Increased prevalence of non-communicable physical health conditions among autistic adults

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Introduction

Autism spectrum conditions (henceforth autism) are lifelong, neurodevelopmental conditions characterized by social and communication difficulties; markedly restricted, repetitive interests and behaviour; and differences in cognitive profile, including atypical sensory perception and information processing, motor abilities, and intellectual ability (APA, 2013). Although historically autism was classified as a rare condition, prevalence estimates have increased in recent years and now approximately 1-2% of the population are diagnosed as autistic (likely due to expansion of diagnostic criteria and greater recognition of the condition due to increased awareness) (Baio et al., 2018). In addition, there is a sex-bias in autism, with males being diagnosed approximately three to four times more frequently than females (Baio et al., 2018; Loomes, Hull, and Mandy, 2017). Due to historic increases in prevalence, greater numbers of autistic individuals continue to reach adolescence and adulthood.

Autistic individuals are at higher risk of premature mortality than non-autistic individuals, with some evidence of further increased risks for those with intellectual disability and for autistic females; in addition, chronic physical health conditions or poor physical health are associated with premature mortality for autistic individuals across the spectrum of intellectual ability (Bishop-Fitzpatrick et al., 2018; DaWalt et al., 2019; Hirvikoski et al., 2016; Hwang et al., 2019; Woolfenden et al., 2012). Despite these risks, there are very few studies of autistic adults with a large enough sample size to accurately identify medical conditions that frequently co-occur with autism.

To date, eight large-scale studies have attempted to identify the common medical comorbidities of autistic adults in a variety of ways. However, almost none of these studies effectively consider physical health across the lifespan: three studies only include autistic individuals younger than 40 years of age, and an additional three include less than 325 autistic people aged 40+ years each. Despite these limitations, all of these six studies indicate that autistic individuals are at increased risk of nearly every physical health condition asked about; taken collectively, this includes increased risk of neurological conditions and CNS anomalies (and in particular epilepsy/ seizure disorders), cardiovascular conditions (including dyslipidemia/ lipid metabolism disorders, hypertension, and stroke), gastrointestinal conditions, metabolic conditions and diabetes (including Type I diabetes, being overweight, and obesity), pulmonary/ respiratory conditions (including asthma and COPD), immune/ autoimmune conditions, endocrine conditions (including thyroid conditions), pubertal disorders, genitourinary/ kidney conditions, musculoskeletal conditions, sleep disturbances/ disorders, nutritional conditions, muscular dystrophy, genetic disorders, physical disabilities, skin disorders, infections, hematological disorders, jaw and teeth disorders, ENT (ear, nose, and throat) conditions, and ophthalmological conditions for young autistic individuals compared to young non-autistic individuals (Croen et al., 2015; Davignon et al., 2018; Fortuna et al., 2016; Kohane et al., 2012; Vohra, Madhavan, and Sambamoorthi, 2017; Weiss et al., 2018).

It should be noted that some of these studies reported that autistic individuals were at relatively lower risk for some conditions compared to non-autistic individuals, including migraines,

musculoskeletal conditions, genitourinary conditions, cancer, cardiovascular disorders, diabetes, and respiratory conditions (Croen et al., 2015; Davignon et al., 2018; Fortuna et al., 2016; Vohra, Madhavan, and Sambamoorthi, 2017); however, there are conflicting results across different studies for each of these conditions. For example, there is genetic and epidemiological evidence to suggest that autistic individuals have a different likelihood of developing cancer than those in the general population, yet due to methodological differences across studies (primarily regarding limited sample sizes and age range), the direction of this risk is still under debate (Chiang et. al, 2015; Crawley, Heyer, and LaSalle, 2016; Crespi, 2011; Darbro et al., 2016; Kao et al., 2010; Mouridsen et al., 2016; Vohra, Madhavan, and Sambamoorthi, 2017; Wen, Alshikho, and Herbert, 2016). Even taking these limitations into account, there appears to be a pattern of increased health burden for most physical health conditions among autistic individuals.

Further, three studies (including two of the above) of primarily younger autistic adults considered healthcare utilization (in regards to number of visits or expense), showing that autistic individuals are more likely than non-autistic individuals to have outpatient, inpatient, primary care, emergency room, mental health/ psychiatric, neurology, speech therapy, and laboratory visits; have prescription drug claims; and to be hospitalized (Vohra, Madhavan, and Sambamoorthi, 2017; Weiss et al., 2018; Zerbo et al., 2018). Thus, it is unsurprising that they also had higher mean annual expenditure for outpatient, primary care, emergency, mental health/ psychiatry, neurology, home health care, and skilled nursing visits; prescription drug claims; and overall healthcare than non-autistic individuals (and the presence of a psychiatric or physical health

comorbidity increased expenditure further) (Vohra, Madhavan, and Sambamoorthi, 2017; Weiss et al., 2018; Zerbo et al., 2018).

In addition to the six studies of primarily younger adults, two recent studies attempt to quantify increased physical health comorbidity burden for autistic adults across the lifespan. The first utilized census records in the Scottish population (n = 6,649 autistic adults) and identified increased risks for autistic adults over the age of 25 compared to non-autistic adults in all the categories surveyed, with odds ratios (ORs) of 6.2 and 2.6 for physical disability and other conditions (which may include physical health conditions), respectively (Rydzewska et al., 2018). Unfortunately, the census data did not provide any information about physical health specifically, or about any particular physical health conditions.

The second utilized a large, cross-sectional sample of Medicare data (n= 4,685 autistic adults) to determine whether older autistic adults (specifically those 65 years of age or older) are at increased risk of physical and mental health conditions (Hand et al., 2020). They found that, compared to individuals in the general population, autistic adults were at increased risk of nearly every condition tested (except menopausal disorders, multiple sclerosis, back conditions, and substance use disorders, whose findings were non-significant); for physical health specifically, the study confirmed previous findings from studies of younger adults (increased risk of all other metabolic, neurological, respiratory, gastrointestinal, circulatory/ cardiovascular, and musculoskeletal conditions) and identified that older autistic adults were also at increased risk of cancer, heart disease, and cerebrovascular disease (Hand et al., 2020). The findings of this study

highlight the need for research in autistic adults across the lifespan (and particularly in older adults), as they may have greater and/ or different risks than younger autistic individuals.

Finally, in addition to increased risk of specific health conditions, some studies indicate that there may be risk factors that have knock-on effects for autistic adults, placing them at even higher likelihood of developing a variety of physical health conditions than those in the general population. First, all of the studies that investigated potential sex differences in healthcare burden found that autistic females had even greater risks for most physical health conditions and lower reported health status overall than autistic males (Croen et al., 2015; Davignon et al., 2018; Fortuna et al., 2016; Rydzewska et al., 2018); these findings are in line with mortality data which shows that autistic females are at uniquely increased risk of premature mortality even compared to autistic males (Hirvikoski et al., 2016; Hwang et al., 2019; Woolfenden et al., 2012). Based on these findings, new research should focus on identifying physical health risks in autistic males and females separately, as well as quantifying relative risk between these groups. Second, two recent studies show evidence of cardiovascular risk factors that may contribute to greater risk of a variety of conditions among autistic individuals compared to non-autistic individuals, including reduced cardiorespiratory capacity and reduced heart-rate variability (Bricout et al., 2018; Thapa et al., 2019). Third, a systematic review and meta-analysis confirm the findings of Croen et al. and Hand et al. to suggest that autistic individuals are at greater risk of obesity than non-autistic people (Croen et al., 2015; Hand et al., 2020; Zheng et al., 2017). Obesity has been shown to be significantly associated with increased risk of several non-communicable diseases, including type II diabetes, cancer, cardiovascular conditions overall, and asthma (Guh et al., 2009). Fourth, there

is still significant debate regarding frequency of substance use and abuse in autism, and how this may affect physical health of autistic adults. Several small studies indicate decreased substance use among autistic individuals overall (Croen et al., 2015; Davignon et al., 2018; Fortuna et al., 2016; Vohra, Madhavan, and Sambamoorthi, 2017). Conversely, other studies have suggested increased substance use problems among autistic adults, including a large population-based study in Sweden (n = 26,986 autistic individuals) which suggests that autism is a risk factor for substance use-related problems, with elevated risks even for relatives of autistic individuals (Butwicka et al., 2016; Weiss et al., 2018). Substance use/ abuse increases risks of respiratory problems (including asthma), cancer, heart disease, hypertension, heart attack, stroke, reproductive morbidity, diabetes, liver damage/disease, and sleep conditions (Schulte and Hser, 2014). We are unaware of any large-scale studies of physical health comorbidity burden of autistic adults that take into account lifestyle factors like obesity, smoking, or alcohol use. Thus, it appears that autistic adults, and particularly autistic females, may experience higher rates of nearly all types of physical health conditions, which may affect both quality and length of life.

Considering the significantly increased risks of premature mortality among autistic adults, it is of particular import to identify which physical health conditions are contributing the most risk. In 2016, the WHO reported that 71% of worldwide mortality was accounted for by four non-communicable diseases: cancers, cardiovascular conditions, respiratory conditions, and diabetes; therefore, research on physical health of autistic adults should focus on identifying differences in these key areas to maximize potential public health impact. In order to create effective interventions to reduce risk of physical health conditions and premature mortality, new research

must aim to identify risks for cancers, cardiovascular conditions, respiratory conditions, and diabetes across the lifespan, quantify risks for autistic females specifically, and determine whether lifestyle factors may serve as key points of intervention for reducing risk.

Methods

The Survey

We developed an anonymous, online physical health survey that included questions about demographic information, a short version of the Autism Spectrum Quotient (a measure of autistic traits, AQ-10) (Allison et al 2012; Greenberg et al, 2018), daily habits (including exercise, diet, sleep, disability, and social/ sexual history), as well as personal and family medical histories of common medical conditions. The medical history sections included lists of conditions from the broad categories of cancer; cardiovascular; respiratory; gastrointestinal; hormonal/reproductive; musculoskeletal; neurological; eye; ear, nose, and throat; liver and kidney; blood and lymph; skin; diabetes; and autoimmune conditions.

The questionnaire comprised 512 questions, asking about more than 150 medical conditions and daily habits. To avoid survey fatigue, the medical history sections utilized a tiered structure. Participants were directed to first select the broad health category that corresponded to each of their health conditions and, based on their selections, additional questions appeared with lists of common conditions within the selected category. In addition, each category list included a free text box where participants could report a diagnosis of any condition about which the survey did not specifically inquire. Further, there was a final text box at the end of the medical history section asking if there was any additional information that participants wished to provide about their health or medical history. As the survey used a tiered design, we scanned all free text boxes to ensure that conditions listed throughout the personal medical history section were appropriately coded, and that conditions listed met our requirements for inclusion. Medical conditions were ascertained by asking "Which of the following conditions have you ever had? Please select all that apply:" for each of the selected categories, indicating that individuals should provide a cumulative medical history across their lifespan rather than over a specified time limit (e.g. the last five years). See Supplementary Information for additional details. The conditions were selected using online, publicly available materials from the National Health Service (NHS), Cancer Research United Kingdom (CRUK), National Institute for Health and Care Excellence (NICE), National Institutes of Health (NIH), and the World Health Organization (WHO).

Recruitment

This study utilized a convenience sampling framework, recruiting online participants via the Cambridge Autism Research Database (CARD), Autistica's Discover Network, autism support

groups and charities (including the Autism Research Trust), and social media (specifically Twitter and Facebook). These sampling methods may be biased toward those with autism or an interest in autism, as we advertised to groups/ forums related to autism; however, all advertisements encouraged participation from both autistic and non-autistic individuals. In addition, we used Facebook to advertise our study to the general population, in an attempt to limit bias from recruiting individuals via only autism-specific groups/ forums; in this phase of recruitment, both autistic and non-autistic Facebook users from around the world were invited to participate. The study aimed to include an international cohort of individuals from all countries, and respondents from over 60 different countries were included in the sample.

Survey collection took place between February 2018 to August 2019. There were two periods within this time where survey collection was paused; no changes were made to the survey during these periods. We performed a sensitivity analysis covarying for time period in Model 2 and used z-tests to determine if the pauses in survey collection affected our results; we found no statistically significant differences in the results.

The Cohort

N = 3,657 individuals accessed the survey. Participants included any individual who was at least 16 years of age and consented to participate. We excluded 1,102 individuals due to 'incomplete' response, meaning that they exited the survey before providing their medical history. 914 of the individuals excluded due to incomplete response (83%) did not even complete the demographics section of the survey (and answered no questions related to lifestyle or physical health), making

their responses unusable for this analysis. Some questions were optional, and individuals were not excluded from analysis if they chose to skip optional questions; however, all questions related to medical history were required. We excluded one individual that indicated 'Other' for their biological sex, as our analysis strategy splits participants by biological sex.

As the survey was anonymous, we used an algorithm to exclude potential duplicate responses (n = 108). We excluded all records that matched a previous record on 11 criteria (autism diagnosis (yes/no), specific autism diagnosis, type of diagnosing practitioner, year of autism diagnosis, country of residence, biological sex, current gender identity, education-level, age, maternal age at birth, and paternal age at birth).

We used a case-control design to divide our sample into an autistic cohort and a control cohort. Our autistic cohort included individuals with an autism diagnosis, provided by a medical practitioner. Autism diagnoses were self-reported; however, we asked participants to provide additional information to verify their diagnosis, such as the type of practitioner who diagnosed them (e.g. Psychiatrist, Clinical Psychologist, Pediatrician, etc), year of their diagnosis, specific diagnosis (Autism Spectrum Disorder, Asperger's, etc), and whether they have a syndromic form of autism. As we followed a case-control design, individuals who self-diagnosed as autistic, suspected autism, or were waiting to be assessed for autism were excluded from both the autistic and non-autistic (control) groups (n = 44). We also excluded those who reported a syndromic form of autism (n = 34) that carries known physical health risks (i.e. Klinefelter/XXY, PTEN Hamartoma Tumor Syndrome, etc.,). Our control population included any individuals who do not

have autism or suspect autism; as noted above, individuals who report a self-diagnosis of autism, suspected autism, or who are waiting to be assessed with autism were excluded from the control group in order to preserve the case-control design. There were no additional exclusion criteria for controls. The final sample was comprised of n = 2,368 individuals, including 1,156 autistic individuals.

Analysis

As noted above, approximately 71% of worldwide mortality can be attributed to four non-communicable diseases: cancers, cardiovascular conditions, respiratory conditions, and diabetes. Considering the increased risks of premature mortality to autistic individuals, we limited our analyses to these four broad categories of physical health and tested risks overall, as well as by condition for all conditions reported with at least 1% prevalence in the cohort being tested. By restricting our analyses to these conditions that account for such a large proportion of worldwide mortality, we were able to employ more in-depth analyses on the differences in prevalence between autistic and non-autistic adults, as well as consider effects of lifestyle factors (smoking, alcohol, BMI), age, and sex. As such, we designed this analysis with the hopes of identifying specific points of intervention for healthcare providers, autistic individuals, and caregivers which, in turn, might serve to reduce risks of chronic disease and premature mortality among autistic individuals.

We used *R Version 3.6.2* to employ three sex-stratified statistical models, comparing rates of medical conditions among autistic females vs. non-autistic females, and separately, autistic males

vs. non-autistic males. We chose to segregate all our analyses by biological sex, as mortality and prevalence of physical health conditions in the general population vary greatly by biological sex (Oksuzyan et al., 2008; Verbrugge, Wingard, and Hayworth Continuing Features Submission, 1987), and some studies suggest that autistic females may be at even higher risk of health conditions and premature mortality (Croen et al., 2015; Davignon et al., 2018; Hirvikoski et al., 2016; Hwang et al., 2019; Rydzewska et al., 2018; Woolfenden et al., 2012).

The first model used sex-stratified one-tailed Fisher's exact tests. The second utilized sex-stratified binomial logistic regression (specifically Firth's Bias-Reduced Logistic Regression using the R package 'logistf') and controlled for demographic factors, including age, ethnicity, country of residence, and educational level (as a crude measure of socioeconomic status). The third also utilized sex-stratified binomial logistic regression and controlled for the same demographic factors, as well as some factors that may be related to lifestyle choices and daily habits, including Body Mass Index (BMI), alcohol use, and smoking. We used frequency of current alcohol consumption, as measured by the number of days per week with the following options: "I do not consume alcoholic beverages", "1-2 days per week", "3-4 days per week", and "5-7 days per week", to quantify alcohol use among participants. We used highest frequency of smoking ever, as measured by the regularity of smoking when smoking most frequently with the following options: "I have never smoked regularly", "Monthly", "Weekly", and "Daily", to quantify smoking among participants. We employed multiple imputation (using predictive mean matching within the MICE package) to address missingness in the data for the variables of age, BMI, educational-level, ethnicity, country of residence, smoking, and alcohol (Azur et al., 2011). We used

imputation exclusively for the covariates, therefore, the imputation only affected Model 2 and Model 3. We employed the False Discovery Rate correction to minimize the risks of Type I errors from multiple testing in both models and used a p-threshold of 0.05 for all three models (Benjamini & Hochberg, 1995). We also conducted z-tests to compare the relative risk of conditions between females and males, in order to determine whether our study replicates previous findings to suggest relatively larger risk of physical health conditions among autistic females in our sample, compared to autistic males. Finally, we performed post-hoc analyses on Model 2 to investigate the interaction of age and diagnosis on the likelihood of developing each of our outcomes of interest.

Ethical Approval

This study received ethical approval (HBREC.2017.28) from the University of Cambridge Human Biology Research Ethics committee.

Results

The mean age of the autistic group was 40.98 years of age (sd = 14.41) and the mean age of the control group was 41.84 years (sd = 15.50). The groups did not differ in age (Chi^2 = 81.878, df = 67, p > 0.05). Our sample was biased toward females, white individuals, and UK residents, and there were significant group differences. This was expected based on the methodology and recruitment strategies employed. Table 1 includes a summary of demographic information for both the autistic and non-autistic participants.

Table 1: Participant Demographics

Characteristics	Autism (n = 1,156)	Controls (n = 1,212)	p-values (Signif. Level)
Age (years), mean (SD)	40.98 (14.41)	41.84 (15.50)	0.304
Age (years), categories, N (%)			
16-29	298 (25.78)	311 (25.66)	
30-39	246 (21.28)	245 (20.21)	
40-49	243 (21.02)	256 (21.12)	
50-59	212 (18.34)	210 (17.33)	
60-69	108 (9.34)	124 (10.23)	
70+	25 (2.16)	52 (4.29)	
Missing	24 (2.08)	14 (1.16)	
Biological Sex, N (%)			0.017 (*)
Female	738 (63.84)	830 (68.48)	
Male	418 (36.16)	382 (31.52)	
Missing	0	0	
Ethnicity, N (%)			5.074×10^{-7} (***)
White	1021 (88.32)	1029 (84.90)	
Mixed Race	74 (6.40)	75 (6.19)	
Asian	18 (1.56)	41 (3.38)	
Latin American/ Hispanic	7 (0.61)	23 (1.90)	
Arab/ Middle Eastern	0 (0.00)	17 (1.40)	
Jewish	16 (1.38)	17 (1.40)	
African/ Black/ Caribbean	6 (0.52)	9 (0.74)	
Missing	14 (1.21)	1 (0.08)	
Education, N (%)			1.609×10^{-16} (***)
No formal qualifications	53 (4.58)	13 (1.07)	
Further vocational qualifications	206 (17.82)	140 (11.55)	
Secondary School/ High School	208 (17.99)	171 (14.11)	

University Undergraduate	348 (30.10)	358 (29.54)	
University Postgraduate	339 (29.33)	527 (43.48)	
Missing	2 (0.17)	3 (0.25)	
Country of Residence			3.126×10^{-7} (***)
United Kingdom	821 (71.02)	765 (63.12)	
United States of America	118 (10.21)	175 (14.44)	
Germany	30 (2.60)	33 (2.72)	
Australia	32 (2.77)	21 (1.73)	
Canada	25 (2.16)	24 (1.98)	
Ireland	13 (1.12)	30 (2.48)	
Netherlands	28 (2.42)	8 (0.66)	
Other	89 (7.70)	156 (12.87)	
Missing	1 (0.09)	3 (0.25)	
Body Mass Index (kg), mean (SD)	27.74 (8.30)	26.60 (6.87)	3.999×10^{-3} (***)
Missing	25 (2.16)	20 (1.65)	
Most Frequent Smoking, N (%)			0.031 (*)
Never	783 (67.73)	779 (64.27)	
Monthly	2 (0.17)	9 (0.74)	
Weekly	25 (2.16)	41 (3.38)	
Daily	346 (29.93)	382 (31.52)	
Missing	0	1 (0.08)	
Current Alcohol Frequency, N (%)			2.344×10^{-20} (***)
0 days per week	675 (58.39)	469 (38.70)	
1-2 days per week	292 (25.26)	475 (39.19)	
3-5 days per week	119 (10.29)	183 (15.10)	
6-7 days per week	69 (5.97)	84 (6.93)	
Missing	1 (0.09)	1 (0.08)	

SD = standard deviation
p-values were from Pearson's Chi Square test (categorical) or from a Mann-Whitney U test (means)
Note: These are demographic data before imputation. The results remain highly similar after imputation.

The following figures illustrate the reported prevalence of non-communicable diseases among autistic and non-autistic adults. Figure 1 shows the prevalence of the four large categories of non-communicable diseases that cumulatively account for the majority of worldwide mortality each year, as reported by the WHO. Figure 2 clarifies the prevalence of the specific conditions with at least 1% prevalence among the cohort being tested.

<INSERT FIGURES 1 and 2 HERE>

Summary of Results from all Three Models

Using one-tailed Fisher's exact tests, Model 1 provided us with an unadjusted model and is, thereby, the least conservative in estimating group differences between autistic and non-autistic adults. Model 1 found that autistic females are at increased risk of cardiovascular conditions overall and respiratory conditions overall, as well as specifically for low blood pressure, arrhythmias, asthma, and prediabetes than non-autistic females. Autistic males have elevated risks of cardiovascular conditions overall, as well as high cholesterol, arrhythmias, and Type II Diabetes, compared to non-autistic males. Supplementary Table 1 provides the complete results for Model 1.

Model 2 employed binomial logistic regression and controlled for demographic factors to reduce bias from our sampling methods (age, ethnicity, country of residence, and education-level) and attempts to quantify the group differences, regardless of which factors account for these differences. Model 2 found that autistic females have higher rates of cardiovascular, respiratory, and diabetic conditions overall, as well as specifically for low blood pressure, arrhythmias, asthma, and prediabetes than non-autistic females. Compared to non-autistic males, autistic males are at increased risk of arrhythmias. Supplementary Table 2 provides the complete results for Model 2.

Finally, Model 3 also used binomial logistic regression and controlled for the same demographic factors, and also controlled for factors that could be related to lifestyle and daily habits, including BMI, alcohol use, and smoking. Thus, Model 3 attempts to quantify risks between autistic and

non-autistic females and males, respectively, that expands beyond particular lifestyle choices, such as BMI, smoking, and alcohol use. Model 3 found that autistic females are more likely than non-autistic females to have cardiovascular, respiratory, and diabetic conditions overall, as well as specifically for low blood pressure, arrhythmias, asthma, and prediabetes; in addition, it found higher risk of arrhythmias for autistic males than for non-autistic males. Supplementary Table 3 provides the complete results for Model 3. Table 2 shows the results of the three models together for each of the categories or conditions tested.

Table 2: Summary of All Three Sex-Stratified Models

Conditions	Model 1			Model 2			Model 3			Signif. Models
	OR	*95% CI*	*Sig.*	*OR*	*95% CI*	*Sig.*	*OR*	*95% CI*	*Sig.*	
Cancer										
Female	0.830	0.517, Inf		1.098	0.627, 1.911		1.068	0.605, 1.872		
Male	0.864	0.484, Inf		0.840	0.431, 1.628		0.739	0.367, 1.473		
Cardiovascular										
Female	1.306	1.039, Inf	*	1.511	1.139, 2.010	**	1.383	1.033, 1.854	*	1, 2, 3
Male	1.438	1.082, Inf	*	1.590	1.104, 2.302	▲	1.542	1.056, 2.262		1
Respiratory										
Female	1.898	1.511, Inf	***	2.016	1.541, 2.647	***	2.054	1.557, 2.719	***	1, 2, 3
Male	1.067	0.745, Inf		0.955	0.623, 1.464		0.903	0.583, 1.399		
Diabetic										
Female	1.450	1.034, Inf	▲	1.835	1.223, 2.771	**	1.692	1.109, 2.599	*	2, 3
Male	1.668	1.015, Inf	▲	1.731	0.979, 3.132		1.509	0.822, 2.830		
Low Blood Pressure										
Female	2.941	1.842, Inf	***	2.900	1.716, 5.073	***	2.541	1.494, 4.467	**	1, 2, 3
High Blood Pressure										
Female	0.755	0.549, Inf		0.965	0.650, 1.426		0.873	0.578, 1.313		
Male	1.185	0.838, Inf		1.292	0.850, 1.975		1.158	0.743, 1.812		
High Cholesterol										
Female	0.980	0.666, Inf		1.435	0.892, 2.313		1.382	0.850, 2.248		
Male	1.679	1.110, Inf	*	1.523	0.924, 2.542		1.451	0.867, 2.456		1
Heart Disease										
Male	1.307	0.652, Inf		1.146	0.520, 2.593		1.121	0.501, 2.562		
Arrhythmia										
Female	2.871	1.913, Inf	***	2.941	1.854, 4.783	***	2.928	1.829, 4.804	***	1, 2, 3
Male	2.917	1.644, Inf	**	2.979	1.556, 6.047	*	3.085	1.561, 6.458	*	1, 2, 3
Asthma										
Female	1.978	1.565, Inf	***	2.069	1.571, 2.736	***	2.092	1.576, 2.789	***	1, 2, 3
Male	0.925	0.631, Inf		0.832	0.527, 1.313		0.796	0.499, 1.267		
Type II Diabetes										
Female	0.805	0.455, Inf		1.237	0.637, 2.386		1.028	0.510, 2.055		
Male	3.388	1.374, Inf	*	2.483	0.995, 7.150		1.799	0.688, 5.266		1
Prediabetes										
Female	3.153	1.687, Inf	**	4.337	2.147, 9.395	***	4.379	2.102, 9.772	***	1, 2, 3
Male	0.767	0.353, Inf		1.075	0.461, 2.483		1.020	0.419, 2.474		

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)
OR = Odds Ratio
95% CI = 95% Confidence Interval
Sig. = Significance Level
Sig. Models = Significant Models

In addition, we performed an interaction analysis, again using binomial logistic regression to determine if there was a significant interaction between age and autism diagnosis. There were marginally significant interactions between age and diagnosis for cardiovascular conditions overall for autistic females (compared to non-autistic females), as well as for high cholesterol and heart disease for autistic males (compared to non-autistic males); however, these results did not survive correction. Full results for this analysis are provided in Supplementary Table 4.

Finally, we performed z-tests on Models 2 and 3 to determine if there was relatively increased risk for any of the physical health conditions tested, based on biological sex. Our results support that autistic females are significantly more likely than autistic males to have respiratory conditions overall, as well as asthma and prediabetes specifically. There were no significant differences between autistic males and females for any other condition tested; full results are provided in Table 3 below.

Table 3: Risks of Conditions for Autistic Females vs. Autistic Males

Conditions	Model 2				Model 3			
	Female OR	Male OR	FDR p-value	Sig. Level	Female OR	Male OR	FDR p-value	Sig. Level
Cancer	1.098	0.840	0.876		1.068	0.739	0.655	
Cardiovascular	1.511	1.590	0.966		1.383	1.542	0.900	
Respiratory	2.016	0.955	0.018	*	2.054	0.903	8.754×10^{-3}	**
Diabetic	1.835	1.731	0.966		1.692	1.509	0.900	
High Blood Pressure	0.965	1.292	0.630		0.873	1.158	0.655	
High Cholesterol	1.435	1.523	0.966		1.382	1.451	0.900	
Arrhythmia	2.941	2.979	0.975		2.928	3.085	0.900	
Asthma	2.069	0.832	7.500×10^{-3}	**	2.092	0.796	4.481×10^{-3}	**
Type II Diabetes	1.237	2.483	0.497		1.028	1.799	0.655	
Prediabetes	4.337	1.075	0.027	*	4.379	1.020	0.024	*

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)

Note: We could not test sex differences for Low Blood Pressure or Heart Disease, as these were only tested in one sex each (females and males, respectively) for the purposes of this study

OR = Odds Ratio

Discussion

By utilizing three statistical models, we were able to parse out risks to a population of autistic adults more specifically than in previous studies. Results that demonstrate differences in physical health comorbidity across all three models suggests that these differences exist, regardless of both demographic and lifestyle-related factors. We found that, compared to non-autistic females, autistic females are more likely to have a cardiovascular condition (OR: 1.51), approximately twice as likely to have a respiratory condition (OR: 2.02) and asthma specifically (OR: 2.07), nearly 3 times as likely to have low blood pressure (OR: 2.90) and arrhythmias (OR: 2.94), and over 4 times as likely to have prediabetes (OR: 4.34); and that autistic males are also nearly three times as likely to have arrhythmias (OR: 2.98) than non-autistic males. It seems that both autistic females and males carry these increased risks, even when accounting for age, ethnicity, education-level, country of residence, BMI, smoking, and alcohol use. Therefore, this suggests that autistic adults have these increased health risks, even after taking into account the potential risks associated with obesity and substance use problems (which may be higher in autistic individuals) (Butwicka et al., 2016; Croen et al., 2015; Weiss et al., 2018; Zheng et al., 2017).

There is also limited evidence of elevated risks of diabetic conditions (OR: 1.84) for autistic females, as well as greater risks of cardiovascular conditions (OR: 1.59), high cholesterol (OR: 1.52), and Type II diabetes (OR: 2.48) for autistic males. However, these results are only supported by one or two models, so need to be taken as preliminary evidence at this stage.

In sum, the present results confirm previous findings of increased risks for diabetes (including prediabetes and Type II diabetes), cardiovascular conditions (including high cholesterol), and asthma (Croen et. al, 2015; Davignon et al., 2018; Weiss et al., 2018). Our findings do not confirm the results reported by Vohra and colleagues, which found decreased risk of cardiovascular, respiratory, and diabetic conditions; however, our participants may display greater physical health burden due to our sample's wider age range, as the earlier study only included 255 autistic participants over the age of 40 years (Vohra, Madhavan, and Sambamoorthi, 2017). Finally, our results extend previously reported conditions for autistic adults to include elevated risk of low blood pressure for autistic females, as well as increased risk of arrhythmias for both autistic females and autistic males.

We also tested the effects of age on developing these physical health conditions. Within our sample, we found no significant interaction between autism diagnosis and age. These results could reflect true patterns, suggesting that increasing age may similarly affect risk of developing chronic physical health conditions among both autistic and non-autistic individuals; alternatively, our sample could be underpowered to detect the interaction between autism diagnosis and age. Another important point to note is that we ask participants to report whether they have ever had a condition and do not ask the age at which the condition was diagnosed. As such, our study may not have the sensitivity in detecting effects of age. This may be particularly true for conditions, such as asthma, which are frequently diagnosed during childhood; thus, our results reflect the

cumulative likelihood of developing these conditions across the lifespan of each individual, rather than the conditions diagnosed exclusively during adulthood or over a particular time frame.

In regard to sex differences, our results suggest that autistic females may have excess risk of developing respiratory conditions, asthma, and prediabetes compared to autistic males. We found no significant differences in any other conditions tested which again may reflect true differences, or we may be underpowered due to undersampling of males. Increased risks among autistic females reported in our study align with previous findings from both mortality data (Hirvikoski et al., 2016; Woolfenden et al., 2012) and physical health studies (Croen et al., 2015; Davignon et al., 2018; Rydzewska et al., 2018), but expand the specific list of conditions for which autistic females may have excess risk. Further, these findings may have important policy implications for healthcare providers of autistic females: this group may require additional healthcare surveillance and patient education to reduce risk of developing physical health comorbidities.

Limitations

Whilst both autistic males and females appear to have increased physical health risks, this study is under-powered to provide reliable effect size differences between autistic and non-autistic adults, and particularly for rare medical conditions. Due to its relatively small sample size for epidemiological research, it may be subject to the 'winner's curse', resulting in artificially inflated odds ratios. Instead, it provides evidence of relatively increased risk for autistic adults across the

lifespan, which should be investigated further. In addition, future research should attempt to recruit larger samples, in order to consider differences in risk of physical health comorbidity across age groups, by comparing prevalence of health conditions among young, middle-aged, and older adults separately.

This study used a self-report survey measure, rather than medical records. Thus, our study relied on participants to provide an accurate account of their physical health conditions, which may introduce bias into our sample. The study may also be subject to sampling bias, as we advertised the study via various sources of social media, and autism support groups and charities. Further, the survey was only available in English, and this may have biased our sample as well.

Another limitation is that our methodology excluded participants who are unable to participate in an online, self-report survey. This likely limited our analyses to individuals with access to the internet, as well as average intellectual ability and physical functioning, which is not representative of the entire autistic population. Evidence from mortality data (Hirvikoski et al., 2016; Hwang et al., 2019; Woolfenden et al., 2012) suggests that autistic individuals with intellectual disability may be at particularly high risk for premature mortality and that the specific risk factors for premature mortality in this group may be different to autistic individuals without intellectual disability. Future research should focus on identifying the physical health risks of autistic individuals across the spectrum of intellectual ability and physical functioning.

Our control population may not be representative of the general population, as our recruiting methods may have been more likely to reach individuals with an interest in autism, or who may suspect that they are autistic. We excluded individuals from both the autistic and control groups who reported self-diagnosis of autism or suspected they are autistic. However, even with these exclusions, we cannot preclude the possibility that our control group may include some individuals with undiagnosed autism, high autistic traits, a broad autistic phenotype, or genetic liability for autism. Thus, our results may underestimate true group differences between autistic and non-autistic individuals.

It was particularly challenging to recruit males (both autistic and non-autistic) to the sample; this was expected, as self-report surveys are typically heavily biased toward female respondents, and this pattern is reported specifically for online surveys focused on healthcare (Aerny-Perreten et al., 2015; Cheung et al., 2017; Cull et al., 2005; Listyowardojo et al., 2011). We expect that under-sampling of males limited our power and, thereby, our sensitivity in identifying smaller differences in physical health risks between autistic and non-autistic males. However, our results support that autistic females and males both have increased risks compared to the non-autistic population, and also that risk may vary based on biological sex.

Strengths

Although previous studies have found increased health risks for autistic individuals, the current research expands the breadth of conditions that are associated with autistic adults. Self-report

survey measures tend to attract female respondents disproportionately (Aerny-Perreten et al., 2015; Cheung et al., 2017; Cull et al., 2005; Listyowardojo et al., 2011), allowing us to sample a large group of autistic females. Existing studies of autistic adults use medical, insurance, or census records to determine physical health comorbidities. Thus, their data will include a strong sex bias toward males within their autism population (approximately 3:1 or 4:1). As such, the existing study of physical health of autistic adults fails to consider unique risks of autistic females, due to under-sampling of this population; however, prevalence of physical health conditions varies greatly by biological sex in the general population (Oksuzyan et al., 2008; Verbrugge, Wingard, and Hayworth Continuing Features Submission, 1987). Our methodology also allowed us to recruit a large, international cohort and, thereby, to reach a greater number of autistic adults across the lifespan, and especially understudied groups: 738 autistic females, an average age of approximately 41 years in both the autistic and control groups, and 588 autistic participants aged 40 years or older. As the largest sample of middle-aged and older autistic females, our results make clear that there are significant health risks to this group, even when taking lifestyle factors into account.

Another advantage of our methodology is that our study had very little missing data; missing data and the biases introduced by imputation are significant issues in retrospective medical record analysis. Model 1 in our study avoided any biases from imputation; and while some values for the seven covariates were imputed in Model 2 and Model 3, 2.16% or less of the data for any variable were missing for either the autistic or non-autistic groups.

A final strength of our methodology is that we are the first large-scale study to quantify the effect of lifestyle factors (such as smoking, alcohol use, and BMI) on risk of developing chronic physical health conditions among autistic adults. Specifically, our analyses focus on identifying differences in prevalence of cancers, cardiovascular conditions, respiratory conditions, and diabetic conditions, and their relationship to lifestyle factors; collectively these conditions account for over 70% of worldwide mortality, and our study provides insight into some of the increased physical health risks that may contribute to premature mortality seen among autistic individuals across the spectrum. As our results suggest that these physical health risks remain even after accounting for differences in lifestyle factors, this study may have implications for future healthcare of autistic adults, and the importance of healthcare maintenance checks in preventing premature mortality among autistic individuals.

Contributing Factors

There are several reasons that autistic adults may carry a greater physical health burden than others. As autism is polygenic in nature, there may be overlapping genetic risks from either rare or common variants between autism and physical health conditions. A recent study utilized pathway network analyses to show that genes associated with autism may also provide vulnerability to chronic medical conditions, including cancer, cardiovascular conditions, and metabolic conditions (and specifically Type II diabetes) (Wen, Alshikho, and Herbert, 2016). We excluded individuals who reported genetic syndromes that are known to have clear physical health risks; however, future research should focus on utilizing both genetic and health data together, in order to establish relative genetic risk of particular conditions. Another biological

factor that may affect risk of developing physical health conditions is dysregulation of sex steroid hormones; autistic individuals may be more likely to have elevated prenatal steroidogenic activity, later hormone dysregulation, and/or hormone-related health conditions in later adulthood (Baron-Cohen et al., 2015; Baron-Cohen & Tsompanidis et al., 2019; Berni et al., 2018; Cherskov et al., 2018; Kosidou et al., 2016; Pohl et al., 2014; Ruta et al., 2011; Schwarz et al., 2011), which may in turn increase likelihood of developing obesity and a variety of physical health conditions including cancer, diabetes, cardiovascular conditions (Berni et al., 2018; Bhupathy, Haines, & Leinwand, 2010; Brand et al., 2011; Cherskov et al., 2018; Kosidou et al., 2016; Mantovani & Fucic, 2014).

Further, while our study attempts to control for some lifestyle factors, these measures are limited in their ability to detail actual lifestyle differences between autistic and non-autistic adults. Our sample only accounts for participants' currently alcohol consumption frequency and the frequency of their smoking when smoking the most; additionally, we know that body mass index may correspond to lifestyle choices, including diet and exercise, but also may relate to genetic or other unknown factors as well. Future research should focus on establishing lifestyle differences between middle-aged and older autistic and non-autistic adults that could contribute to physical health risks.

Recent research has identified that autistic adults may be at higher risk of negative life experiences (Griffiths et al., 2019) and that, in children, these negative life experiences can affect their health (Rigles 2016). Finally, differences in the prevalence of physical health conditions may

be related to the quality of care received by autistic individuals. There is evidence of increased healthcare utilization among autistic adults, with one study even suggesting that autistic adults may carry double the total annual mean healthcare costs of individuals in the general population (Vohra, Madhavan, and Sambamoorthi, 2017; Weiss et al., 2018; Zerbo et al., 2019). Despite this, autistic adults report lower satisfaction with patient-provider communication, lower self-efficacy for both general healthcare and chronic conditions, higher odds of unmet healthcare needs related to physical health, and greater odds of using emergency care (Nicolaidis et al., 2013). Further, a recent systematic review found that patient-provider communication, sensory sensitivities, and executive functioning/ planning issues served as significant barriers to accessing healthcare for autistic individuals; in addition, negative experiences with healthcare providers and healthcare providers' lack of knowledge of autism both served as barriers in at least one of the studies included (Mason et al., 2019). Lack of appropriate healthcare services and of useful support may magnify underlying healthcare risks by failing to provide early intervention.

In order to reduce the risk of physical health comorbidities in autistic adults, future research must focus on establishing the relative contribution of each of these factors to the physical health risks and premature mortality of autistic individuals.

Conclusions

This study reports evidence of increased physical health risks for autistic adults in the areas of cardiovascular, respiratory, and diabetic conditions. Many of these risks remain for autistic individuals, even when taking alcohol use, smoking, and BMI into account. The 2016 WHO report states that these conditions account for a large proportion of premature mortality in the general population. We know that autistic individuals are at elevated risk of premature mortality. Therefore, future research should focus on further clarifying physical health risks to autistic adults across the lifespan that may contribute to premature mortality, as well as establishing the reasons for increased physical health risks among autistic adults.

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Supplementary Material

We have provided images of the questionnaire to display how the relevant physical health survey questions appeared to participants, including the categories or specific non-communicable conditions for which this paper provided results. As the study employed a tiered structure design, participants were first directed to the question shown in Figure 1 below, and were asked to identify the relevant categories for their personal medical history:

Figure 1: List of Condition Categories

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 1 HERE>

Follow-up questions would only appear for participants that selected particular category. We provided different questions for types of cancer females and males, based on participants' selection for their gender assigned at birth, as certain cancers are sex-specific (such as ovarian or testicular cancer) and others are far more common in one sex (such as breast cancer). The cancer questions are shown in Figures 2 and 3.

Figure 2: List of Cancer Types for Females

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 2 HERE>

Figure 3: List of Cancer Types for Males

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 3 HERE>

Participants were also able to select two broad categories that related to cardiovascular conditions, Heart Condition or Risk of Stroke. Both of these conditions led to the same list of conditions related to cardiovascular health; this follow-up question is shown in Figure 4.

Figure 4: List of Cardiovascular Conditions

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 4 HERE>

Participants that selected the category for Lung Condition were directed to the following set of conditions, shown in Figure 5.

Figure 5: List of Respiratory Conditions

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 5 HERE>

Participants that selected the category for Prediabetes or Diabetes were directed to the following set of conditions, shown in Figure 6.

Figure 6: List of Diabetic Conditions

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 6 HERE>

Finally, participants were directed to a final free-text question, in case they had missed out on a condition or wanted to provide information relating to their health or medical history that was not covered by the preceding questions of the survey. This question is show in Figure 7.

Figure 7: Free-text Question on Health or Medical History

<INSERT SUPPLEMENTARY MATERIAL, FIGURE 7 HERE>

As our study utilized the tiered structure design, data cleaning involved searching all free text boxes of each record to ensure that all conditions were coded correctly. We performed this data cleaning in order to correct for any errors introduced by the tiered structure design of the survey.

We corrected coding as necessary, to ensure that any condition listed throughout the survey (including the questions relating to syndromes, disabilities, autoimmune conditions, and the final free-text question) was coded in the appropriate category. In addition, we corrected coding in order to meet our criteria for non-communicable diseases. For example, individuals who selected the broad category of 'Lung Condition' but only listed a particular infection and no other respiratory conditions, such as pneumonia or whooping cough (which are communicable diseases), were re-coded to note that they did not possess a respiratory condition. While the vast majority of respondents coded all conditions correctly, we wanted to ensure that conditions listed anywhere by participants were associated with the correct category.

Supplementary Table 1: Model 1, Sex-Stratified Health Risks by Condition (Unadjusted)

Conditions	Odds Ratios	95% Confidence Interval	Fisher's Exact Test p-value	False Discovery Rate	Signif. Level
Cancer (Overall)					
Female	0.830	0.517—Inf	0.799	0.882	
Male	0.864	0.484—Inf	0.732	0.801	
Cardiovascular (Overall)					
Female	1.306	1.039—Inf	0.027	0.049	*
Male	1.438	1.082—Inf	0.017	0.049	*
Respiratory (Overall)					
Female	1.898	1.511—Inf	8.821×10^{-7}	4.851×10^{-6}	***
Male	1.067	0.745—Inf	0.417	0.573	
Diabetic (Overall)					
Female	1.450	1.034—Inf	0.035	0.054	▲
Male	1.668	1.015—Inf	0.045	0.098	▲
Low Blood Pressure					
Female	2.941	1.842—Inf	2.135×10^{-5}	5.872×10^{-5}	***
High Blood Pressure					
Female	0.755	0.549—Inf	0.949	0.949	
Male	1.185	0.838—Inf	0.226	0.414	
High Cholesterol					
Female	0.980	0.666—Inf	0.579	0.796	
Male	1.679	1.110—Inf	0.018	0.049	*
Heart Disease					
Male	1.307	0.652—Inf	0.306	0.481	
Arrhythmia					
Female	2.871	1.913—Inf	2.091×10^{-6}	7.667×10^{-6}	***
Male	2.917	1.644—Inf	4.492×10^{-4}	4.942×10^{-3}	**
Asthma					
Female	1.978	1.565—Inf	3.473×10^{-7}	3.821×10^{-6}	***
Male	0.925	0.631—Inf	0.680	0.801	
Type II Diabetes					
Female	0.805	0.455—Inf	0.802	0.882	
Male	3.388	1.374—Inf	8.764×10^{-3}	0.048	*
Prediabetes					
Female	3.153	1.687—Inf	5.405×10^{-4}	1.189×10^{-3}	**
Male	0.767	0.353—Inf	0.801	0.801	

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)

Supplementary Table 2: Model 2, Sex-Stratified Health Risks by Condition (Adjusting for Age, Ethnicity, and Education-Level)

Conditions	Odds Ratios	95% Confidence Interval	Binomial Logistic Regression p-value	False Discovery Rate	Signif. Level
Cancer (Overall)					
Female	1.098	0.627—1.911	0.741	0.815	
Male	0.840	0.431—1.628	0.603	0.830	
Cardiovascular (Overall)					
Female	1.511	1.139—2.010	4.192×10^{-3}	6.587×10^{-3}	**
Male	1.590	1.104—2.302	0.013	0.069	▲
Respiratory (Overall)					
Female	2.016	1.541—2.647	2.636×10^{-7}	1.450×10^{-6}	***
Male	0.955	0.623—1.464	0.832	0.866	
Diabetic (Overall)					
Female	1.835	1.223—2.771	3.285×10^{-3}	6.022×10^{-3}	**
Male	1.731	0.979—3.132	0.059	0.163	
Low Blood Pressure					
Female	2.900	1.716—5.073	5.046×10^{-5}	1.110×10^{-4}	***
High Blood Pressure					
Female	0.965	0.650—1.426	0.857	0.857	
Male	1.292	0.850—1.975	0.230	0.423	
High Cholesterol					
Female	1.435	0.892—2.313	0.136	0.188	
Male	1.523	0.924—2.542	0.099	0.218	
Heart Disease					
Male	1.146	0.520—2.593	0.736	0.866	
Arrhythmia					
Female	2.941	1.854—4.783	2.855×10^{-6}	1.047×10^{-5}	***
Male	2.979	1.556—6.047	7.885×10^{-4}	8.674×10^{-3}	*
Asthma					
Female	2.069	1.571—2.736	1.850×10^{-7}	1.450×10^{-6}	***
Male	0.832	0.527—1.313	0.430	0.676	
Type II Diabetes					
Female	1.237	0.637—2.386	0.526	0.643	
Male	2.483	0.995—7.150	0.051	0.163	
Prediabetes					
Female	4.337	2.147—9.395	2.523×10^{-5}	6.937×10^{-5}	***
Male	1.075	0.461—2.483	0.866	0.866	

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)

Supplementary Table 3: Model 3, Sex-Stratified Health Risks by Condition (Adjusting for Age, Ethnicity, Education-Level, BMI, Alcohol, and Smoking)

Conditions	Odds Ratios	95% Confidence Interval	Binomial Logistic Regression p-value	False Discovery Rate	Signif. Level
Cancer (Overall)					
Female	1.068	0.605—1.872	0.820	0.902	
Male	0.739	0.367—1.473	0.390	0.612	
Cardiovascular (Overall)					
Female	1.383	1.033—1.854	0.029	0.046	*
Male	1.542	1.056—2.262	0.025	0.136	
Respiratory (Overall)					
Female	2.054	1.557—2.719	2.830×10^{-7}	1.557×10^{-6}	***
Male	0.903	0.583—1.399	0.647	0.792	
Diabetic (Overall)					
Female	1.692	1.109—2.599	0.015	0.027	*
Male	1.509	0.822—2.830	0.186	0.511	
Low Blood Pressure					
Female	2.541	1.494—4.467	4.821×10^{-4}	1.061×10^{-3}	**
High Blood Pressure					
Female	0.873	0.578—1.313	0.514	0.628	
Male	1.158	0.743—1.812	0.517	0.711	
High Cholesterol					
Female	1.382	0.850—2.248	0.192	0.263	
Male	1.451	0.867—2.456	0.157	0.511	
Heart Disease					
Male	1.121	0.501—2.562	0.782	0.860	
Arrhythmia					
Female	2.928	1.829—4.804	5.002×10^{-6}	1.834×10^{-5}	***
Male	3.085	1.561—6.458	9.726×10^{-4}	0.011	*
Asthma					
Female	2.092	1.576—2.789	2.554×10^{-7}	1.557×10^{-6}	***
Male	0.796	0.499—1.267	0.335	0.612	
Type II Diabetes					
Female	1.028	0.510—2.055	0.938	0.938	
Male	1.799	0.688—5.266	0.237	0.522	
Prediabetes					
Female	4.379	2.102—9.772	5.011×10^{-5}	1.378×10^{-4}	***
Male	1.020	0.419—2.474	0.964	0.964	

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)

Supplementary Table 4: Interaction of Age and Diagnosis in Autistic and Non-Autistic Females and Males, respectively

Conditions	Age by Diagnosis Interaction Coefficient	p-value	False Discovery Rate	Age Coefficient	p-value	False Discovery Rate
Cancer (Overall)						
Female	-8.395×10^{-3}	0.672	0.878	0.066	4.185×10^{-8}	1.151×10^{-7}
Male	-0.028	0.187	0.687	0.063	1.038×10^{-5}	3.805×10^{-5}
Cardiovascular (Overall)						
Female	-0.023	0.021	0.228	0.056	1.110×10^{-16}	6.106×10^{-16}
Male	-4.459×10^{-4}	0.971	0.971	0.057	1.091×10^{-10}	1.200×10^{-9}
Respiratory (Overall)						
Female	-1.453×10^{-3}	0.878	0.878	-1.511×10^{-3}	0.824	0.824
Male	4.317×10^{-3}	0.749	0.971	3.496×10^{-3}	0.730	0.775
Diabetic (Overall)						
Female	0.013	0.361	0.878	0.042	1.173×10^{-5}	2.580×10^{-5}
Male	4.356×10^{-3}	0.823	0.971	0.029	0.056	0.084
Low Blood Pressure						
Female	0.025	0.178	0.654	4.622×10^{-3}	0.754	0.824
High Blood Pressure						
Female	-9.833×10^{-3}	0.490	0.878	0.071	0	0
Male	-0.012	0.417	0.971	0.053	2.012×10^{-7}	1.107×10^{-6}
High Cholesterol						
Female	5.345×10^{-3}	0.762	0.878	0.070	6.404×10^{-11}	2.348×10^{-10}
Male	0.039	0.033	0.205	0.039	2.477×10^{-3}	6.812×10^{-3}
Heart Disease						
Male	0.068	0.037	0.205	0.050	5.396×10^{-3}	0.012
Arrhythmia						
Female	-2.667×10^{-3}	0.867	0.878	0.020	0.123	0.181
Male	9.363×10^{-3}	0.667	0.971	0.035	0.054	0.084
Asthma						
Female	3.451×10^{-3}	0.724	0.878	-9.248×10^{-3}	0.194	0.237
Male	5.660×10^{-4}	0.969	0.971	-3.064×10^{-3}	0.775	0.775
Type II Diabetes						
Female	0.013	0.596	0.878	0.061	1.656×10^{-5}	3.035×10^{-5}
Male	0.039	0.757	0.971	0.027	0.169	0.206
Prediabetes						
Female	-0.010	0.106	0.582	0.043	0.131	0.181
Male	-6.969×10^{-3}	0.807	0.971	0.037	0.061	0.084

Significance Level: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), ▲ ($p < 0.10$)

These are the full results for our analysis on the interaction between age and diagnosis. Although there were marginally significant interactions between age and diagnosis for cardiovascular conditions overall for autistic females (compared to non-autistic females), as well as for high

cholesterol and heart disease for autistic males (compared to non-autistic males), these results did not survive correction.