Running Head: HEALTH OF OLDER ADULTS WITH AUTISTIC RELATIVES

The mental and physical health of older adults with a genetic predisposition for autism

Running title: Health of older adults with autistic relatives

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Lay summary

Children and adults with an autistic relative have been found to experience more psychiatric difficulties than those with no family links to autism. However, few studies have explored what happens when these individuals get older. Examining over 20,000 adults age 50+, we found that older adults with an autistic relative experienced elevated rates of most psychiatric conditions, but not physical conditions. Older adults with autistic relatives may benefit from close monitoring to mitigate this susceptibility and to provide timely intervention.

Keywords

Autism, ASD, Broad Autism Phenotype, BAP, Older Adults, Aging, Psychiatric conditions, Mental Health, Physical Health

Abstract

Autism commonly aggregates in families, with twin studies estimating heritability to be around 80%. Subclinical autism-like characteristics have also been found at elevated rates in relatives of autistic probands. Physical and psychiatric conditions have been reported at elevated rates in autistic children and adults, and also in their relatives. However, to date there has been no exploration of how ageing may affect this pattern. This study examined cross-sectional data from the ongoing online PROTECT study. A total of 20,220 adults aged 50 years and older reported whether they have an autistic first-degree relative. In total, 739 older adults reported having an autistic first-degree relative (AFDR group) and 11,666 were identified as having no family history of any neurodevelopmental disorder (NFD group). The AFDR group demonstrated significantly higher frequencies of self-reported psychiatric diagnoses and a

greater total number of co-occurring psychiatric diagnoses than the NFD group. Furthermore, the AFDR group reported elevated current self-report symptoms of depression, anxiety, traumatic experience, and post-traumatic stress than the NFD group. By contrast, few differences between AFDR and NFD groups were observed in physical health conditions, and no differences were observed in the total number of co-occurring physical health diagnoses. These findings suggest that adults who have an autistic first-degree relative may be at greater risk of poor mental, but not physical, health in later life. Older adults with autistic relatives may benefit from close monitoring to mitigate this susceptibility and to provide timely intervention.

INTRODUCTION

Autism is a set of lifelong heterogenous neurodevelopmental conditions characterised by early onset social communication and interaction impairments, with rigid or repetitive behaviours and interests (DSM-5; American Psychiatric Association, 2013). Autism affects approximately 1% of the population and has been found to have a strong genetic component, commonly aggregating in families (Lai, Lombardo, & Baron-Cohen, 2014; Sandin et al., 2014). Twin studies have estimated the proportion of the phenotypic variance due to genetic factors of autism to be approximately 80-90% (Colvert et al., 2015; Sandin et al., 2017). However, the aetiology of autism is complex and likely the result of large numbers of genetic variants in combination with non-genetic factors (Happé, Ronald, & Plomin, 2006). Due to this complex interaction of genetic and non-genetic factors, autism and other psychiatric disorders likely result from common influences and vary in expression depending on individual differences (Caspi & Moffitt, 2018). These common influences have been described as the p-factor, a general latent dimension that describes the overlap and interrelatedness of psychopathology, and the proclivity of experiencing co-occurring conditions (Ronald, 2019). While autism has not been included in the p-factor model to date, the high comorbidity observed with psychiatric conditions among autistic populations and those with autistic relatives does suggest a general susceptibility for psychiatric difficulties (Croen et al., 2015; Daniels et al., 2008; Hand, Angell, Harris, & Carpenter, 2019; Jokiranta et al., 2013; Lever & Geurts, 2016).

Autism has been conceptualised as part of a spectrum from typical to atypical levels of autistic traits, and this dimensional approach is supported by genetic studies (Robinson et al., 2011). Characteristics similar to the defining features of autism but at a subclinical level have been found in relatives of autistic individuals (Bolton et al., 1994; Constantino & Todd, 2003; Losh & Piven, 2007; Sandin et al., 2014), referred to as the 'broad autism phenotype' (BAP). Clinical

and population-based studies have demonstrated that psychiatric difficulties and elevated comorbidity of psychiatric conditions commonly experienced by autistic individuals are also often reported by their non-autistic relatives and those with the BAP. These studies have found an increased prevalence of almost all psychiatric conditions, including both common diagnoses (e.g. major depressive disorder and anxiety disorders) and rarer diagnoses (e.g. schizophrenia and personality disorders), in BAP groups (Bölte, Knecht, & Poustka, 2007; Daniels et al., 2008; Hodge, Hoffman, & Sweeney, 2011; Jokiranta et al., 2013; Larsson et al., 2005; Miller et al., 2019; Yirmiya & Shaked, 2005). Adults with autistic relatives also report higher symptom levels on mood and anxiety scales and a higher rate of suicidal behaviours compared to those without an autistic relative (Hastings et al., 2005; Hirvikoski et al., 2019; Meltzer, 2011). In contrast, prevalence rates of substance abuse or dependency have been mixed, with some studies documenting elevated rates (Jokiranta et al., 2013), while others report no differences between adults with and without an autistic relative (Daniels et al., 2008). Increased rates of environmental stressors have also been reported by relatives of autistic individuals, with elevated rates of caregiving responsibilities and stress being reported by parents (in particular mothers) of autistic children (Tehee, Honan, & Hevey, 2009). This influence of caregiver stress has also been found to extend to those with an autistic sibling, who have been reported to feel responsible for their sibling's future (Moss, Eirinaki, Savage, & Howlin, 2018). These studies have predominately consisted of young or middle-aged adults, with little exploration of older adult outcomes. While the patterns of psychiatric difficulties in adults with an autistic relative are convergent with the patterns observed in autistic populations, psychiatric symptoms wax and wane across the lifespan. Therefore, it is unknown whether this genetic susceptibility for poor mental health extends into older age for adults with an autistic relative as it has been found to in autistic populations (Bishop-Fitzpatrick & Rubenstein, 2019; Croen et al., 2015; Hand et al., 2019; Lever & Geurts, 2016).

While mental health has been explored in several studies, to the authors' knowledge, no studies have explored physical health in BAP populations of any age range. Among autistic adult populations, most physical conditions have been found to be elevated compared to non-autistic adults, including cardiovascular disease, metabolic disorders, endocrine and immune conditions, gastrointestinal disorders, sleep disorders, and neurological conditions (Bishop-Fitzpatrick & Rubenstein, 2019; Croen et al., 2015; Davignon, Qian, Massolo, & Croen, 2018; Hand et al., 2019; Starkstein, Gellar, Parlier, Payne, & Piven, 2015). Autistic adults have also been found to experience elevated co- or multi-morbidity of physical conditions, increasing the need for hospitalisation and major medical treatments, such as surgery (Jones et al., 2016). Early mortality rates have also been documented, with cardiovascular disease and neurological conditions such as epilepsy being two leading causes of death in autistic populations (Akobirshoev, Mitra, Dembo, & Lauer, 2019; Bilder et al., 2013; Gillberg, Billstedt, Sundh, & Gillberg, 2010; Hirvikoski et al., 2016; Mouridsen, Brønnum-Hansen, Rich, & Isager, 2008). As the pattern of psychiatric difficulties in adults with an autistic relative is convergent with the difficulties observed in autistic populations, the elevated rates of physical conditions in the latter may also extend to BAP groups. Additionally, as physical health problems become more common in older age, it is important to know whether older adults with an autistic relative are susceptible to poorer health outcomes than those without an autistic relative. As the health profile of older adults who have an autistic relative is currently unknown, a better understanding of health in older age is needed to provide adequate support for those susceptible for poorer outcomes, which may include those with an autistic relative (Happé & Charlton, 2011; Howlin & Taylor, 2015; Perkins & Berkman, 2012). Given the limited literature on ageing and autism, examining the profile of health difficulties in older adults who share some

genetic factors with their autistic relatives may provide insight or generate hypotheses that could be extended to aging in autistic populations.

The current study investigates the health profile of adults aged 50 years and older who have a an autistic first-degree relative, and compares this to self-reported mental and physical health of older adults without an autistic (or other genetically influenced/neurodevelopmental condition) relative. It is hypothesized that older adults with an autistic relative will (1) report more psychiatric diagnoses, (2) report elevated and above clinical cut-off symptoms of psychiatric difficulties currently, and (3) report more physical diagnoses, when compared to a group without an autistic relative due to genetic and environmental influences. Furthermore, to examine possible environmental stressors of being a caregiver, additional comparisons will also be made with those who have a relative with general intellectual impairment but not autism. It is hypothesized that (4) both the autistic and intellectual impairment relative groups will experience elevated health problems when compared to the control group. However, (5) due to a genetic predisposition for psychiatric health problems associated with the autism spectrum, those with an autistic relative are hypothesized to experience more psychiatric health problems than those with a relative with intellectual impairment.

METHODS

Study Design and Participants

This study uses cross-sectional data from the PROTECT study (www.protectstudy.org.uk), an ongoing longitudinal study examining how cognitive functioning and health changes as we age. Inclusion criteria for the PROTECT study are: adults over the age of 50 years, who live in the UK, have a good working understanding of English, and can use a computer with internet access. Participants who have an established diagnosis of dementia are excluded. Participants are required to review the study information sheet and to provide consent via an approved online platform. The PROTECT study received ethical approval from the UK London Bridge National Research Ethics Committee (Ref: 13/LO/1578).

From a total sample of 20,220 participants who responded to the family health diagnoses section, 753 responded "yes" to whether they have any first-degree relatives with a diagnosis of autism. Due to autism and attention-deficit hyperactivity disorder (ADHD) sharing common genetic variants and diagnostic overlap (Nylander, Holmqvist, Gustafson, & Gillberg, 2013; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), those with their own diagnosis of autism or ADHD were excluded (n=14), resulting in 739 individuals forming the Autistic First-Degree Relative (AFDR) group. To form a comparison group from the remaining 19,467 participants who do not report having an autistic first-degree relative, additional participants were excluded from the current analysis for having an existing diagnosis of autism or ADHD (n=21) or a first-degree relative with a neurodevelopmental disorder with known genetic overlap with autism (n=5,482), namely ADHD, obsessive compulsive disorder, personality disorders, bipolar disorder, or psychotic disorders. To match the AFDR and control group on mean age and gender ratio a further 2,079 participants were excluded using random case sampling to balance group age distributions and gender ratio, resulting in a total of 11,666

participants forming a No Family Diagnoses (NFD) control group. See Table 1 for demographic information.

To ensure the excluded individuals did not alter the characteristics of the NFD control group, analyses were reconducted including these excluded samples (i.e. those randomly excluded to match on age/gender, n = 2,079; or those excluded due to a family history of other disorders, n = 5,482). A similar pattern of results was observed; therefore, the results reported henceforth are with AFDR and NFD groups as described above.

To examine the possible influence of environmental stressors from providing care to a family member with additional needs, an additional group was created of individuals who reported having a first-degree relative with intellectual impairment (but not autism). This condition was selected due to intellectual impairment having little genetic overlap with autism (Hoekstra, Happé, Baron-Cohen, & Ronald, 2009). Those with a first-degree relative with intellectual impairment formed the General Intellectual Impairment Relatives (GIIR) group (n=219). While the GIIR group was matched on age with the AFDR and NFD groups, due to the smaller sample size, it was not feasible to match the GIIR group on gender, resulting in a higher proportion of males than in the matched AFDR and NFD groups (26% vs. 17%). See Supplementary Table 1 for GIIR demographic information.

TABLE 1 / DEMOGRAPHICS TABLE HERE

Measures

Demographic information - Participants completed an online demographic information questionnaire, including age, gender, marital status, education history, and employment status.

Self-report medical history – Participants reported whether they have ever received a diagnosis of a variety of psychiatric and physical conditions. See Table 2 for full details of psychiatric conditions and Table 5 for full details of physical conditions.

Self-rated questionnaire measures – The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer and Williams, 2001) was used to assess the presence of recent depressive symptoms. Scores are totalled, with ≤4 indicating low symptoms, 5-9 mild, 10-14 moderate, 15-19 moderately severe, and 20-27 severe. Using a cut-off score of ≥10, the PHQ-9 has a sensitivity of 88% and a specificity of 88% for major depressive disorder. The PHQ-9 is reported to have excellent internal consistency (Cronbach's *a*=.89). In the current study, a good to acceptable internal consistency is found (Cronbach's *a* NFD = .77; GIIR = .77; AFDR = .84).

The Generalised Anxiety Disorder Assessment (GAD-7; Spitzer et al., 2006) was used to assess the presence of recent anxiety symptoms. The GAD-7 has seven items asking the participant to report whether they have been bothered by a range of problems over the past two weeks. Scores are totalled, with ≤5 indicating low symptoms, 5-9 mild, 10-14 moderate, 14-21 severe. Using a cut-off score of ≥10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for generalised anxiety disorder. It is moderately good at screening other common anxiety disorders, such as panic disorder (sensitivity 74%, specificity 81%) and social anxiety disorder (sensitivity 72%, specificity 80%). The GAD-7 is reported to have excellent internal

consistency (Cronbach's *a*=.92). In the current study, an excellent to good internal consistency is found (Cronbach's *a* NFD = .87; GIIR = .77; AFDR = .90).

The Post-Traumatic Stress Disorder Checklist (PCL-5; Wilkins, Lang, & Norman, 2011) was used to assess the experience of post-traumatic stress symptoms. The PCL-5 has five items, which ask the participant to report whether they have been bothered by a range of problems over the past month. Scores are totalled, with higher scores indicating greater post-traumatic stress symptoms. A cut-off of ≥10 was used to identify those who had experienced probable symptomatic post-traumatic stress disorder. The PCL-5 is reported to have good internal consistency (Cronbach's *a*=.75). In the current study, a good internal consistency is found (Cronbach's *a* NFD = .82; GIIR = .83; AFDR = .85).

The Childhood Trauma Screener (CTS-5; Grabe et al., 2012) was used to assess the retrospective experience of sexual abuse and emotional and physical abuse or neglect. The CTS-5 has five items asking the participant to report the frequency of a type of abuse or neglect during childhood. Scores are totalled, with higher scores indicating greater abuse or neglect. A cut-off score of ≥10 was used to identify those who had experienced at least moderate abuse or neglect. The CTS-5 is reported to have good internal consistency (Cronbach's *a*=.76). In the current study, a good internal consistency is found (Cronbach's *a* NFD = .72; GIIR = .74; AFDR = .76).

The Adult Trauma Screener (ATS-5; Khalifeh et al., 2015) was used to assess the experience of sexual, emotional and physical abuse or neglect from a partner during adulthood. The ATS-5 was designed to share its psychometric properties with the CTS-5. A cut-off score of ≥10 was used to identify those who had experienced moderate or more severe abuse or neglect. The

internal consistency of the ATS-5 was not reported in the original article. In the current study, an acceptable internal consistency is found (Cronbach's *a* NFD = .64; GIIR = .67; AFDR = .64).

Statistical Analyses

All statistical analyses were performed using SPSS (version 25.0; IBM Corp., 2017). Variables of interest were examined for distribution and normality and conform to assumptions required for parametric analyses (Fagerland, 2012). Group differences in demographic variables were analysed using analysis of variance (ANOVA) and Chi-square (χ^2). Differences in frequency of individual and total diagnoses of psychiatric and physical health conditions were evaluated using χ^2. ANOVA was also used to evaluate differences in self-rated questionnaire measures, with χ^2 being used to evaluate differences in frequency of participants reporting above cut-off levels of questionnaire symptoms. These analyses were rerun using multivariate analysis of variance (MANOVA) and χ^2 with gender entered as a dependent variable to explore gender differences. Multiple comparisons were controlled for using the False Discovery Rate (Benjamini & Hochberg, 1995), with an alpha of 0.05 being used.

RESULTS

Demographics

Table 1 shows full demographic characteristics for the participants. Age, gender ratio and education history did not differ between the AFDR and NFD groups. Group differences were observed in marital status and employment status: the AFDR were more often divorced or separated, and more often unemployment.

Gender differences were observed for age, marital status, education history, and employment status. For marital status, females were more often divorced or widowed while males were more often married. For education history, males more often had postgraduate degrees while females more often had undergraduate degrees. For employment status, males were more often employed, while females were more often retired.

The only significant interaction of group (AFDR vs. NFD) with gender was for age, with males in the NFD group being older than males in the AFDR group, $F(1,12404)=16.31$, $p<.001$.

Self-reported psychiatric diagnoses

The AFDR group reported significantly higher rates of all psychiatric diagnoses than those in the NFD group, with the exception of schizophrenia which showed no group difference. See Table 2 for full details of psychiatric diagnoses frequencies.

Co-occurring conditions

The AFDR group reported a significantly higher total number of co-occurring psychiatric diagnoses than those in the NFD group. See Table 2.

Age was found to be negatively associated with the total number of co-occurring mental health conditions in both the AFDR (r=-.15, p<.001) and the NFD groups (r=-.04, p<.001).

Gender differences in psychiatric conditions

In the whole sample, some significant differences by gender were observed. More females than males reported diagnoses of major depressive disorder (26.7% vs. 18.0%), generalised anxiety disorder (14.5% vs. 10.0%), panic attacks (5.1% vs. 3.3%), anorexia nervosa (0.9% vs. 0.1%), bulimia nervosa (0.6% vs. no cases) and binge eating (0.5% vs. 0.2%), $\chi 2$s=4.41-72.01, ps=<.001-.036. By contact, more males than females reported diagnoses of social anxiety (1.5% vs. 1.0%) and OCD (0.8% vs. 0.3%), $\chi 2$s=4.82-7.80, ps=.005-.028.

Furthermore, females reported a higher total number of psychiatric conditions than males, $\chi 2$=99.03, p<.001. No interaction of group (AFDR vs. NFD) with gender was observed.

TABLE 2 / MENTAL HEALTH CONDITIONS TABLE HERE

Self-report questionnaires

The AFDR group reported significantly more symptoms of recent/current depression, anxiety, and post-traumatic stress than individuals in the NFD group. Additionally, the AFDR group reported significantly more childhood and adulthood traumatic experiences than individuals in the NFD group. See Table 3 for self-report questionnaire summary.

Gender differences

Within the whole sample, a difference in gender was observed, with females reporting more adult traumatic experiences than males.

The only significant interaction of group (AFDR vs. NFD) with gender was also in adulthood traumatic experience, with females in the AFDR group reporting more experiences compared to females in the NFD group, while males did not differ by group. See Figure 1 for interaction graph.

TABLE 3 / SELF-REPORT QUESTIONNAIRE TABLE HERE

FIGURE 1 / INTERACTION GRAPH HERE

Self-report questionnaires (cut-offs)

When using questionnaire cut-off scores to identify those with probable clinical symptoms, more individuals in the AFDR group were above cut-off levels for recent/current depression, anxiety, and post-traumatic stress than in the NFD groups. Additionally, more individuals in the AFDR group were above cut-off levels of both childhood and adulthood traumatic experience than in the NFD group. See Table 4 for self-report questionnaire cut-off summary.

Gender differences

Within the whole sample, some differences in gender are observed. More females than males reported above cut-off levels of childhood traumatic experience (1.8% vs. 0.7%) and adulthood traumatic experience (1.8% vs. 0.7%), $\chi 2$s=13.16-59.06, *p*s<.001.

No interactions of group (AFDR vs. NFD) with gender were observed in relation to any cut-off score.

TABLE 4 / QUESTIONNAIRE CUT-OFF TABLE HERE

Self-reported physical diagnoses

Few differences were observed between AFDR and NFD groups. The AFDR group reported significantly higher rates of hypothyroidism and hyperthyroidism. No further group differences were observed. See Table 5 for full details of physical diagnoses frequencies.

Co-occurring conditions

No group differences were observed between AFDR and NFD in total number of co-occurring physical health condition diagnoses. See Table 5.

Age was found to be positively associated with the total number of co-occurring physical conditions in both the AFDR (*r*=.21, *p*<.001) and the NFD groups (*r*=.22, *p*<.001).

Gender differences in physical conditions

Within the whole sample, some differences by gender were observed. More males than females reported diagnoses of cardiovascular conditions, such as high blood pressure (29.9.0% vs. 22.0%), heart disease (6.7% vs. 2.7%), diabetes (5.6% vs. 2.9%), and stroke (1.9% vs. 1.1%), $\chi 2$s=8.33-87.87, *p*s=<.001-.004. By contrast, more females than males reported diagnoses of arthritic conditions (4.5% vs. 2.0%), as well as endocrine conditions, such as hypothyroidism (1.9% vs. 0.4%) and hyperthyroidism (0.4% vs. 0.1%), $\chi 2$s=4.92-30.57, *p*s=<.001-.027.

Furthermore, males reported a higher total number of co-occurring physical conditions than females, $\chi 2$=58.01, *p*<.001. No interaction of group (AFDR vs. NFD) with gender was observed.

TABLE 5 / PHYSICAL HEALTH CONDITIONS TABLE HERE

Comparisons with GIIR group

For psychiatric health - some significant group differences were observed between AFDR and GIIR groups in the frequencies of diagnoses. Those in the AFDR group reported more diagnoses of major depressive disorder and generalised anxiety disorder than the GIIR group. Furthermore, no differences in rates were observed between GIIR and NFD groups. For the total number of co-occurring psychiatric conditions, those in the GIIR group reported significantly more diagnoses than the NFD; however, the AFDR group reported significantly more diagnoses than both the NFD and the GIIR group. See Supplementary Table 2 for GIIR psychiatric diagnoses details.

For self-report symptoms – those in the GIIR group reported significantly higher current symptoms of depression and anxiety than the NFD group. Furthermore, the GIIR group also reported more experiences of childhood and adulthood trauma than the NFD group. However, the AFDR group reports more symptoms of depression, anxiety, and post-traumatic stress than the GIIR group, with no differences being observed in traumatic experience. See Supplementary Table 3 for GIIR self-report information.

For above cut-off symptoms – those in the GIIR group reported more above cut-off experiences of trauma than the NFD group; however, no differences are observed in above cut-off rates of depression and anxiety. Few differences were observed between GIIR and AFDR, with higher rates being reported in anxiety by the AFDR group. See Supplementary Table 4 for GIIR cut-off score information.

For physical health diagnoses – few differences were observed. Those in the NFD group reported more diagnoses of hypothyroidism than in the GIIR group. However, those in the GIIR group reported more diagnoses of hyperthyroidism. No differences were observed between GIIR and AFDR groups. For the total number of co-occurring physical conditions, no differences were observed between the GIIR, AFDR and NFD groups. See Supplementary Table 5 for GIIR physical health information.

DISCUSSION

For the first time, this study documents the health profile and psychiatric difficulties of a large sample (>700) of older adults with an autistic first-degree relative. As expected, based on the strong genetic contribution to autism, previous work on the broad autism phenotype, and the possible influence of caregiver stress, those with an autistic relative reported significantly more diagnoses of co-occurring psychiatric conditions when compared to the control group (with no close relatives with neurodevelopmental or psychiatric conditions). Additionally, those with an autistic relative reported elevated self-report symptoms of current depression, anxiety, post-traumatic stress, and experiences of trauma, compared to those without an autistic relative. However, this pattern of results did not extend to physical conditions; few differences were reported in individual physical health diagnoses, and no differences were observed in total co-occurring physical conditions. Furthermore, to examine whether these findings are specific to those with an autistic relative, or more broadly applicable to those with any family member who may require additional support, comparisons were made with those have a relative with intellectual impairment. Those with an autistic relative experienced elevated rates of depression and anxiety diagnoses and symptoms compared to the intellectually impaired relatives group, suggesting that while environmental factors do influence the rates of psychiatric conditions, the genetic predisposition for poor psychiatric health in autism may lead to higher rates of psychiatric difficulties over and above that of caregiving stress. Therefore, our results suggest that older adults with a genetic predisposition to autism (inferred from having an autistic first-degree relative) may be more susceptible to poorer psychiatric (but not physical) health in later life.

Consistent with the previous literature exploring the mental health of children and younger adults with an autistic relative, a similar pattern of high rates of psychiatric diagnoses was

observed in our older adult sample from the PROTECT cohort (Daniels et al., 2008; Jokiranta et al., 2013; Yirmiya & Shaked, 2005). Those with an autistic relative reported higher rates of almost all psychiatric diagnoses compared to the comparison sample. For common disorders like major depressive and generalised anxiety disorders, this elevated rate represented a near twofold risk increase, comparable with the rates previously described in population-based studies for both younger/midlife parents with an autistic child (Daniels et al., 2008; Jokiranta et al., 2013). This may be of importance as depression and anxiety have both been identified as risk factors for poorer physical health and for early mortality in older adults in the general population (Janszky, Ahnve, Lundberg, & Hemmingsson, 2010; Schulz et al., 2000). As such, older adults with an autistic relative may benefit from intervention to mitigate this vulnerability. Furthermore, elevated rates of rarer disorders like eating disorders were also observed for those with an autistic relative when compared to those without an autistic relative, representing over a twofold risk increase. To the authors' knowledge, no previous studies have explored the prevalence of eating disorders among individuals with an autistic relative, although there has been considerable interest in the overlap between autism and anorexia in those with elevated autistic traits (see Westwood *et al.*, 2016 for review/meta-analysis) and among autistic populations (see Westwood and Tchanturia, 2017 for review).

However, one condition that deviated from the rates described in the previous literature is schizophrenia. Elevated rates of schizophrenia have previously been observed in parents of autistic children (Daniels et al., 2008; Jokiranta et al., 2013); however, this was not observed in the current study. Schizophrenia has often been compared to autism, with both being described as spectrum conditions and having substantial genetic overlap; as such, autistic individuals have been documented to experience up to a twofold risk increase for also having schizophrenia compared to non-autistic individuals (Chisholm, Lin, Abu-Akel, & Wood, 2015). Among the general population, schizophrenia has a lifetime prevalence rate of 4%

(Saha, Chant, Welham, & McGrath, 2005); however, in the current study, very few individuals reported a diagnosis of schizophrenia (n=7, <.1%), with no group difference being observed in the prevalence rate. This could in part be due to the early mortality rates documented among those with schizophrenia (Laursen, Nordentoft, & Mortensen, 2013; Olfson, Gerhard, Huang, Crystal, & Stroup, 2015). Furthermore, previous research has also explored the generalisability of medical research suggesting that older adults who engage in voluntary studies are often healthier than the general population that they are taken to represent (Golomb et al., 2012), so those with severe and persistent conditions (such as schizophrenia) may not be as likely to participate in voluntary longitudinal studies such as PROTECT.

When considering the number of total co-occurring psychiatric conditions reported by our sample, 48% of those with an autistic relative reported one or more co-occurring psychiatric condition compared to 32% in our control sample. This was also found to be negatively associated with age, suggesting that the oldest among our current sample had received fewer psychiatric diagnoses than those just entering older age. The number of co-occurring psychiatric conditions or its association with age has not been examined in those with autistic relatives before. However, the findings from the current study show a similar pattern previously demonstrated in autistic adults, but to a lesser extent. Lever and Geurts (2016) noted that autistic individuals across adulthood demonstrated a higher total number of co-occurring conditions compared to a control group, with 79% of autistic adults reporting one or more co-occurring conditions compared to 49% in their control group. This finding was found to decrease with age, which is also consistent with the current study. As such, the findings from the current study suggest that not only are individuals with an autistic relative more susceptible to psychiatric conditions, they are also more likely to experience a higher number of comorbidities. While this susceptibility decreases with age, experiencing poor

mental health is a risk factor for poorer long-term outcomes, and needs to be addressed to mitigate future risks.

This increased risk of psychiatric ill-health was also evident in high levels of self-reported current psychiatric symptoms. Elevated scores of self-reported recent symptoms of depression, anxiety, and post-traumatic stress, and experiences of childhood and adult trauma were observed in those with an autistic family member when compared to the control group. Despite this, both groups demonstrated scores that were mostly in the 'mild' range of the scales for all questionnaire measures. However, when examining the frequency of those reporting above cut-off scores, significantly more individuals with an autistic relative demonstrated clinical levels of current depression and anxiety, symptomatic levels of post-traumatic stress, and severe childhood and adulthood abuse and neglect, when compared to those in the control group. To the authors' knowledge, no studies have documented self-report current psychiatric symptoms and experience of trauma among older individuals with an autistic relative. While overall prevalence of clinical levels of current depression and anxiety symptoms are lower than the lifetime diagnosis prevalence of major depressive and generalised anxiety disorders in the current study, those with an autistic relative were at a twofold to threefold risk for current depression and anxiety compared to those without an autistic relative. Furthermore, a similar pattern is also observed in rates of symptomatic current post-traumatic stress (threefold risk) and the experience of severe childhood and adulthood trauma (twofold risk) – with females being particularly susceptible to traumatic experience. Previous studies have explored the association between post-traumatic stress and autistic traits in child and adult populations, and suggest that an increased susceptibility to victimisation may lead to elevated rates of post-traumatic stress (Mehtar & Mukaddes, 2011; Roberts, Koenen, Lyall, Robinson, & Weisskopf, 2015; Rumball, 2018). This finding, along with the elevated rates of clinical levels of current depression, may be of importance as both post-traumatic stress and depression have been

described as mechanisms to suicidal thoughts, behaviours and attempts in autistic populations (Cassidy et al., 2014; Storch et al., 2013). Suicide has been identified in a large population-based study as a leading cause of early mortality for autistic individuals (Hirvikoski et al., 2016). Elevated rates of suicidal behaviours have been documented in a large population-based study, with those with an autistic relative experiencing more suicidal thoughts, behaviours and attempts compared to those with no family history of autism (Hirvikoski et al., 2019). Therefore, the findings of the current study provide further support for the notion that those with an autistic relative – and those with the BAP – may be at elevated risk for psychiatric difficulties. Furthermore, this susceptibility to traumatic experience and post-traumatic stress may also increase the likelihood for suicidal thoughts and behaviours.

Interestingly, the same pattern of results was not observed for physical conditions. No group differences in diagnosis rates were observed across most physical conditions, including cardiovascular, metabolic, or neurological conditions. Furthermore, no differences were observed in total number of co-occurring physical conditions. The total number of co-occurring conditions was found to be positively associated with age, showing that the oldest among our current sample had received more physical diagnoses than those just entering older age. This pattern of physical health declining with age is convergent with both the autism and general population literatures (Bishop-Fitzpatrick & Kind, 2017; Bishop-Fitzpatrick & Rubenstein, 2019; Croen et al., 2015; Hand et al., 2019; Rydzewska et al., 2019). To the authors' knowledge, no other studies have collectively explored the prevalence rates of physical conditions among BAP of any age range. However, studies exploring the physical health of autistic adults using health records, document an elevated rate of most conditions when compared to control populations, including cardiovascular disease, metabolic disorders, endocrine and immune conditions, gastrointestinal disorders, sleep disorders, and neurological

conditions such as epilepsy and Parkinson's disease (Bishop-Fitzpatrick & Rubenstein, 2019; Cashin, Buckley, Trollor, & Lennox, 2018; Croen et al., 2015; Hand et al., 2019).

While our findings are not consistent with the autism literature, the current study does report elevated rates of endocrine conditions (i.e. hypo- and hyperthyroidism) in females with an autistic relative when compared to those with no family history of autism. Maternal thyroid conditions associated with autoimmune problems during pregnancy have been identified as a potential biomarker for autism (Brown et al., 2015; A. Meltzer & Van De Water, 2017). However, whether these thyroid conditions are associated with autoimmune problems is not known in the current study. Furthermore, elevated rates of hypothyroidism are common in older adults in the general population, with health record reports documenting a 5% prevalence rate at age 50 and older (Ingoe et al., 2017), while hyperthyroidism is less common with a prevalence rate of 1% (Vanderpump, 2011). Among autistic adults, thyroid disease and endocrine conditions more broadly were found to significantly elevated, with a prevalence rates of 7% compared to 3% in non-autistic controls (Croen et al., 2015), however, some samples document rates of thyroid disease up to 32% in autistic populations (Hand et al., 2019). The rates of endocrine (and most other conditions more broadly) observed in the current study are below that of the autistic and general population reports, which could suggest a selection effect for study participants to have overall good health. As previously discussed, older adults who engage in voluntary medical research studies often differ from the population they are taken to represent as they are often more healthy and able (Golomb et al., 2012). Thus, while the previous literature documents that autistic individuals may be at risk for poorer physical health across the lifespan, the findings from the current study suggest that this risk is not conferred to the physical health of older adults with an autistic relative – although these findings may not be wholly generalisable from the rates described in the current sample.

The pattern of findings is open to a range of interpretations, but one construal may be that genetic predisposition for autism overlaps with genetic predisposition to a range of poor mental health outcomes (Caspi & Moffitt, 2018; Ronald, 2019). This genetic predisposition may be influenced by caregiving stress associated with supporting a family member with additional needs. Thus, relatives of autistic probands, like their autistic relatives, show high rates of psychiatric problems due to genetic factors being influenced by environmental stressors. By contrast, autistic probands but not their first-degree relatives (who share genetic predisposition to autism) show elevated rates of many physical conditions. This might indicate that some forms of physical ill health may emerge as a consequence of autism (Rubenstein & Bishop-Fitzpatrick, 2019); that is, as a phenotypic downstream consequence of, e.g., social isolation, reduced help-seeking due to communication difficulties, or socio-economic disadvantage and stress from stigma, exclusion and marginalisation. This downstream effect may be particularly important for conditions influenced by lifestyle factors, such as cardiovascular disease or sleep-related problems, but may not be the case for neurological conditions observed in autistic populations, e.g. epilepsy and Parkinson's disease. However, as the findings of the current study may not be wholly generalisable, further research that can disentangle these genetic and environmental influences on health is required to understand factors contributing to the differences in health outcomes in autistic and broader autism populations, as well as those with autistic relatives.

It is important to consider limitations when contextualising the results of the current study. A strength of the PROTECT cohort is the use of an online platform for data collection allowing the recruitment of many participants from a wide geographical spread across the UK. However, this is also a limitation as there is no way of objectively verifying the subjective responses of the participants. As such, all health diagnoses are self-reported and not clinically verified.

Previous studies examining differences between self-reported health and clinician-reported health in the general population have found that self-reported health more accurately identifies chronic/serious conditions than less serious conditions (Doiron, Fiebig, Johar, & Suziedelyte, 2015). This may be due to more severe conditions being emphasized for importance when individuals are asked to list health difficulties. However, as the PROTECT data collection prompts participants to select from a list which conditions they have been diagnosed with rather than to describe their health or self-generate their medical history, this may improve the validity of the prevalence rates of less serious conditions. Furthermore, the questions related to family health history only specifies 'first-degree relative'. As such, there is not information about the type of relation this is (i.e. parent, sibling, or child) or the frequency or nature of contact with this individual. Another point to consider is that the PROTECT study is a voluntary research project conducted online, thus sampling biases may apply, e.g. older adults who are not comfortable using technology may be excluded. As previously mentioned, older adults who engage in medical research typically are physical well and mentally able, which may lead to poor generalisability of findings (Golomb et al., 2012), e.g. the prevalence rates of less common conditions in the PROTECT sample are below that of general population levels. Furthermore, rates of above-cut off symptoms were low in all three groups, which may further limit the generalisability of these findings. Moreover, the PROTECT sample in the current study are predominately female (82%) and well educated, with approximately 50% holding an undergraduate or postgraduate-level degree. And finally, the design of this study cannot infer causation; as such, it is not possible to tease apart whether mental health difficulties are due to genetic susceptibility, caregiving stress, or other influences. Whilst these factors may limit the overall generalisability of the findings, the results still provide important new information about the health profile in a large study population of older adults.

In conclusion, our study exploring the health profile of older adults suggests that those with an autistic first-degree relative may be at greater risk for poorer psychiatric, but not physical, health than those who have no family history of autism or other disorders, as well as those who are also likely to experience caregiver stress. This risk to mental health also extends to current elevated rates of above cut-off psychiatric symptoms and traumatic experiences. The findings of the current study highlight the need for adequate mental health support for those with an autistic relative, and to autistic and broader autism/high autism trait populations to ensure that they receive appropriate support due to the increased risk of mental health problems and crises. Research incorporating polygenic scores could elucidate the possible genetic links between the autism spectrum and psychiatric risk, versus the proposed phenotypic link between autism - but not familial risk - and poor physical health. Future studies should explore whether those on the autism spectrum experience barriers to accessing mental health care support and whether the findings of the current study extend to older adults who meet diagnostic criteria for autism.

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Table 1. Demographic characteristics of the AFDR and NFD groups.

		No Family Diagnoses (n = 11,666)		Autistic First-Degree Relative (n = 739)		Group difference	Effect Size	Gender Differences
Age	*M (SD)*	63.58	(6.85)	63.19	(7.65)	F(1,12402) = 2.29, *p* = .130	.06 [-.01 - .13]	Yes (Interaction)
	95% CI	63.46 - 63.79		62.64 - 63.73				
	Range	50 - 90		50 - 90				
Gender	*male : female*	2097 : 9585		130 : 623		$\chi2$ = .26, *p* = .611	.01 [-.03 - .04]	-
	%	18.0% : 82.0%		17.3% : 82.7%				
Marital status	*Married*	7676	(65.9%)	477	(63.3%)	$\chi2$ = 24.90, *p* < .001***	.09 [.05 - .12]	Yes
	Widowed	785	(6.7%)	46	(6.1%)			
	Separated	179	(1.5%)	23	(3.1%)			
	Divorced	1325	(11.4%)	111	(14.7%)			
	Civil Partnership	70	(0.6%)	3	(0.4%)			
	Co-habiting	795	(6.8%)	61	(8.1%)			
	Single	823	(7.1%)	32	(4.2%)			
Education history	*School to 16*	1905	(16.3%)	113	(15.0%)	$\chi2$ = 5.71, *p* = .127	.04 [.01 - .07]	Yes
	School to 18	3792	(32.5%)	236	(31.3%)			
	Undergraduate	3751	(32.2%)	234	(31.1%)			
	Postgraduate	2205	(18.9%)	170	(22.6%)			
Current employment status	*Employed*	5705	(49.0%)	400	53.1%	$\chi2$ = 20.18, *p* < .001***	.08 [.04 - .11]	Yes
	Retired	5606	(48.1%)	314	41.7%			
	Unemployed	342	(2.9%)	39	5.2%			

Note: Gender differences, Age - males are older in the NFD group than in AFDR group; Martial Status - more females who are divorced or widowed, and more males who are married; Education History - more males with postgraduate degrees, more females with undergraduate degrees; Current employment status - more females currently employed and unemployed, more males retired.
* p < .05, ** p < .01, *** p < .001

Table 2. Prevalence of self-reported diagnoses of psychiatric conditions of the AFDR and NFD groups

		No Family Diagnoses (n = 11,666)		Autistic First-Degree Relative (n = 739)		Group Difference	Effect Size	Odds Ratio
Psychiatric conditions	*Major depressive disorder*	2850	(24.4%)	290	(38.5%)	$\chi2 = 74.68$, $p < .001$***	.38 [.29 - .46]	1.87 [1.60 - 2.19]
	Generalised anxiety disorder	1551	(13.3%)	158	(21.0%)	$\chi2 = 35.434$, $p < .001$***	.31 [.21 - .41]	1.68 [1.40 - 2.03]
	Social Anxiety	122	(1.0%)	19	(2.5%)	$\chi2 = 13.80$, $p < .001$***	.50 [.23 - .77]	2.06 [1.19 - 3.55]
	Mania	40	(0.3%)	9	(1.2%)	$\chi2 = 13.11$, $p < .001$***	.70 [.30 - 1.15]	3.44 [1.59 - 7.41]
	Agoraphobia	34	(0.3%)	13	(1.7%)	$\chi2 = 38.71$, $p < .001$***	.99 [.64 - 1.35]	5.14 [2.51 - 10.54]
	Panic Attacks	535	(4.6%)	61	(8.1%)	$\chi2 = 19.22$, $p < .001$***	.34 [.19 - .49]	1.78 [1.34 - 2.36]
	OCD	45	(0.4%)	13	(1.7%)	$\chi2 = 27.41$, $p < .001$***	.84 [.50 - 1.19]	3.80 [1.90 - 7.59]
	Anorexia nervosa	91	(0.8%)	12	(1.6%)	$\chi2 = 5.72$, $p = .017$*	.41 [.07 - .74]	1.60 [.80 - 3.19]
	Bulimia nervosa	53	(0.5%)	11	(1.5%)	$\chi2 = 14.01$, $p < .001$***	.66 [.29 - 1.02]	2.81 [1.37 - 5.73]
	Binge eating	48	(0.4%)	13	(1.7%)	$\chi2 = 25.01$, $p < .001$***	.81 [.46 - 1.15]	3.90 [2.01 - 7.57]
	Schizophrenia	6	(0.1%)	0	(0%)	$\chi2 = .83$, $p = .361$	-	-
	Other psychotic illness	27	(0.2%)	6	(0.8%)	$\chi2 = 8.55$, $p = .003$**	.69 [.21 - 1.18]	3.17 [1.21 - 8.31]
	Personality disorder	22	(0.2%)	7	(0.9%)	$\chi2 = 16.07$, $p < .001$***	.89 [.42 - 1.36]	3.52 [1.18 - 10.43]
Number of psychiatric condition diagnoses	*No diagnoses*	7778	(66.7%)	383	(51.8%)			
	1	2787	(23.9%)	231	(31.3%)	$\chi2 = 96.14$, $p < .001$***	.36 [.28 - .43]	-
	2	807	(6.9%)	74	(10.0%)			
	3 or more	294	(2.5%)	51	(6.9%)			

Note: * p < .05, ** p < .01, *** p < .001

Table 3. Self-report questionnaire means, standard deviations and confidence intervals of the AFDR and NFD groups

		No Family Diagnoses (n = 11,666)	Autistic First-Degree Relative (n = 739)	Group Difference	Effect Size	Gender Differences
Depression *(max score = 27)*	*Mean (SD)*	2.52 (3.08)	3.68 (4.16)	F(1,12399) = 92.89,	.36	-
	95% CI	2.46 - 2.57	3.37 - 3.97	*p* < .001***	[.29 -.44]	
Anxiety *(max score = 21)*	*Mean (SD)*	1.44 (2.54)	2.39 (3.48)	F(1,12395) = 93.76,	.37	-
	95% CI	1.39 - 1.48	2.14 - 2.64	*p* < .001***	[.29 - .44]	
Post-traumatic Stress *(max score = 20)*	*Mean (SD)*	1.26 (2.23)	2.29 (3.23)	F(1,12403) = 140.08,	.44	-
	95% CI	1.21 - 1.30	2.06 - 2.52	*p* < .001***	[.37 - .52]	
Childhood Trauma *(max score = 20)*	*Mean (SD)*	1.85 (2.46)	2.64 (2.98)	F(1,12403) = 70.09,	.32	-
	95% CI	1.80 - 1.89	2.42 - 2.86	*p* < .001***	[.24 - .39]	
Adult Trauma *(max score = 20)*	*Mean (SD)*	4.41 (2.00)	4.98 (2.39)	F(1,12403) = 44.87,	.25	F ↑ (interaction)
	95% CI	4.38 - 4.45	4.81 - 5.15	*p* < .001***	[.18 - .33]	

Note: Depression measured using PHQ-9; Anxiety measured using GAD-7; Post-traumatic Stress measured using PCL-5; Childhood Trauma measured using CTS-5; Adulthood Trauma measured using the ATS-5.
* p < .05, ** p < .01, *** p < .001

Table 4. Self-report questionnaire cut-off scores of the AFDR and NFD groups

		No Family Diagnoses (n = 11,666)		Autistic First-Degree Relative (n = 739)		Group Difference	Effect Size	Odds Ratio	Gender Differences
Depression *(cut off =>10)*	*Frequency (%)*	461	(4.0%)	63	(8.5%)	χ^2 = 35.89, p < .001***	.45 [.30 - .60]	2.26 [1.72 - 2.98]	-
Anxiety *(cut off =>10)*	*Frequency (%)*	201	(1.7%)	41	(5.5%)	χ^2 = 53.09, p < .001***	.66 [.47 - .85]	3.35 [2.37 - 4.72]	-
Post-traumatic Stress *(cut off => 10)*	*Frequency (%)*	183	(1.5%)	34	(4.6%)	χ^2 = 39.72, p < .001***	.56 [.39 - .72]	3.13 [2.15 - 4.55]	-
Childhood Trauma *(cut off => 10)*	*Frequency (%)*	173	(1.5%)	25	(3.4%)	χ^2 = 15.97, p < .001***	.46 [.23 - .70]	2.32 [1.52 - 3.56]	F ↑
Adult Trauma *(cut off => 10)*	*Frequency (%)*	318	(2.7%)	39	(5.3%)	χ^2 = 16.18, p < .001***	.37 [.19 - .56]	1.98 [1.41 - 2.79]	F ↑

Note: Depression measured using PHQ-9; Anxiety measured using GAD-7; Post-traumatic Stress measured using PCL-5; Childhood Trauma measured using CTS-5; Adulthood Trauma measured using the ATS-5.
* p < .05, ** p < .01, *** p < .001

Table 5. Prevalence of self-reported diagnoses of physical health conditions of the AFDR and NFD groups

		No Family Diagnoses (n = 11,666)		Autistic First-Degree Relative (n = 739)		Group Difference	Effect Size	Odds Ratio
Physical conditions	*High Blood Pressure*	2713	(23.4%)	175	(23.5%)	$\chi2 = .001$, $p = .967$	.01 [-.08 - .10]	1.06 [.84 - 1.20]
	High Cholesterol	477	(4.1%)	32	(4.3%)	$\chi2 = .06$, $p = .814$	.03 [-.17 - .23]	1.07 [.74 - 1.54]
	Stroke	145	(1.3%)	13	(1.7%)	$\chi2 = .39$, $p = .246$	.19 [-.12 - .51]	1.43 [.81 - 2.53]
	Heart Disease	387	(3.3%)	34	(4.6%)	$\chi2 = 3.17$, $p = .075$	.19 [-.01 - .38]	1.36 [.95 - 1.97]
	Diabetes	389	(3.4%)	25	(3.4%)	$\chi2 = .000$, $p = .997$	0.01 [-.21 - .23]	1.02 [.68 - 1.54]
	Mild Cognitive Impairment	24	(0.2%)	3	(0.4%)	$\chi2 = 1.22$, $p = .269$	.38 [-.28 - 1.03]	1.98 [.59 - 6.59]
	Parkinson's Disease	30	(0.3%)	1	(0.1%)	$\chi2 = .44$, $p = .510$	-.35 [-1.45 - .74]	.53 [.07 - 3.87]
	Hypothyroidism	181	(1.6%)	19	(2.5%)	$\chi2 = 4.28$, $p = .039$*	.28 [.02 - .54]	1.67 [1.04 - 2.71]
	Hyperthyroidism	36	(0.3%)	6	(0.8%)	$\chi2 = 5.04$, $p = .025$*	.53 [.05 - 1.01]	2.65 [1.11 - 6.31]
	Arthritic conditions	464	(4.0%)	40	(5.4%)	$\chi2 = 3.32$, $p = .069$	.18 [.00 - .36]	1.27 [.91 - 1.80]
Number of physical condition diagnoses	*No diagnoses*	7871	(68.0%)	478	(65.3%)	$\chi2 = 3.27$, $p = .352$	.07 [-.01 - .01]	-
	1	2834	(24.5%)	187	(25.5%)			
	2	691	(6.0%)	53	(7.2%)			
	3 or more	187	(1.6%)	14	(1.9%)			

Note: * p < .05, ** p < .01, *** p < .001

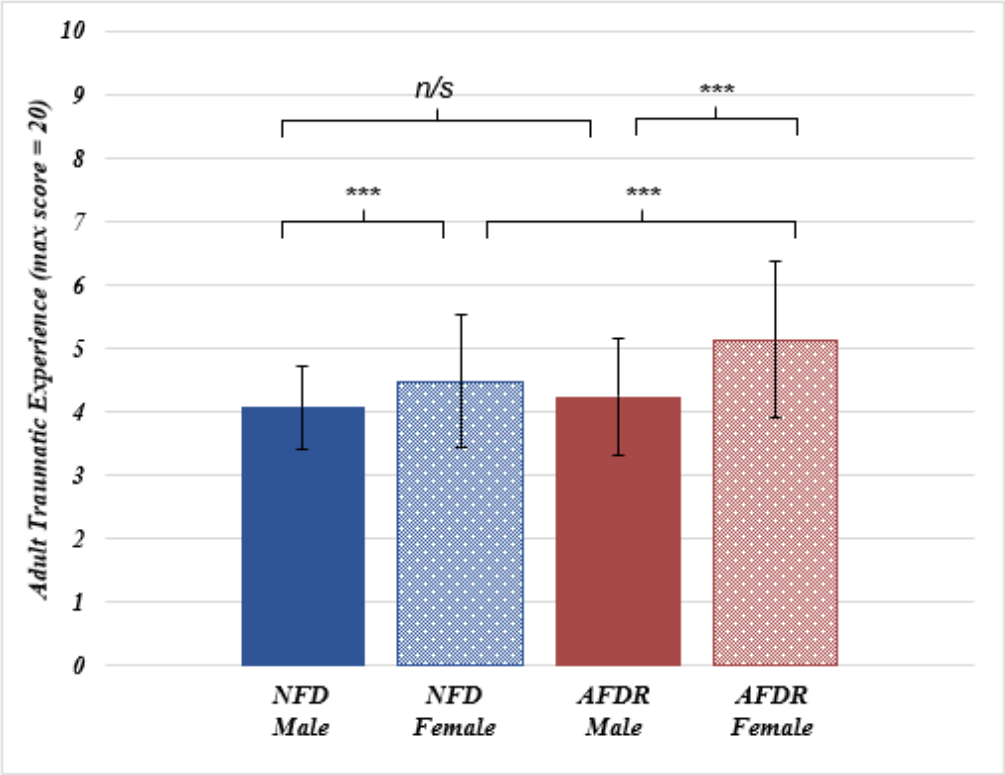

Figure 1: Interaction of group (AFDR vs. NFD) and gender on Adulthood Traumatic Experience.

Supplementary Table 1. Demographic characteristics of NFD, GIIR, and AFDR groups.

		NFD (n = 11,666)	GIIR (n = 219)	AFDR (n = 739)	Group Difference ǂ (Effect Size)			
					All Groups	GIIR vs. NFD	AFDR vs. NFD	GIIR vs. AFDR
Age	*M (SD)*	63.58 (6.85)	64.23 (7.32)	63.19 (7.65)				
	95% CI	63.46 - 63.79	63.25 - 65.20	62.64 - 63.73	.05	-	-	-
	Range	50 - 90	50 - 90	50 - 90				
Gender	*male : female*	2097 : 9585	57 : 162	130 : 623	**.06****	**.06**** GIIR M↑	.03	**.20**** GIIR M↑
	%	18.0% : 82.0%	26.3% : 73.7%	17.3% : 82.7%				

Note: NFD: No Family Diagnoses; GIIR: General Intellectual Impairment Relative; AFDR: Autistic First-Degree Relative.
ǂ Group difference presented as effect size and significance level. Analyses used: Age = ANOVA, Gender = $\chi 2$.
Age is matched between all groups. Gender is matched between NFD and AFDR groups, but not GIIR.
* $p < .05$, ** $p < .01$, *** $p < .001$

Supplementary Table 2. Prevalence of self-reported diagnoses of psychiatric health conditions of NFD, GIIR, and AFDR groups.

		NFD (n = 11,666)		GIIR (n = 219)		AFDR (n = 739)		Group Difference ǂ (Effect Size)			
								All Groups	GIIR vs. NFD	AFDR vs. NFD	GIIR vs. AFDR
Psychiatric health conditions	*Major depressive disorder*	2850	(24.4%)	52	(24.0%)	290	(38.5%)	**.14*** **	.02	**.38*** ** *AFDR>NFD*	**.41*** ** *AFDR>GIIR*
	Generalised anxiety disorder	1551	(13.3%)	25	(11.5%)	158	(21.0%)	**.10*** **	.10	**.31*** ** *AFDR>NFD*	**.40*** ** *AFDR>GIIR*
	Social Anxiety	122	(1.0%)	2	(0.9%)	19	(2.5%)	**.05***	.07	**.50*** ** *AFDR>NFD*	.58
	Mania	40	(0.3%)	1	(0.5%)	9	(1.2%)	**.06****	.15	**.70*** ** *AFDR>NFD*	.54
	Agoraphobia	34	(0.3%)	0	-	13	(1.7%)	**.09*** **	-	**.99*** ** *AFDR>NFD*	-
	Panic Attacks	535	(4.6%)	14	(6.5%)	61	(8.1%)	**.07*** **	.19	**.34*** ** *AFDR>NFD*	.15
	OCD	45	(0.4%)	2	(0.9%)	13	(1.7%)	**.07*** **	.47	**.84*** ** *AFDR>NFD*	.37
	Anorexia nervosa	91	(0.8%)	0	-	12	(1.6%)	.03	-	**.41*** *AFDR>NFD*	-
	Bulimia nervosa	53	(0.5%)	0	-	11	(1.5%)	**.06****	-	**.66*** ** *AFDR>NFD*	-
	Binge eating	48	(0.4%)	1	(0.5%)	13	(1.7%)	**.08*** **	.05	**.81*** ** *AFDR>NFD*	.75
	Schizophrenia	6	(0.1%)	0	-	0	(0%)	.01	-	-	-
	Other psychotic illness	27	(0.2%)	1	(0.5%)	6	(0.8%)	**.04***	.37	**.69**** *AFDR>NFD*	.32
	Personality disorder	22	(0.2%)	0	-	7	(0.9%)	.05*	-	**.89*** ** *AFDR>NFD*	-
Number of psychiatric condition diagnoses	*No diagnoses*	7778	(66.7%)	136	(62.7%)	383	(51.8%)	**.18*** **	**.12*** *GIIR>NFD*	**.36*** ** *AFDR>NFD*	**.20*** ** *AFDR>GIIR*
	1	2787	(23.9%)	50	(23.0%)	231	(31.3%)				
	2	807	(6.9%)	26	(12.0%)	74	(10.0%)				
	3 or more	294	(2.5%)	5	(2.3%)	51	(6.9%)				

Note: NFD: No Family Diagnoses; GIIR: General Intellectual Impairment Relative; AFDR: Autistic First-Degree Relative. ǂ Group difference presented as effect size and significance level. Analyses used: $\chi 2$.* $p < .05$, ** $p < .01$, *** $p < .001$

Supplementary Table 3. Self-report questionnaire means, standard deviations and confidence intervals of NFD, GIIR, and AFDR groups.

		NFD (n = 11,666)	GIIR (n = 219)	AFDR (n = 739)	Group Difference ǂ (Effect Size)			
					All Groups	GIIR vs. NFD	AFDR vs. NFD	GIIR vs. AFDR
Depression *(max score = 27)*	*Mean (SD)*	2.52 (3.08)	2.97 (3.39)	3.68 (4.16)	**.28*** **	**.14*** *GIIR>NFD*	**.36*** ** *AFDR>NFD*	**.53*** *AFDR>GIIR*
	95% CI	2.46 - 2.57	2.51 - 3.42	3.37 - 3.97				
Anxiety *(max score = 21)*	*Mean (SD)*	1.44 (2.54)	1.81 (2.53)	2.39 (3.48)	**.36*** **	**.14*** *GIIR>NFD*	**.37*** ** *AFDR>NFD*	**.18*** *AFDR>GIIR*
	95% CI	1.39 - 1.48	1.46 - 2.14	2.14 - 2.64				
Post-traumatic Stress *(max score = 20)*	*Mean (SD)*	1.26 (2.23)	1.53 (2.59)	2.29 (3.23)	**.44*** **	0.12	**.45*** ** *AFDR>NFD*	**.53*** ** *AFDR>GIIR*
	95% CI	1.21 - 1.30	1.18 - 1.87	2.06 - 2.52				
Childhood Trauma *(max score = 20)*	*Mean (SD)*	1.82 (2.44)	2.36 2.77	2.61 (2.97)	**.31*** **	**.22*** ** *GIIR>NFD*	**.32*** ** *AFDR>NFD*	.08
	95% CI	1.77 - 1.86	1.98 - 2.74	2.42 - 2.86				
Adult Trauma *(max score = 20)*	*Mean (SD)*	2.31 (2.26)	2.69 (3.27)	4.98 (2.39)	**.19*** **	**.14** ** *GIIR>NFD*	**.25*** ** *AFDR>NFD*	.03
	95% CI	2.25 - 2.35	2.24 - 3.14	4.81 - 5.15				

Note: NFD: No Family Diagnoses; GIIR: General Intellectual Impairment Relative; AFDR: Autistic First-Degree Relative.
ǂ Group difference presented as effect size and significance level. Analyses used: ANOVA.
* $p < .05$, ** $p < .01$, *** $p < .001$

Supplementary Table 4. Self-report questionnaire cut-off scores of NFD, GIIR, and AFDR groups.

		NFD (n = 11,666)		GIIR (n = 219)		AFDR (n = 739)		Group Difference ł (Effect Size)			
								All Groups	GIIR vs. NFD	AFDR vs. NFD	GIIR vs. AFDR
Depression *(cut off =>10)*	*Frequency (%)*	461	(4.0%)	13	(6.0%)	63	(8.5%)	**.11*** **	.23	**.45*** ** *AFDR>NFD*	.21
Anxiety *(cut off =>10)*	*Frequency (%)*	201	(1.7%)	5	(2.3%)	41	(5.5%)	.13	.15	**.66*** ** *AFDR>NFD*	**.50*** *AFDR>GIIR*
Post-traumatic Stress *(cut off => 10)*	*Frequency (%)*	183	(1.5%)	5	(2.5%)	34	(4.6%)	**.11*** **	.20	**.56*** ** *AFDR>NFD*	.39
Childhood Trauma *(cut off => 10)*	*Frequency (%)*	173	(1.5%)	7	(3.3%)	25	(3.4%)	**.07*** **	**.42*** *GIIR>NFD*	**.46*** ** *AFDR>NFD*	.03
Adult Trauma *(cut off => 10)*	*Frequency (%)*	318	(2.7%)	11	(5.3%)	39	(5.3%)	**.07*** **	**.33*** ** *GIIR>NFD*	**.37*** ** *AFDR>NFD*	.03

Note: NFD: No Family Diagnoses; GIIR: General Intellectual Impairment Relative; AFDR: Autistic First-Degree Relative.

ł Group difference presented as effect size and significance level. Analyses used: $\chi 2$.

* $p < .05$, ** $p < .01$, *** $p < .001$

Supplementary Table 5. Prevalence of self-reported diagnoses of psychiatric health conditions of NFD, GIIR, and AFDR groups.

		NFD (n = 11,666)		GIIR (n = 219)		AFDR (n = 739)		Group Difference ł (Effect Size)			
								All Groups	**GIIR vs. NFD**	**AFDR vs. NFD**	**GIIR vs. AFDR**
Physical health conditions	*High Blood Pressure*	2713	(23.4%)	55	(25.5%)	175	(23.5%)	.01	.06	.01	.04
	High Cholesterol	477	(4.1%)	9	(4.2%)	32	(4.3%)	.03	.03	.03	.03
	Stroke	145	(1.3%)	4	(1.9%)	13	(1.7%)	.02	.21	.19	.02
	Heart Disease	387	(3.3%)	9	(4.2%)	34	(4.6%)	.03	.12	.19	.06
	Diabetes	389	(3.4%)	8	(3.7%)	25	(3.4%)	.01	.05	.01	.04
	Mild Cognitive Impairment	24	(0.2%)	1	(0.5%)	3	(0.4%)	.02	.44	.38	.06
	Parkinson's Disease	30	(0.3%)	0	-	1	(0.1%)	.01	-	-.35	-
	Hypothyroidism	181	(1.6%)	1	(0.5%)	19	(2.5%)	.05	**-.68*** *NFD>GIIR*	.28	.96
	Hyperthyroidism	36	(0.3%)	1	(0.5%)	6	(0.8%)	**.04***	**.21*** *GIIR>NFD*	.53	.31
	Arthritic conditions	464	(4.0%)	15	(6.9%)	40	(5.4%)	**.05***	.32	**.18*** *AFDR>NFD*	.13
Number of physical health condition diagnoses	*No diagnoses*	7871	(68.0%)	139	(64.4%)	478	(65.3%)	.04	.09	.07	.02
	1	2834	(24.5%)	57	(26.4%)	187	(25.5%)				
	2	691	(6.0%)	14	(6.5%)	53	(7.2%)				
	3 or more	187	(1.6%)	6	(2.8%)	14	(1.9%)				

Note: NFD: No Family Diagnoses; GIIR: General Intellectual Impairment Relative; AFDR: Autistic First-Degree Relative. ł Group difference presented as effect size and significance level. Analyses used: $\chi 2$. * $p < .05$, ** $p < .01$, *** $p < .001$