenvatting

Inleiding

Het verbeteren van de gezondheid(szorg) van volwassenen met een autisme-spectrumstoornis (hierna: autisme) is urgent, met name vanwege hun risico op vervroegde sterfte ten opzichte van volwassenen zonder autisme (Hirvikoski et al., 2016; Hwang et al., 2019; Lunsky et al., 2022; Mouridsen et al., 2008; Pickett et al., 2011; Schendel et al., 2016). De huidige bestaande literatuur beschrijft echter met name de gezondheidsproblemen bij kinderen met autisme. De kennis over de lichamelijke gezondheid van volwassenen met autisme is nog beperkt. Ook het verbeteren van de gezondheid van mantelzorgers van mensen met autisme is een belangrijk speerpunt, omdat zij mogelijk ook een verhoogd risico op vroegtijdige sterfte hebben. Fairthorne en diens collega's publiceerden namelijk in 2014 een cohort studie waarin ze hogere sterftecijfers vonden bij moeders van kinderen met autisme. Daarnaast lijkt de zorglast van mantelzorgers van mensen met autisme hoger te zijn dan die van mantelzorgers van mensen zonder autisme (Bayoumi et al., 2017). We weten echter nog onvoldoende welke gezondheidsrisico's dit mogelijk met zich meebrengt.

Dit proefschrift draagt bij aan het vullen van deze hiaten in onze kennis, wat nodig is om de gezondheidszorg en uiteindelijk de gezondheid van volwassenen met autisme en hun mantelzorgers te verbeteren. Met dit doel hebben we eerst kwantitatief onderzoek gedaan naar cardiovasculair risico (metabool syndroom) bij volwassenen met autisme-kenmerken (Hoofdstuk 2), naar maag-darmklachten bij volwassenen met (kenmerken van) autisme (Hoofdstuk 3), en naar de verschillen tussen mantelzorgers van mensen met en zonder autisme (Hoofdstuk 4). Om de opgedane kennis uit deze onderzoeken ook echt te laten leiden tot een betere gezondheid van deze doelgroepen, moet de zorg die aan hen geleverd wordt ook effectief zijn. We weten namelijk dat de verschillende barrières die mensen met autisme ervaren in de huisartsenzorg onder andere kan leiden tot vertraagde zorg (Mazurek et al., 2020). Daarom hebben we in Hoofdstuk 5 onderzocht hoe huisartsen, praktijkondersteuners en volwassenen met autisme denken dat de huisartsenzorg voor mensen met autisme verbeterd kan worden. In deze samenvatting worden eerst de resultaten van deze vier studies uiteengezet. Tot slot worden een aantal discussiepunten en de aanbevelingen die hieruit volgen, samengevat.

Resultaten

Omdat cardiovasculaire ziekte één van de belangrijkste doodsoorzaken is bij volwassenen met autisme, is het van belang om meer inzicht te krijgen in hun cardiovasculair risico (Hirvikoski et al., 2016; Hwang et al., 2019; Schendel et al., 2016; Shavelle et al., 2001). In de studie die beschreven wordt in Hoofdstuk 2 hebben we daarom 17.705 volwassenen uit het Lifelines Cohort onderzocht op de aanwezigheid van metabool syndroom. Het Lifelines Cohort is een steekproef van de algemene bevolking in Noord-Nederland. Metabool syndroom is de combinatie van minimaal drie van de volgende cardiovasculaire risicofactoren: abdominale obesitas (verhoogde middelomtrek), verhoogd glucose (bijvoorbeeld bij diabetes mellitus type 2), dislipidemie (verstoorde verhouding van cholesterol) en hypertensie (Alberti et al., 2009). De 17.705 geïncludeerde volwassenen uit het Lifelines Cohort hebben we onderverdeeld in kwartielen op basis van hun score op de Autisme Spectrum Quotient-10 (AQ-10) vragenlijst. De AQ-10 omvat tien vragen over autisme-kenmerken; een hoge score op de AQ-10 is een grove aanduiding voor het hebben van relatief veel autisme-kenmerken (Allison et al., 2012). We vergeleken in deze studie de mannen en vrouwen uit de kwartielen met de hoogste AQ-10 scores met de mannen en vrouwen uit de kwartielen met de laagste AQ-10 scores.

Ten eerste vonden we dat de prevalentie van metabool syndroom in het kwartiel van vrouwen met de hoogste AQ-10 scores hoger was dan in het kwartiel van vrouwen met de laagste AQ-10 scores: 10,0% versus 7,5%. De prevalentie van metabool syndroom was echter niet statistisch significant verschillend tussen het kwartiel van mannen met relatief veel autisme-kenmerken (13,8%) en het kwartiel van mannen met relatief weinig autisme-kenmerken (13,1%). Vervolgens hebben we onderzocht welke biologische, psychische en gedragsfactoren (hierna: biopsychosociale factoren) geassocieerd zijn met het hebben van metabool syndroom. Zowel bij de mannen als bij de vrouwen met relatief veel autisme-kenmerken was het hebben van metabool syndroom geassocieerd met slechtere ervaren gezondheid, minder lichamelijke beweging en veranderde leukocyten aantallen in het bloed.

Hoofdstuk 3 van dit proefschrift is gericht op het vergroten van kennis over de biopsychosociale factoren geassocieerd met maag-darmklachten bij volwassenen met autisme, omdat maag-darmproblemen vaak voorkomen bij autisme (Croen et al., 2015; Hand et al., 2020; Tye et al., 2019). Er is echter vooral veel geschreven over factoren geassocieerd met maag-darmproblemen bij kinderen, waardoor we weinig weten over maag-darmklachten bij volwassenen met autisme, terwijl deze klachten wel veel impact kunnen hebben op hun dagelijks leven. In deze studie hebben we wederom volwassenen uit het Lifelines Cohort geïncludeerd: 309 volwassenen met autisme en 30.876

volwassenen zonder autisme. Hierbij was de onderzoeksvraag welke biopsychosociale factoren geassocieerd zijn met het hebben van maag-darmklachten. Maag-darmklachten waren gedefinieerd als het regelmatig last hebben van buikpijn, zuurbranden, obstipatie en/of diarree. De resultaten toonden dat de prevalentie van het hebben van één of meer van deze maag-darmklachten 1,7 keer hoger was bij de volwassenen met autisme dan bij de volwassenen zonder autisme. Ook in het kwartiel van deelnemers met relatief veel autisme-kenmerken was deze prevalentie hoger dan in het kwartiel van deelnemers met relatief weinig autisme-kenmerken (24,7% versus 18,8%). Bij zowel de volwassenen met autisme als bij het kwartiel van deelnemers met relatief veel autisme-kenmerken waren angst, depressie, hogere stress levels en slechtere ervaren gezondheid ieder geassocieerd met het hebben van maag-darmklachten. Tot slot waren minder lichamelijke activiteit en veranderde aantallen van leukocyten, neutrofielen en lymfocyten in het bloed tevens geassocieerd met het hebben van maag-darmklachten bij de groep van volwassenen met relatief veel autisme-kenmerken. Kijk voor een samenvatting van dit onderzoek naar maag-darmklachten ook naar de flyer in de Appendix van dit proefschrift.

Hoofdstuk 4 van dit proefschrift heeft als doel om meer inzicht te krijgen in de mogelijke gezondheidsrisico's van mantelzorgers van mensen met autisme. Daarom hebben we in deze studie 722 volwassenen die mantelzorger zijn voor een persoon met autisme vergeleken met 2632 volwassenen die mantelzorger zijn voor een persoon zonder autisme. Deze mantelzorgers waren allen deelnemers van het Lifelines Cohort. Onze analyses lieten zien dat de mantelzorgers van mensen met autisme ongeveer tweemaal vaker een angststoornis of depressieve stoornis hadden. Tevens rapporteerden de mantelzorgers van mensen met autisme vaker een hoog stressniveau dan de mantelzorgers van mensen zonder autisme. De psychologische verschillen tussen de mantelzorgers van mensen met autisme en de mantelzorgers van mensen zonder autisme leken niet enkel verklaard te kunnen worden door de hypothese dat ze meer ouderlijke stress ervaren. Tot slot waren de lymfocyten en monocyten aantallen lager bij de mantelzorgers van mensen met autisme dan bij de mantelzorgers van mensen zonder autisme. Lymfocyten en monocyten zijn onderdelen van het immuunsysteem die mogelijk uit balans kunnen raken bij chronische stress.

Middels een Delphi-studie, waaraan huisartsen, praktijkondersteuners en volwassenen met autisme deelnamen, had Hoofdstuk 5 van dit proefschrift tot doel het inventariseren van aanbevelingen ter verbetering van de huisartsenzorg voor mensen met autisme. Daarvoor hebben we eerst de belemmerende rol van 20 barrières in de huisartsenzorg onderzocht. Deze lijst van 20 barrières was gebaseerd op eerder internationaal onderzoek, 11 semigestructureerde

interviews en de input van leden van onze projectgroep van de Academische Werkplaats Autisme (AWA). Onze Delphi-studie, bestaande uit drie rondes van digitale vragenlijsten, toonde ten eerste dat alle barrières werden herkend door zowel de deelnemende huisartsen en praktijkondersteuners als de deelnemers met autisme. Echter schatten de deelnemers met autisme de belemmerende rol van de barrières groter in dan de huisartsen en praktijkondersteuners. Vervolgens hebben we 22 aanbevelingen geformuleerd op basis van eerdere literatuur, input van de AWA projectgroepleden en input van de Delphi-deelnemers in ronde één van de vragenlijsten. Deze aanbevelingen, ter verbetering van de huisartsenzorg voor mensen met autisme, zijn door de Delphi-deelnemers in ronde twee en drie beoordeeld op nut en haalbaarheid. De 22 aanbevelingen zijn gericht op 1) huisartsen en praktijkondersteuners, 2) de organisatie van de huisartsenzorg, en 3) volwassenen met autisme. Voorbeelden van aanbevelingen die de Delphi-deelnemers helpend/nuttig vonden, zijn: meer onderwijs voor huisartsen en praktijkondersteuners, het plannen van een dubbele afspraak met de huisarts en het verbeteren van de voorspelbaarheid van een huisartsenbezoek voor mensen met autisme. Zie voor een samenvatting van de aanbevelingen uit deze Delphi-studie de flyer in de Appendix van dit proefschrift.

Discussie en aanbevelingen

De grootste kracht van de kwantitatieve studies in dit proefschrift (Hoofdstuk 2-4) is de brede analyse van verschillende type data, te weten: biologische maten die fysiek zijn gemeten (lengte, gewicht, middelomtrek, leukocyten aantallen in het bloed), zelf-gerapporteerde variabelen (stress, ervaren gezondheid, lichamelijke beweging, roken, alcoholgebruik) en semi-gestructureerde interviews (angst en depressie gemeten met de MINI). Daarnaast hebben we grote onderzoekspopulaties uit het Lifelines Cohort kunnen includeren, wat de validiteit van de onderzoeksuitkomsten vergroot. Vervolgens heeft het gebruik van de Delphi-methode (Hoofdstuk 5) geleid tot meer consensus ten aanzien van de onderzochte aanbevelingen binnen het panel van huisartsen, praktijkondersteuners en volwassenen met autisme (Niederberger & Spranger, 2020).

Het is ook belangrijk een aantal kanttekeningen bij de resultaten van dit proefschrift te benoemen. Ten eerste zijn in de beschreven studies in dit proefschrift geen volwassenen met een verstandelijke beperking geïncludeerd, terwijl een relatief groot deel van de mensen met autisme een verstandelijke beperking heeft en we weten ook dat somatische comorbiditeiten hierbij prevalent zijn. De deelnemers van het Lifelines Cohort moesten in staat zijn om zelfstandig

vragenlijsten in de kunnen vullen, dus mensen met een ernstige verstandelijke beperking hebben daardoor niet kunnen deelnemen. Dit gold ook voor onze Delphi-studie. Hierdoor kunnen de resultaten van dit proefschrift niet zonder meer toegepast worden op de populatie van mensen met autisme en een (ernstige) verstandelijke beperking. Dit behoeft separaat onderzoek.

Ook dient benoemd te worden dat in de Lifelines studies en de Delphi-studie de culturele en etnische diversiteit laag was. Het Lifelines Cohort is een steekproef van de algemene populatie in Noord-Nederland, waar met name mensen wonen met een Europese achtergrond. Bij de werving van deelnemers voor de Delphi-studie is het ook moeilijk gebleken om volwassenen met autisme, huisartsen en praktijkondersteuners met diverse culturele achtergronden te werven voor deelname.

Tot slot is een belangrijke kanttekening bij onze Lifelines studies dat de statistische associaties die we hebben gerapporteerd geen causaliteit aantonen tussen de onderzochte biopsychosociale factoren en de verschillende uitkomstmaten. Zodoende moeten de gevonden associaties als mogelijk werkend in beide richtingen geïnterpreteerd worden.

Algemene aanbevelingen

Figuur 1 toont een samenvatting van de hieronder beschreven aanbevelingen voor zorgverleners, beleid, onderzoek, volwassenen met autisme en mantelzorgers van mensen met autisme. Het doel van deze aanbevelingen is op de langere termijn verbeteren van de gezondheid(szorg) van mensen met autisme en hun mantelzorgers. Mogelijk kan een deel van deze aanbevelingen versneld gerealiseerd worden middels het ontwikkelen van betere psychiatrisch-somatisch geïntegreerde zorg. Dit laatste sluit aan bij de doelen van het Nederlandse Integraal Zorgakkoord (versie 1.0, september 2022), de Nederlandse Gezondheidsraad (Integrale zorg voor mensen met lichamelijke en psychische aandoeningen, 27 mei 2020) en de Wereld Gezondheidsorganisatie (Integrated Health Services Department of the World Health Organization; https://www.who.int/teams/integrated-health-services/about).

Aanbevelingen voor zorgverleners

In dit proefschrift komt naar voren dat volwassenen met relatief veel autisme-kenmerken in onze algemene bevolking een verhoogd risico hebben op metabool syndroom en op maag-darmklachten. Deze uitkomsten suggereren dat de autisme-kenmerken een rol spelen bij deze verhoogde gezondheidsrisico's. Dit betekent dat zorgverleners, zoals huisartsen en psychiaters, in hun patiëntenzorg rekening moeten houden met deze gezondheidsrisico's bij volwassenen met autisme-kenmerken, ongeacht of bij hen (al) een autisme diagnose is gesteld. Deze bredere alertheid kan wellicht leiden tot eerdere herkenning en behandeling, en daarmee een reductie van cardiovasculaire

ziekten en maag-darmproblemen. Hierbij is het logischerwijs van belang om patiënten niet alleen te verwijzen naar associaties tussen hun klachten en het biopsychosociale model, maar ook op indicatie adequaat door te verwijzen voor aanvullende somatische diagnostiek (Federatie Medisch Specialisten, Richtlijn SOLK en somatoforme stoornissen). Adequate communicatie tussen de artsen/zorgverleners en patiënt is hierbij zeer van belang, gezien ook uit de Delphi-studie bleek dat driekwart van de deelnemers met autisme 'het gevoel van niet begrepen worden' als een zeer belemmerende barrière in de huisartsenzorg rapporteerden. Hier kunnen mogelijk stigma's en barrières in de communicatie ook een rol bij spelen.

Bij bovenstaande aanbevelingen is de verspreiding van kennis middels educatie aan zorgverleners een belangrijke stap. Uit de Delphi-studie kwam ook naar voren dat onderwijs aan zorgverleners bijvoorbeeld kan gaan over de diagnose autisme, de verhoogde gezondheidsrisico's bij volwassenen met autisme(-kenmerken), geassocieerde biopsychosociale factoren, en ervaren barrières in de zorg. Dergelijk onderwijs zou in ieder geval gericht kunnen zijn op huisartsen (in opleiding), praktijkondersteuners, geneeskunde studenten en psychiaters (in opleiding), aangezien allerlei verschillende medisch specialisten en praktijkondersteuners patiënten met autisme kunnen tegenkomen in hun klinische praktijk. Bij het opzetten van dit onderwijs kan er gedacht worden aan het inzetten van de expertise van psychologen/psychiaters die veel met mensen met autisme werken. Daarnaast kunnen ervaringsdeskundigen met autisme bij de ontwikkeling en/of uitvoering van dit onderwijs betrokken worden, omdat zij de verschillende perspectieven/ervaringen t.a.v. de zorgverlening vanuit een patiënt met autisme kunnen overdragen.

Daarnaast vragen de uitkomsten van dit proefschrift en resultaten van eerder onderzoek (zoals Micai et al., 2023) om verbetering van klinische richtlijnen en zorgstandaarden. Dit zou bijvoorbeeld een verrijking kunnen betreffen van de richtlijnen t.a.v. cardiovasculair risicomanagement in de psychiatrie (geestelijke gezondheidszorg (GGZ) Standaard Autisme) en de huisartsenzorg (Nederlands Huisartsen Genootschap (NHG) richtlijn Cardiovasculair risicomanagement). Tevens kan er gedacht worden aan een NHG-Richtlijn Autisme, aangezien er bijvoorbeeld ook al NHG-richtlijnen zijn voor ADHD, angststoornis en depressieve stoornis. Een NHG-Richtlijn Autisme zou huisartsen zowel kunnen helpen bij het herkennen van autisme kenmerken, als bij het signaleren van vaak voorkomende somatische comorbiditeiten. Bovendien kwam uit de Delphi-studie naar voren dat huisartsen behoefte hebben aan een centrale plek met dergelijke informatie, zoals ook informatie over verwijsmogelijkheden.

Dit proefschrift roept tevens op tot meer aandacht voor de gezondheid van mantelzorgers van mensen met autisme. Eerder onderzoek toonde reeds aan dat mantelzorgers van mensen met autisme hogere zorglasten ervaren dan mantelzorgers van mensen zonder autisme (Bayoumi et al., 2017). Op basis van

ons Lifelines onderzoek moeten zorgverleners zich er specifiek bewust van zijn dat mantelzorgers van mensen met autisme hoge stress niveaus ervaren en vaker last hebben van angst en depressie. Het is van belang dat bijvoorbeeld huisartsen en psychiaters deze klachten bij de mantelzorgers monitoren en inzetten op stress-verlagende/preventieve interventies.

De Delphi-studie resulteerde in een aantal specifieke aanbevelen voor de huisartsenzorg van mensen met autisme. Ten eerste wordt geadviseerd dat zorgverleners in de huisartsenpraktijk (huisartsen, praktijkondersteuners, doktersassistenten) onderling bespreken welke barrières mogelijk een rol spelen in de huisartsenzorg die zij leveren aan mensen met autisme. Het advies is om indien mogelijk vervolgens ook aan patiënten met autisme binnen de huisartsenpraktijk te vragen welke specifieke barrières zij in de huisartsenzorg ervaren. Hierbij kan het overzicht van barrières uit onze Delphi-studie (en de flyer in de Appendix) als handreiking voor een gesprek dienen. Dit kan het bewustzijn en daarmee herkenning van deze barrières vergroten. Vervolgens hebben zorgverleners in de huisartsenpraktijk de verantwoordelijkheid om te inventariseren wat mogelijkheden ter verbetering zijn; dit kan per huisartsenpraktijk verschillen. Hierbij kunnen de aanbevelingen die in de Delphi-studie onderzocht zijn op nut en haalbaarheid als leidraad dienen. De Delphi-studie was specifiek gericht op de huisartsenzorg. Echter zullen verschillende barrières en mogelijkheden ter verbetering van zorg ook gelden voor andere typen zorg voor mensen met autisme. Dit is niet direct te concluderen uit ons onderzoek, maar onze resultaten kunnen wel richting geven aan (vervolgonderzoek naar) verbetermogelijkheden in andere vakgebieden zoals o.a. neurologie, fysiotherapie, tandheelkunde, chirurgie of interne geneeskunde.

Aanbevelingen voor beleid

Een eerste aanbeveling voor beleidsmakers is het faciliteren van de ontwikkeling van meer psychiatrisch-somatisch geïntegreerde zorg, bestaande uit bijvoorbeeld nauwere samenwerkingsverbanden tussen medisch specialisten in ziekenhuizen, GGZ-hulpverleners en eerstelijnszorgverleners (Leue et al., 2020). Ook kan somatische screening, op bijvoorbeeld metabool syndroom, in psychiatrische instellingen verbeterd worden (Simoons et al., 2019). Hoe dit in de Nederlandse gezondheidszorg meer geïntegreerd zou kunnen worden, moet nog nader onderzocht worden. Beleidsveranderingen ten aanzien van psychiatrisch-somatisch geïntegreerde zorg zouden vervolgens ook moeten leiden tot revisies van klinische richtlijnen, zoals Hoofdstuk 8 van de Zorgstandaard Autisme (https://https//www.ggzstandaarden.nl/zorgstandaarden/autisme).

Het concept van psychiatrisch-somatisch geïntegreerde zorg omvat logischerwijs niet alleen patiënten met autisme, maar de bredere psychiatrische populatie met verhoogde somatische gezondheidsrisico's. Denk hierbij bijvoorbeeld aan gecombineerde leefstijlinterventie programma's. De ontwikkeling

van meer lokaal geïntegreerde psychiatrisch-somatische zorg sluit aan bij het Integraal Zorgakkoord dat in 2022 is gesloten door onder meer de Nederlandse Overheid, GGZ en Federatie van Medisch Specialisten (Integraal Zorgakkoord, versie 1.0, september, 2022). Hierin is tevens een statement opgenomen dat pleit voor de verbetering van gezondheidzorg voor mensen met verhoogde gezondheidsrisico's middels meer geïntegreerde zorg.

Tot slot resulteerde onze Delphi-studie in diverse aanbevelingen voor de organisatie van de huisartsenzorg, waar landelijk Overheidsbeleid ook invloed op kan hebben. Zo is het bijvoorbeeld in Nederland al mogelijk dat huisartsen een dubbel consult declareren bij de zorgverzekeraar op basis van het gegeven dat de patiënt een autisme diagnose heeft, zodat er meer tijd is voor het huisartsenconsult. Tevens zouden beleidsmakers zich kunnen richten op autisme-vriendelijke of neurodiverse stigma-verminderende campagnes, gezien maatschappelijk onbegrip door kan sijpelen in de gezondheidszorg. Uiteindelijk is immers voor het verbeteren van de gezondheid van mensen met autisme beleidsverandering nodig in de huisartsenzorg, maar zeker ook in andere takken van de gezondheidszorg, om zo adequate psychiatrisch-somatisch geïntegreerde zorg voor mensen met autisme te kunnen realiseren.

Aanbevelingen voor onderzoek

Ten eerste kan wetenschappelijk onderzoek zich op basis van de uitkomsten van dit proefschrift richten op specifieke autisme kenmerken die gezondheidsrisico's verhogen. Dit helpt om de onderliggende mechanismes van somatische klachten en comorbiditeiten in de algemene populatie van mensen met autisme kenmerken of autisme diagnose beter te begrijpen. Er zijn ook meer longitudinale studies nodig om causale verbanden te onderzoeken. Vervolgens zou dergelijke kennis over causale verbanden in de klinische praktijk meer handvatten kunnen geven voor preventieve maatregelen in bijvoorbeeld cardiovasculair risicomanagement bij mensen met bepaalde autisme kenmerken. Het is van belang om in vervolgonderzoek ook volwassenen met autisme(-kenmerken) en een verstandelijke beperking en andere etnische achtergronden te includeren.

De resultaten van dit proefschrift zijn tevens een oproep voor meer onderzoek met een biopsychosociale benadering ten aanzien van somatische comorbiditeiten bij volwassenen met autisme(-kenmerken). Denk hierbij bijvoorbeeld aan één van de andere belangrijke doodsoorzaken in de algemene bevolking, zoals kanker. De biopsychosociale factoren die in dit proefschrift zijn meegenomen kunnen in toekomstig onderzoek aangevuld worden met meer contextuele factoren, zoals ingrijpende levensgebeurtenissen en leefomstandigheden. De inzichten die we in dit proefschrift hebben verkregen over immunologische variabelen bij volwassenen met autisme(-kenmerken) vragen ook naar meer onderzoek; bijvoorbeeld over de aanwezigheid van en effecten

van chronische laaggradige inflammatie bij deze populatie. Het immuunsysteem speelt namelijk onder andere een belangrijke rol in de ontwikkeling van atherosclerotische cardiovasculaire ziekten (Bahrar et al., 2023).

Tot slot zou toekomstig onderzoek zich in ieder geval ook moeten richten op 1) ontwikkeling en implementatie van nieuwe klinische richtlijnen die leiden tot meer psychiatrisch-somatisch geïntegreerde zorg, en 2) implementatie van organisatorische veranderingen in de huisartsenzorg die leiden tot minder barrières en minder gezondheidsproblemen bij volwassenen met autisme.

Aanbevelingen voor volwassenen met autisme en voor mantelzorgers

Zowel de Lifelines studies als de Delphi-studie impliceren dat volwassenen met autisme en mantelzorgers van mensen met autisme betere gezondheidszorg nodig hebben vanwege hun verhoogde gezondheidsrisico's. Kennis over deze gezondheidsrisico's moet echter niet alleen beschikbaar zijn voor hun zorgverleners, maar ook voor deze doelgroepen zelf. Deze kennis kan onder andere in de GGZ en binnen de huisartsenzorg verspreid worden middels (online) factsheets/flyers. Zo heeft onze AWA-projectgroep reeds (online) twee factsheets over maag-darmklachten en aanbevelingen voor verbetering van de huisartsenzorg ontwikkeld en verspreid (zie de Appendix). Volwassenen met autisme kunnen deze factsheets bijvoorbeeld delen met hun zorgverleners en bespreken welke gezondheidsproblemen en barrières zij herkennen. Echter is het niet de verantwoordelijkheid van mensen met autisme zelf om deze onderwerpen aan te kaarten, maar de verantwoordelijkheid van hun zorgverleners om somatische klachten en barrières in de zorg te herkennen en voorkomen. Daarnaast zouden volwassenen met autisme kunnen overwegen om iemand uit hun steunsysteem te betrekken bij contacten met zorgverleners als ze barrières en/of somatische klachten ervaren, maar het moeilijk vinden om dit bespreekbaar te maken.

Tot slot kunnen de resultaten uit dit proefschrift over de gezondheidsrisico's van mantelzorgers van mensen met autisme een bijdage leveren aan persoonlijke validatie van het ervaren van chronische stress, angst en depressie bij deze groep van mantelzorgers. Validatie van wat je voelt/ervaart als individu is een belangrijk aspect bij het herkennen en verminderen van deze psychologische aspecten van het geven van mantelzorg, omdat het bijdraagt aan het gevoel begrepen te worden. Echter bestaat er nu nog een gat tussen deze wetenschappelijke resultaten en het actief verbeteren van de gezondheid van deze mantelzorgers. Daarom is de verspreiding van nieuwe kennis en ervaringen hierover een belangrijke stap. Hier kunnen online platforms (zoals www.mamavita.nl), die mantelzorgers van mensen met autisme met elkaar in contact laten komen, bijvoorbeeld een rol bij spelen.

Figuur 1. Aanbevelingen voor...

Conclusie

Dit proefschrift is een oproep om verbetering van de gezondheid van volwassenen met autisme(-kenmerken) en van mantelzorgers van mensen met autisme hoger op de agenda te plaatsen van zorgverleners, onderzoekers en beleidsmakers. De in dit proefschrift beschreven associaties tussen factoren uit het biopsychosociaal model en respectievelijk metabool syndroom, maag-darmklachten en het zijn van mantelzorger voor iemand met autisme vragen om de ontwikkeling van meer psychiatrisch-somatisch geïntegreerde zorgverlening. Hierbij moet onder andere rekening worden gehouden met de verschillende barrières in de zorg die volwassenen met autisme en hun zorgverleners ervaren. Voor de huisartsenzorg biedt dit proefschrift tot slot een aantal aanbevelingen om die barrières te verminderen en daarmee de zorg en gezondheid van volwassenen met autisme uiteindelijk te verbeteren.

Referenties

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., Smith, S. C., Jr, International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, & International Association for the Study of Obesity (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Allison, C., Auyeung, B., & Baron-Cohen, S. (2012). Toward brief "Red Flags" for autism screening: The Short Autism Spectrum Quotient and the Short Quantitative Checklist for Autism in toddlers in 1,000 cases and 3,000 controls [corrected]. Journal of the American Academy of Child and Adolescent Psychiatry, 51(2), 202–212.e7. https://doi.org/10.1016/j.jaac.2011.11.003

Bahrar, H., Bekkering, S., Stienstra, R., Netea, M. G., & Riksen, N. P. (2024). Innate immune memory in cardiometabolic disease. Cardiovascular research, 119(18), 2774–2786. https://doi.org/10.1093/cvr/cvad030

Bayoumi M, Ezzat O, & Samarkandi O. (2017). Quality of Life and Subjective Burden on Family Caregiver of Children with Autism. American Journal of Nursing Science, 6, 33-39. https://doi.org/10.11648/j.ajns.20170601.15

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. https://doi.org/10.1177/1362361315577517

Fairthorne, J., Hammond, G., Bourke, J., Jacoby, P., & Leonard, H. (2014). Early mortality and primary causes of death in mothers of children with intellectual disability or autism spectrum disorder: a retrospective cohort study. PloS one, 9(12), e113430. https://doi.org/10.1371/journal.pone.0113430

Gezondheidsraad, (2020). Integrale zorg voor mensen met lichamelijke en psychische aandoeningen. Nr. 2020/07, Den Haag, 27 May 2020.

Hand, B. N., Angell, A. M., Harris, L., & Carpenter, L. A. (2020). Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism, 24(3), 755–764. https://doi.org/10.1177/1362361319890793

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. The British journal of psychiatry, 208(3), 232–238. https://doi.org/10.1192/bjp.bp.114.160192

Hwang, Y. I. J., Srasuebkul, P., Foley, K. R., Arnold, S., & Trollor, J. N. (2019). Mortality and cause of death of Australians on the autism spectrum. Autism research, 12(5), 806–815. https://doi.org/10.1002/aur.2086

Integraal Zorgakkoord, version 1.0, September, 2022. https://www.rijksoverheid.nl/documenten/rapporten/2022/09/16/integraal-zorgakkoord-samen-werken-aan-gezonde-zorg

Leue, C., van Schijndel, M.A., Keszthelyi D., van Koeveringe G., Ponds R.W., Kathol R.G., Rutten B.P. (2020). The multi-disciplinary arena of psychosomatic medicine – Time for a transitional network approach. The European Journal of Psychiatry, 34(2), 63-73.

Lunsky, Y., Lai, M. C., Balogh, R., Chung, H., Durbin, A., Jachyra, P., Tint, A., Weiss, J., & Lin, E. (2022). Premature mortality in a population-based cohort of autistic adults in Canada. Autism research, 15(8), 1550–1559. https://doi.org/10.1002/aur.2741

Mazurek, M. O., Harkins, C., Menezes, M., Chan, J., Parker, R. A., Kuhlthau, K., & Sohl, K. (2020). Primary care providers' perceived barriers and needs for support in caring for children with autism. The Journal of Pediatrics, 221, 240. e1–245.e1. https://doi.org/10.1016/j.jpeds.2020.01.014

Micai, M., Fatta, L. M., Gila, L., Caruso, A., Salvitti, T., Fulceri, F., Ciaramella, A., D'Amico, R., Del Giovane, C., Bertelli, M., Romano, G., Schünemann, H. J., & Scattoni, M. L. (2023). Prevalence of co-occurring conditions in children and adults with autism spectrum disorder: A systematic review and meta-analysis. Neuroscience and biobehavioral reviews, 155, 105436. https://doi.org/10.1016/j.neubiorev.2023.105436

Mouridsen, S. E., Brønnum-Hansen, H., Rich, B., & Isager, T. (2008). Mortality and causes of death in autism spectrum disorders: an update. Autism, 12(4), 403–414. https://doi.org/10.1177/1362361308091653

Niederberger, M., & Spranger, J. (2020). Delphi Technique in Health Sciences: A Map. Frontiers in public health, 8, 457. https://doi.org/10.3389/fpubh.2020.00457

Pickett, J., Xiu, E., Tuchman, R., Dawson, G., & Lajonchere, C. (2011). Mortality in individuals with autism, with and without epilepsy. Journal of child neurology, 26(8), 932–939. https://doi.org/10.1177/0883073811402203

Schendel, D. E., Overgaard, M., Christensen, J., Hjort, L., Jørgensen, M., Vestergaard, M., & Parner, E. T. (2016). Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. JAMA pediatrics, 170(3), 243–250. https://doi.org/10.1001/jamapediatrics.2015.3935

Shavelle, R. M., Strauss, D. J., & Pickett, J. (2001). Causes of death in autism. Journal of autism and developmental disorders, 31(6), 569–576. https://doi.org/10.1023/a:1013247011483

Simoons, M., Mulder, H., Doornbos, B., Raats, P. C. C., Bruggeman, R., Cath, D. C., Schoevers, R. A., Ruhé, H. G., & van Roon, E. N. (2019). Metabolic Syndrome at an Outpatient Clinic for Bipolar Disorders: A Case for Systematic Somatic Monitoring. Psychiatric services, 70(2), 143–146. https://doi.org/10.1176/appi.ps.201800121

Tye, C., Runicles, A. K., Whitehouse, A. J. O., & Alvares, G. A. (2019). Characterizing the Interplay Between Autism Spectrum Disorder and Comorbid Medical Conditions: An Integrative Review. Frontiers in psychiatry, 9, 751. https://doi.org/10.3389/fpsyt.2018.00751

Dankwoord

Dit proefschrift is gebouwd op de pilaren van het Lifelines Cohort en de Academische Werkplaats Autisme. Daarom bedank ik als eerste alle deelnemers van het Lifelines Cohort, de deelnemers van de interviews en de deelnemers van de Delphi-studie. Vervolgens gaat ook veel dank uit naar alle projectgroepleden van de Academische Werkplaats Autisme, waar ik met name veel heb kunnen leren van de ervaringsdeskundigen en andere belanghebbenden.

Robert, heel erg bedankt voor de kansen en vrijheid die je me hebt gegeven. Sinds ik bij jou aanklopte als jonge basisarts heb ik kunnen vertrouwen op jouw prettige en kundige begeleiding. Door jou is mijn carrière als arts en onderzoeker vliegend van start gegaan.

Wietske, heel veel dank voor je tomeloze aanmoediging en vertrouwen, wat mij meermaals extra motivatie heeft gegeven om onze gezamenlijke doelen en ambities te behalen.

Laura, enorm bedankt voor jouw altijd opbouwende feedback en fijne sturing, waar ik op heb kunnen bouwen en wat mij inspiratie gaf om mijn PhD traject naar eigen inzicht vorm te geven.

Graag wil ik een aantal onderzoekers extra bedanken voor hun expertise en relevante bijdrages aan de totstandbrenging van de studies in dit proefschrift: Mary Beth Terry en Susan Lloyd van Columbia University, Liesbeth van Rossum en Pieter Leenen van het Erasmus MC, Hilde Geurts van de Universiteit van Amsterdam, en Wijbrand Hoek van Parnassia.

Lieve Rianne en Chanel, onze band is als vanzelf ontstaan tijdens het thuiswerken in onze stad Amsterdam en is al snel uitgegroeid tot een vriendschap waar ik heel trots op ben. Jullie hebben mij meer gebracht dan alleen een mooie PhD-tijd: ik kan voortaan zowel binnen als buiten kantoortijden alles met jullie delen, waar ik jullie heel dankbaar voor ben.

Collega's van de Curium onderzoeksgroep, heel erg bedankt voor jullie enthousiasme en gezelligheid afgelopen jaren. Ondanks de lockdowns hebben we toch als hechte collega's kunnen samenwerken, wat heel waardevol was tijdens het schrijven van onze proefschriften.

Uiteraard wil ik ook alle LUMC en Curium A(N)IOS-collega's bedanken voor jullie support en vooral humor op de werkvloer, waardoor ik tijdens het afgelopen 1e jaar van mijn opleiding tot psychiater dit proefschrift met plezier heb kunnen afronden.

Lieve Annelies, Lalitha, Anne, Yasmin, Roos, Nina, we zijn begonnen als dispuutsgenoten, maar nu zijn jullie zonder twijfel mijn beste vriendinnen. Ik wil jullie bedanken voor wat jullie voor mij betekenen: ik kan bij jullie altijd terecht en mezelf zijn.

Lieve papa en mama, jullie zijn mijn belangrijke en liefdevolle thuisbasis. Met jullie steun jaag ik mijn ambities na, wat onder meer heeft geleid tot dit proefschrift. Lieve Marloes en Daan, mijn kleine zusje en broertje, ik ben heel erg trots op jullie.

Schoonfamilie Wouters en Frijns, ik voel me ook door jullie altijd gesteund, ik ben dankbaar voor jullie warme welkom in de familie.

Lieve Roel, het staat buiten kijf dat wij elkaar versterken als academici en psychiaters in spé. Jij hebt mij geïnspireerd om deze promotie te doen en altijd aangemoedigd om het beste uit mezelf te halen. Ons samenzijn brengt mij iedere dag iets waardevols in mijn ontwikkeling als mens, arts en onderzoeker. Hierdoor heb ik dit proefschrift kunnen schrijven op mijn eigen manier. In mijn PhD-tijd hebben we de start gemaakt van onze opgedeelde wereldreis, die we de rest van ons leven zullen voortzetten. Dit proefschrift is één van de vele bekroningen op onze relatie.

Curriculum vitae

Eva Britt Warreman was born on February 14th, 1995, in Woerden, the Netherlands. She was raised in Alphen aan den Rijn, where she completed her secondary education (Gymnasium) at the *Groene Hart Lyceum* in 2012. In the last two years of high school, she participated in an extracurricular program, Pre-University College at the Leiden University, during which she got inspired to study Medicine.

In 2012, she started Medical School at the Leiden University Medical Center (LUMC). At the beginning of her Masters, she wanted to gain more research experience. Therefore, she first helped to build a scientific database at the Department of Infectious Diseases at the LUMC, and she co-authored on the corresponding scientific articles. During her Masters, she did her elective clinical internships at the Departments of Pediatrics and Child and Adolescent Psychiatry.

After her graduation from medical school in 2019, she combined clinical work with research at LUMC Curium. Her clinical work in the Department of Child and Adolescent Psychiatry took place at the High Intensive Care department and the inpatient clinic for adolescents with autism spectrum disorder. In this clinical work, she often encountered autistic patients with somatic problems, which motivated her to perform more research on this topic. Therefore, in 2020, she joined the Dutch *Academische Werkplaats Autisme* as a junior-researcher. Next, in 2020, she worked as a full-time PhD candidate at LUMC Curium. Since April 2023, she is a resident in psychiatry at the LUMC. Recently, she was selected to join the 2024 American Psychiatric Association Research Colloquium.

Publications

In this dissertation

Warreman, E. B., Nooteboom, L. A., Leenen, P. J. M., Geurts, H. M., Terry, M. B., Bos, J. H. J., Hak, E., Hoek, H. W., van Rossum, E. F. C., Vermeiren, R. R. J. M., & Ester, W. A. (2023). Metabolic syndrome in adults with autistic traits: associated psychological, behavioral, and biological factors in females and males - a PharmLines initiative. Frontiers in psychiatry, 14, 1303840. https://doi.org/10.3389/fpsyt.2023.1303840

Warreman, E. B., Lloyd, S. E., Nooteboom, L. A., Leenen, P. J. M., Terry, M. B., Hoek, H. W., van Rossum, E. F. C., Vermeiren, R. R. J. M., & Ester, W. A. (2023). Psychological, behavioural, and physical aspects of caregiver strain in autism-caregivers: a cohort study. EClinicalMedicine, 64, 102211. https://doi.org/10.1016/j.eclinm.2023.102211

Warreman, E. B., Ester, W. A., Geurts, H. M., Vermeiren, R. R., & Nooteboom, L. A. (2024). How do primary care providers and autistic adults want to improve their primary care? A Delphi-study. Autism: the international journal of research and practice, 28(2), 449–460. https://doi.org/10.1177/13623613231172865

Warreman, E. B., Nooteboom, L. A., Terry, M. B., Hoek, H. W., Leenen, P., van Rossum, E., Ramlal, D., Vermeiren, R., & Ester, W. A. (2023). Psychological, behavioural and biological factors associated with gastrointestinal symptoms in autistic adults and adults with autistic traits. Autism: the international journal of research and practice, 27(7), 2173–2186. https://doi.org/10.1177/13623613231155324

Other publications

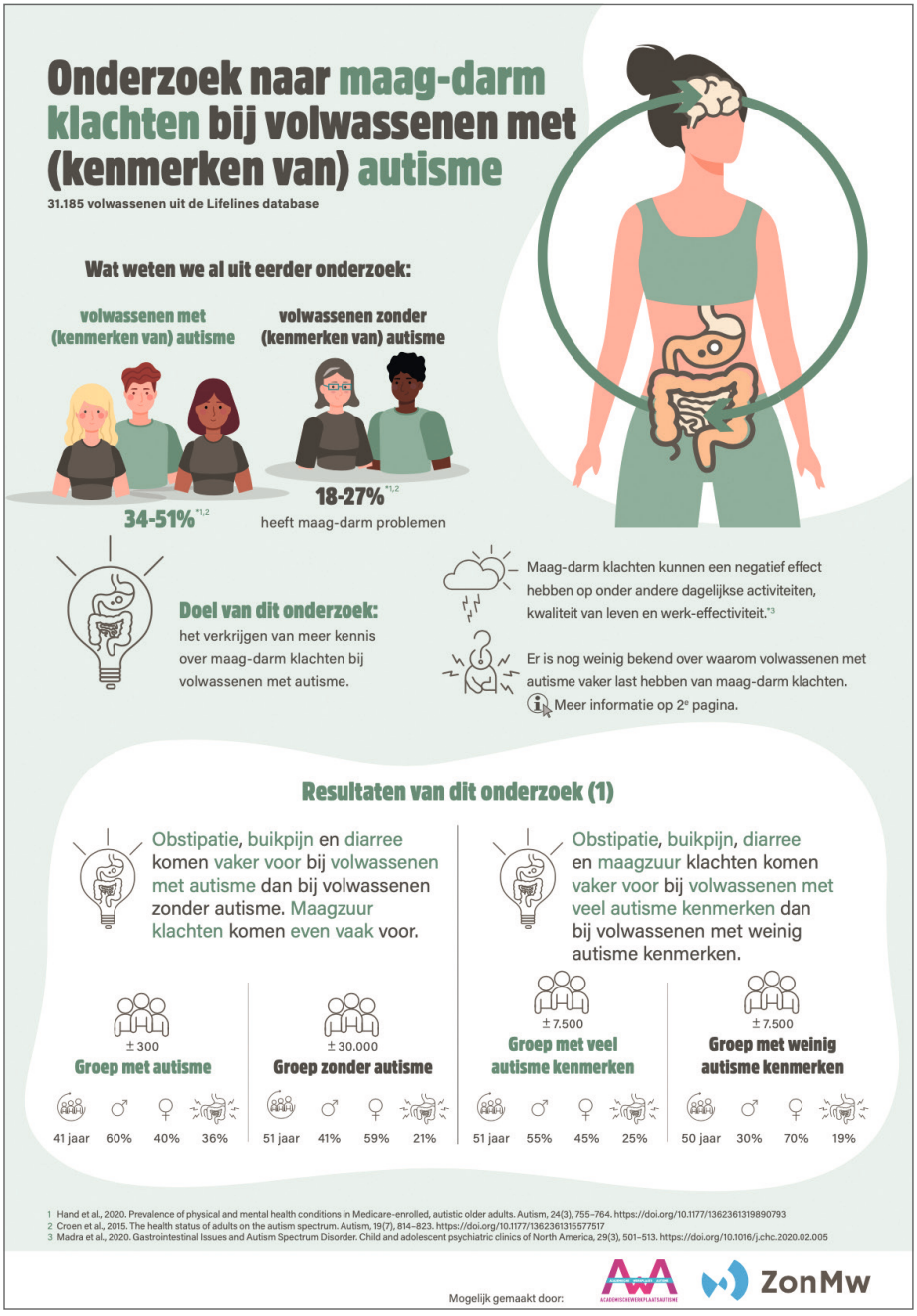
Warreman, E. B., Ester, W. A. Geurts, H. M., Meuleman, A., Konz, D., Teunisse, S., Nooteboom, L. A., (2023). Welke verbeterpunten liggen er voor de huisartsenzorg bij autisme? Huisarts & Wetenschap, 4 October 2023, page 1-5.

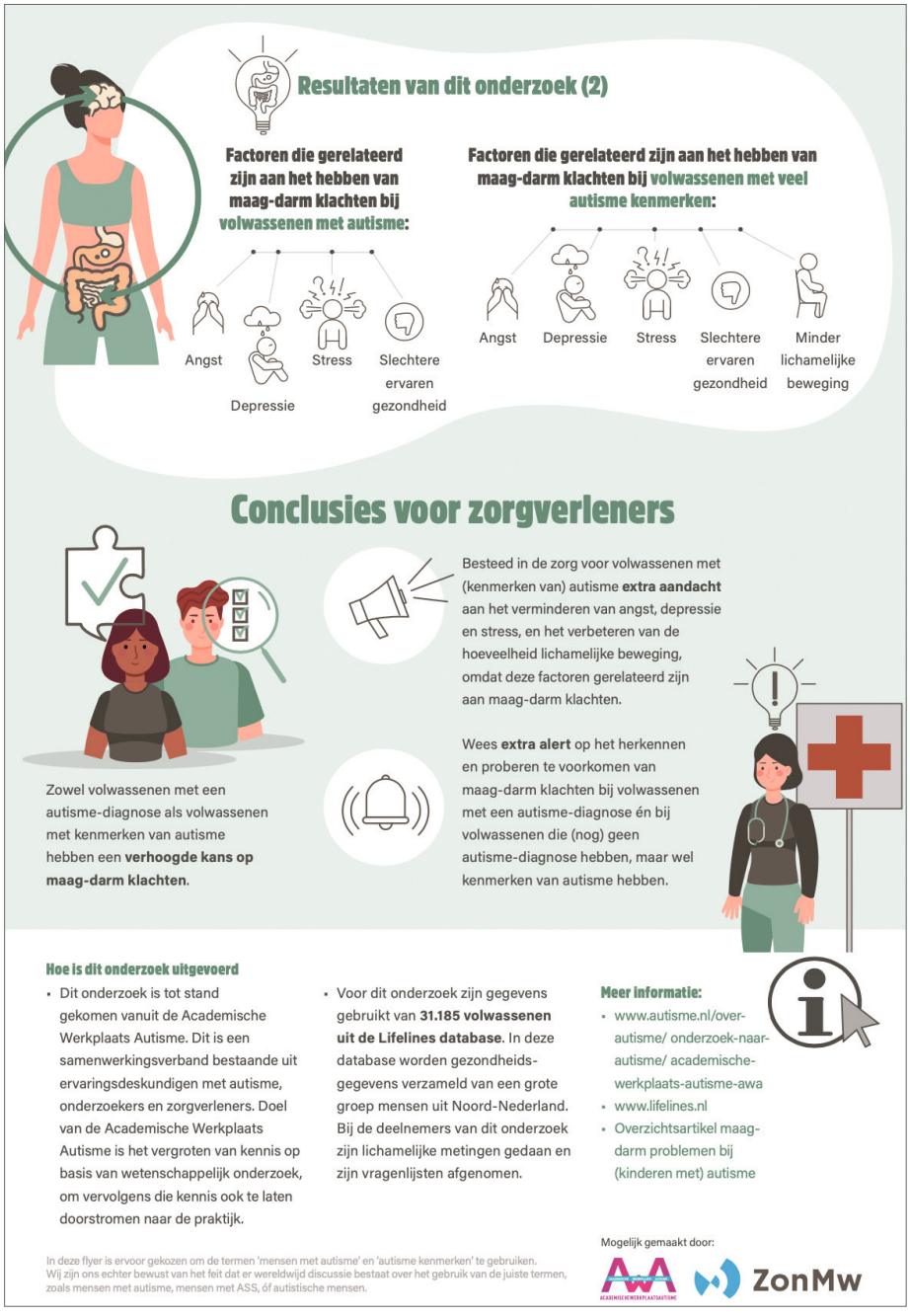
Warreman, E. B., Lambregts, M. M. C., Wouters, R. H. P., Visser, L. G., Staats, H., van Dijk, E., & de Boer, M. G. J. (2019). Determinants of in-hospital antibiotic prescription behaviour: a systematic review and formation of a comprehensive framework. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 25(5), 538–545. https://doi.org/10.1016/j.cmi.2018.09.006

Lambregts, M. M. C., Warreman, E. B., Bernards, A. T., Veelken, H., von dem Borne, P. A., Dekkers, O. M., Visser, L. G., & de Boer, M. G. (2018). Distribution and clinical determinants of time-to-positivity of blood cultures in patients with neutropenia. European journal of haematology, 100(2), 206–214. https://doi.org/10.1111/ejh.13001

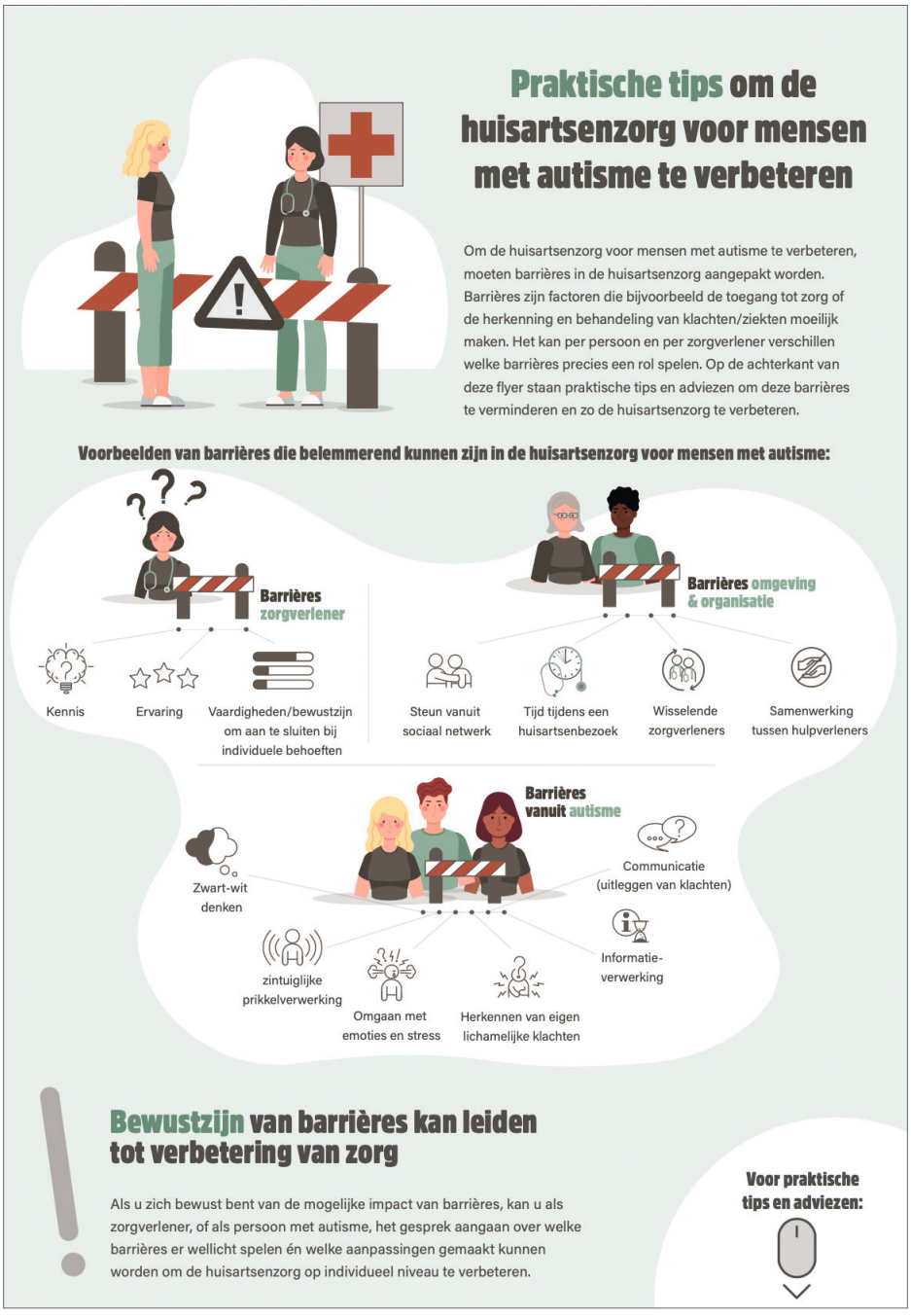
Appendix

Flyer AWA-projectgroep over resultaten van ons Lifelines onderzoek naar maag-darmklachten




Resultaten van dit onderzoek (2)
Factoren die gerelateerd zijn aan het hebben van maag-darm klachten bij volwassenen met autisme:
Angst
Depressie
Stress
Slechtere ervaren gezondheid
Factoren die gerelateerd zijn aan het hebben van maag-darm klachten bij volwassenen met veel autisme kenmerken:
Angst
Depressie
Stress
Slechtere ervaren gezondheid
Minder lichamelijke beweging
Conclusies voor zorgverleners
Zowel volwassenen met een autisme-diagnose als volwassenen met kenmerken van autisme hebben een verhoogde kans op maag-darm klachten.
Besteed in de zorg voor volwassenen met (kenmerken van) autisme extra aandacht aan het verminderen van angst, depressie en stress, en het verbeteren van de hoeveelheid lichamelijke beweging, omdat deze factoren gerelateerd zijn aan maag-darm klachten.
Wees extra alert op het herkennen en proberen te voorkomen van maag-darm klachten bij volwassenen met een autisme-diagnose én bij volwassenen die (nog) geen autisme-diagnose hebben, maar wel kenmerken van autisme hebben.
Hoe is dit onderzoek uitgevoerd
Dit onderzoek is tot stand gekomen vanuit de Academische Werkplaats Autisme. Dit is een samenwerkingsverband bestaande uit ervaringsdeskundigen met autisme, onderzoekers en zorgverleners. Doel van de Academische Werkplaats Autisme is het vergroten van kennis op basis van wetenschappelijk onderzoek, om vervolgens die kennis ook te laten doorstromen naar de praktijk.
Voor dit onderzoek zijn gegevens gebruikt van 31.185 volwassenen uit de Lifelines database. In deze database worden gezondheids-gegevens verzameld van een grote groep mensen uit Noord-Nederland. Bij de deelnemers van dit onderzoek zijn lichamelijke metingen gedaan en zijn vragenlijsten afgenomen.
Meer informatie:
www.autisme.nl/over-autisme/ onderzoek-naar-autisme/ academische-werkplaats-autisme-awa
www.lifelines.nl
Overzichtsartikel maag-darm problemen bij (kinderen met) autisme
In deze flyer is ervoor gekozen om de termen 'mensen met autisme' en 'autisme kenmerken' te gebruiken. Wij zijn ons echter bewust van het feit dat er wereldwijd discussie bestaat over het gebruik van de juiste termen, zoals mensen met autisme, mensen met ASS, óf autistische mensen.
Mogelijk gemaakt door:
ZonMw

Flyer AWA-projectgroep over resultaten van de Delphi-studie over huisartsenzorg



De praktische tips en adviezen die nu volgen, kunnen eraan bijdragen dat barrières verminderen en dat de huisartsenzorg voor mensen met autisme verbetert.

Praktische tips en adviezen voor huisartsen en praktijkondersteuners (POH)

Ga als zorgverlener het gesprek aan en bespreek samen met de persoon met autisme welke barrières mogelijk een rol spelen en hoe hier beter op ingespeeld kan worden.

Tips: Bespreek samen welke adviezen op deze flyer helpend zijn om de huisartsenzorg te verbeteren.

Vergroot uw kennis over autisme en over vaak voorkomende lichamelijke klachten bij autisme.

Tips: Promoot dit onderwerp als nascholingsthema. Nodig een ervaringsdeskundige uit voor een gastles. Agendeer dit onderwerp tijdens bestaande praktijkbijeenkomsten.

Vergroot uw kennis over doorverwijs-mogelijkheden naar verschillende vormen van hulp: voor mensen met autisme kan het helpend zijn om begeleiding te krijgen van bijv. een autisme- of levensloopcoach (via de gemeente).

Tips: Neem contact op met een regionaal autisme netwerk voor meer informatie over doorverwijsmogelijkheden.

Verbeter de informatie op uw praktijk-website: zo zijn mensen met autisme beter voorbereid.

Tips: Het helpt mensen met autisme om te weten hoe de praktijk eruitziet en wie de medewerkers zijn, dus zet naast foto's en functies van medewerkers ook foto's/filmpjes van praktijkruimten op de website.

Probeer mensen met autisme zoveel mogelijk bij dezelfde zorgverleners in te plannen: continuïteit in zorgverlening is extra belangrijk voor mensen met autisme.

Tips: Maak afspraken over welke zorgverlener het aanspreekpunt is. Maak een melding/pop-up in het dossier over de aanwezigheid van een ASS-diagnose en de individuele afspraken over continuïteit in de zorgverlening.

Probeer een dubbele afspraak in te plannen: mensen met autisme hebben soms meer tijd nodig om hun klachten toe te lichten of hebben meer verwerkingstijd nodig.

Tips: Niet iedereen heeft altijd een dubbele afspraak nodig, dus bespreek per persoon wat helpend is. Wellicht is het juist helpend om na een afspraak met de huisarts een aansluitende afspraak met een POH in te plannen voor extra vragen of uitleg.

Betrek het steunsysteem: een persoon uit het steunsysteem kan bijvoorbeeld helpen bij het verduidelijken van de klachten of behoeften van de persoon met autisme.

Tips: Overleg met de persoon met autisme over toestemming voor en wenselijkheid van het betrekken van iemand uit het steunsysteem. Als niemand uit het steunsysteem beschikbaar is, overweeg het betrekken van een POH ter begeleiding.

Praktische tips en adviezen voor mensen met (kenmerken van) autisme

Als u het moeilijk vindt om uit te leggen wat uw klachten zijn, probeer dit voor te bereiden.

Tips: Denk aan het opschrijven van uw klachten/vragen, evt. met een voorbereidende vragenlijst (bijv. fann-autisme.nl/informatie/producten) of met hulp van iemand uit uw steunsysteem.

Kijk op de website van uw huisartsenpraktijk, ter voorbereiding op een afspraak, om op te zoeken welke zorgverleners er werken en hoe de praktijk er uit ziet.

Tips: Als deze informatie niet op de website staat, vraag dan bijv. een rondleiding in de huisartsenpraktijk.

Geef bij uw huisarts aan dat het belangrijk is om afspraken zoveel mogelijk bij dezelfde zorgverleners (huisarts en POH) in te plannen.

Tips: Vraag welke huisarts en/of POH uw aanspreekpunt is.

Vraag of u een dubbele afspraak kunt krijgen, als u bijv. extra tijd nodig heeft om uw klachten uit te leggen.

Tips: Overweeg het stellen van aanvullende vragen aan uw huisarts per mail of het plannen van een aansluitende afspraak bij de POH (ter nabespreking).

Overweeg een familielid of steunend persoon mee te nemen naar een huisartsenafspraak.

Tips: Bespreek uw huisartsenafspraak voor of na met een steunend persoon. Als u geen steunend persoon heeft, vraag dan aan de POH of huisarts of het mogelijk is extra begeleiding te krijgen van de POH rondom huisartsenafspraken.

Ga met uw huisarts in gesprek over wat u nodig heeft voor een beter bezoek aan de huisarts.

Tips: Geef aan welke kenmerken van autisme bij u een rol spelen bij een huisartsenbezoek. Denk bijv. aan prikkelverwerking, verwerkingstijd, of een bepaald tijdstip waarop de wachtkamer rustiger is. Als het moeilijk is om dit te bespreken: geef deze flyer aan uw huisarts/POH en probeer samen te bedenken welke tips op deze flyer uw huisartsenzorg kunnen verbeteren.

Links voor meer informatie:

- autisme.nl/over-autisme/onderzoek-naar-autisme/academische-werkplaats-autisme-awa
- autismenetwerkennederland.nl
- fann-autisme.nl/informatie/producten
- Flyer over gezondheidszorg voor vrouwen met autisme
- wegwijzer-autisme.nl
- kenniscentrumphrenos.nl/document/een-diagnose-autismeen-dan
- Communicatie met mensen met autisme
- Wetenschappelijk artikel waarop deze flyer is gebaseerd

Mogelijk gemaakt door: AA Academische Werkplaats Autisme, ZonMw

In deze flyer is ervoor gekozen om de termen 'mensen/persoon met autisme' te gebruiken. Wij zijn ons echter bewust van het feit dat er wereldwijd discussie bestaat over het gebruik van de juiste termen, zoals mensen met autisme, mensen met ASS, óf autistische mensen.