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ORIGINAL RESEARCH

The Burden of Attention-Deficit/Hyperactivity Disorder Traits in Adult Patients with Major Depressive Disorder in Japan

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Purpose: Symptoms of attention-deficit/hyperactivity disorder (ADHD) often overlap with and are hidden by those of mood disorders, including major depressive disorder (MDD), resulting in adult ADHD patients being misdiagnosed as MDD. This study aims to examine if diagnosed MDD patients are more likely to exhibit ADHD traits and if the presence of ADHD traits increases the humanistic burden, including the impairment of health-related quality of life (HRQoL), work productivity and activity impairment (WPAI), and health-care resource utilization (HRU), on MDD patients in Japan.

Methods: This study utilized existing National Health and Wellness Survey (NHWS) data. The 2016 Japan NHWS is an internet-based survey comprising a total of 39,000 respondents, including those with MDD and/or ADHD. A randomly selected subset of the respondents responded to the Japanese-version Adult ADHD self-report scale (ASRS-v1.1; ASRS-J) symptom checklist. Respondents were considered ASRS-J-positive if the total score was ≥36. The HRQoL, WPAI, and HRU were assessed.

Results: Among MDD patients (n = 267), 19.9% were screened ASRS-J-positive, while 4.0% of non-MDD respondents (n = 8885) were ASRS-J-positive. There was a significant association between MDD status and ASRS-J status (crude odds-ratio [OR]: 5.9) as well as between MDD status and ADHD-diagnosis status (crude OR: 22.6). MDD patients who were ASRS-J positive experienced significantly lower HRQoL and higher WPAI than those who were ASRS-J negative. Limitations of this study include potential recall bias owing to the self-report nature of the survey and lack of objective confirmation of MDD diagnosis through review of medical records.

Conclusion: This study demonstrated a significant association between MDD status and exhibiting ADHD traits. Adult MDD patients screened ASRS-J-positive experienced significantly higher humanistic burden than patients screened ASRS-J-negative. Our results emphasize the importance of ensuring appropriate screening of ADHD and looking out for potentially hidden ADHD symptoms when diagnosing and treating MDD in adulthood.

Keywords: attention-deficit/hyperactivity disorder, web-based survey, major depressive disorder, undiagnosed ADHD, humanistic burden

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that is characterized by inattention, hyperactivity and impulsivity that negatively impact social and academic/occupational activities.[1] Although ADHD is traditionally recognized in the pediatric population, research effort in recent years has shifted to understand the disorder's manifestation in adults.[2,3] Overall, prevalence estimates of ADHD in adults are lower than in children and adolescents. The adult ADHD prevalence has been estimated to be 2.5–2.8%.[4,5] In Japan, the prevalence of adult ADHD was estimated to be 1.65%.[6]

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Adult ADHD is frequently comorbid with other psychiatric disorders, including mood and anxiety disorders, substance use disorders, and personality disorders.[7,8] The coexistence of these conditions can complicate the recognition and diagnosis of ADHD, leading to an increasing concern that comorbid ADHD in adults with other disorders is not being accurately diagnosed and treated.[9] In clinical populations, the rates of co-occurrence of ADHD and major depressive disorders (MDD) are within the wide range of 16% to 31%.[10] The National Comorbidity Survey Replication[11] estimated that 9.4% of adults who met the criteria for MDD and 22.6% of adults who met the criteria for dysthymic disorder also met the criteria for ADHD. Furthermore, it has been shown that patients with co-occurrence of ADHD and MDD are associated with more severe symptoms compared to those with any one disorder.[12–14] Moreover, in addition to the typical hyperactive-impulsive symptoms described in pediatric population, ADHD in adults is characterized by a more heterogeneous clinical presentation that includes a wider range of emotional dysregulation and functional impairment.[7,15] Hence, the non-specific complaints presented by adults with ADHD may lead to a potential misdiagnosis as MDD.

When ADHD is comorbid with other psychiatric disorders such as MDD,[7,16] a higher treatment priority would be considered for the more disabling condition.[7,16–18] However, adults with ADHD symptoms may not have recognized their ADHD symptoms continuing from the past to the present owing to low environmental demands, family supports, and/or possess mild symptoms below the assessment threshold.[19,20] Under such a scenario, comorbidities such as MDD could develop as a result of worsening ADHD symptoms due to maladjustments under environmental changes. As a result, adults with ADHD may not be aware of the ADHD symptoms and many physicians might end up treating only depressive symptoms because they tend to be more expressed in the clinical setting. The identification and treatment of comorbidities (including mood disorders) in adult ADHD patients, and vice versa, has the potential to alter the trajectory of psychiatric morbidity later in life.[7] Therefore, there is a need to better understand and characterize the burden of ADHD traits on individuals with MDD.

Given both ADHD and MDD can have a significant deleterious impact on many aspects of adult life, affecting social and emotional well-being as well as professional development,[21,22] it is crucial to characterize the social and health implications of ADHD coexisting with MDD for improving patient care and treatment outcomes. In ADHD patients with comorbid MDD, the risk of mortality and suicide attempt is higher.[23,24] Studies also found that MDD individuals with ADHD symptoms had higher resistance to depression treatment and increased psychiatric hospitalizations.[22,25] Despite the frequent co-occurrence of ADHD and MDD in adulthood,[7,26] there is limited literature on the co-occurrence of ADHD and MDD in adults in Japan. A recent study investigating the association between self-perceived ADHD-related characteristics and depression severity estimated that 34% of adult patients with mood and anxiety disorders screened positive on the adult ADHD self-report scale-v1.1 (ASRS-v1.1).[27] However, no study has compared the prevalence of ADHD symptoms between patients with MDD and healthy subjects in Japan. To the best of our knowledge, the impact of ADHD symptoms in adulthood in terms of the humanistic burden on adult MDD patients has not been extensively investigated. Understanding the humanistic burden in terms of health-related quality of life (HRQoL), work productivity and activity impairment (WPAI), and health-care resource utilization (HRU) would provide a wider overview of the socioeconomic burden experienced by these patients in the community.

Using existing data from a web-based survey that was designed to assess the burden of illness in the general Japanese population of adults, we determined 1) whether patients with MDD are more likely to exhibit ADHD traits compared to those without MDD, and 2) whether exhibiting ADHD traits (being screened positive by the ADHD Symptom Checklist) increases the humanistic burden on patients with MDD. The insights from this study would provide not only an understanding of the prevalence of adult MDD with ADHD symptoms in Japan but also an understanding of the burden of ADHD symptoms on MDD patients beyond that of the severity of MDD and ADHD symptoms for effective management of MDD among adult patients with hidden ADHD symptoms.

Materials and Methods

Study Design and Participants

Existing cross-sectional data were utilized in this study. Data was collected from the 2016 Japan National Health and Wellness Survey (NHWS). The NHWS is an internet-based self-administered survey collecting respondents' self-

reported characteristics, disease information, and health outcomes from the general population aged ≥18 years old in Japan. Invitations to participate in the survey were sent to existing members of web-based opt-in consumer panels, who agreed to join the panel and receive periodic invitations to online surveys. Panel members receive honoraria in terms of panel points for completion of online surveys. Respondents to the NHWS Japan were recruited based on an age and gender stratified random sampling frame according to Japan's national census data to ensure that the age and gender distribution of NHWS respondents was comparable to the general adult population in Japan. The 2016 NHWS Japan was determined to be exempted upon review by Pearl International Review Board (Indianapolis, IN, IRB Study Number: 16-KAN-124). Informed online consent was provided by the respondents prior to participation and the respondents had the rights to withdraw from the survey at any time. De-identified data was collected. Patient identification code in the database was anonymized and cannot be linked back to the original respondent.

Study Population

Patients with MDD were defined as respondents who self-reported that they had experienced MDD in the past 12 months and had been diagnosed by a physician of MDD. Respondents who self-reported that they had not experienced MDD were defined as non-MDD respondent group. Respondents who self-reported that they had ever experienced schizophrenia were excluded from this study.

Respondents who self-reported being diagnosed by a physician for ADHD or attention deficit disorder (ADD) were defined as diagnosed ADHD patients.

A random subset of all 2016 NHWS Japan respondents was selected and required to respond to the Japanese version of the Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist. The Japanese ASRS-v1.1 was established from the original ASRS-v1.1 Symptom Checklist, which consists of 18 items on the symptoms of ADHD and measures the frequency of symptoms using a 5-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = very often).[28] The ASRS-v1.1 Symptom Checklist also includes darkly shaded boxes based on the frequency of the symptoms and selection within these boxes indicates more severe symptoms for the respective items.

Two cut-off-scoring metrices were applied to the responses obtained from the ASRS-v.1.1: i) Japanese-specific cut-off metric (ASRS-J) – respondent in this study was considered ASRS-J positive if the total score was 36 or more, as described and validated in a previous study focusing on the Japanese version of the ASRS-v1.1;[28] ii) original ASRS cut-off metric (ASRS-A) – respondent was considered ASRS-A positive if at least 4 out of 6 questions fall under the darkly shaded boxes in Part A.[29] In this study, the ASRS-v1.1 was used to identify ADHD traits, in addition to self-reported ADHD, to investigate the frequency of ADHD traits and the impact of exhibiting ADHD traits on humanistic burden among MDD patients. The focus was not just self-reported diagnosed ADHD patients because we intended to clarify the burden on MDD patients with ADHD traits without a diagnosis of ADHD who have inadaptations that make them difficult to live, and whose depressive symptoms are negatively impacted by their ADHD traits.

Respondents' Characteristics and Outcomes Measures

Demographic characteristics, including age, gender, marital status, level of education, employment status, and household income, were self-reported by the respondents. Respondents also self-reported general health characteristics including body mass index (BMI), Charlson Comorbidity Index (CCI),[30] and lifestyle factors (eg, smoking, alcohol consumption, and exercise behaviour). Severity of depressive symptoms was assessed by the validated Patient Health Questionnaire-9 (PHQ-9).[31] The PHQ-9 is a 9-item questionnaire that measures frequency of depression symptoms, with items scored on a 4-point scale (0 = not at all to 3 = nearly every day).[32]

Health-related quality of life of respondents was assessed using the Short Form 12-Item (version 2) Health Survey (SF-12v2) instrument.[33] It is a validated instrument comprising 12 questions with two summary scores – physical component summary (PCS) and mental component summary (MCS) scores.

Health state utilities were quantified by the EuroQoL 5-dimention scale (EQ-5D) utility score derived from the EQ-5D instrument using the Japanese population norms.[34] The EQ-5D instrument assesses health in five dimensions, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

The WPAI questionnaire, a six-item validated instrument was used to measure the degree of work productivity and activity impairment[35] through four metrics of absenteeism, presenteeism, total work productivity impairment, and activity impairment due to one's health in the past seven days. Only respondents who reported being employed full time, part-time or self-employed were surveyed for absenteeism, presenteeism, and total work productivity impairment. All respondents provided data for activity impairment.

Health-care resource utilization was measured in terms of the number of visits to the health-care provider (HCP) in the past six months for personal medical conditions.

Statistical Analysis

Demographic, general health characteristics and health outcomes were summarized using counts and percentages for categorical variables and means and standard deviations (S.D.s) for continuous variables. One-way analysis of variance (ANOVA) and chi-square tests were used to compare the variables and outcomes of interest between the respondent groups. Post-hoc analysis was conducted to understand the association between PHQ-9 score and ASRS-J score by evaluating the scatter plot and the correlation coefficient.

Crude odds ratio (OR) between ASRS status and MDD status was calculated using the contingency table. Pearson's chi-square test was conducted to assess if the association between ASRS and MDD status was statistically significant. Logistic regression with MDD status being the dependent variable and ASRS status being the independent variable was used to further evaluate the association by adjusting for potential confounding factors, ie, demographic- and general health-related covariates.

Crude OR between ADHD diagnosis status and MDD status was also calculated using the contingency table. Adjusted OR was not calculated due to limited sample size.

The HRQoL, WPAI and HRU, were compared between the groups using generalized linear models (GLMs) to control for demographic and general health covariates (age, gender, marital status, education, employment status, household income, health insurance, CCI, BMI, alcohol consumption, and smoking status) and ensure that the groups were balanced and matched. Approximately normally distributed outcomes including HRQoL summary scores (PCS, MCS, and EQ-5D index scores) were analysed by GLMs and normal distributions with identity link functions. For outcome variables with skewed distribution, such as WPAI and HRU, GLMs and negative binominal distributions with log link functions were used. Covariates used in the GLMs were the same as those used in the logistic regression. Estimated adjusted means with 95% confidence intervals (C.I.s) and p-values for all outcomes were reported.

All statistical analyses were performed using IBM SPSS Statistics Version 25.[36] P-values of <0.05 were considered statistically significant. No formal hypothesis testing was planned for this study and thus correction for multiple testing was not conducted.

Results

Participants

Among the 39,000 respondents to the 2016 Japan NHWS, a subgroup of randomly selected respondents (n = 9657) responded to the ASRS-v1.1 Symptom Checklist (Figure 1). Of these, 267 patients self-reported being diagnosed by a physician for MDD and having never experienced schizophrenia before (MDD patients), while 8885 respondents self-reported that they had never experienced MDD and schizophrenia (non-MDD respondents).

Among MDD patients, 53 and 214 of them were screened to be ASRS-J positive and negative, respectively. Of the non-MDD respondents, 356 and 8529 were screened to be ASRS-J positive and negative, respectively (Figure 1). On the other hand, 42 and 225 MDD patients were screened to be ASRS-A positive and negative, respectively; and 220 and 8665 non-MDD respondents were ASRS-A positive and negative, respectively (Supplementary Figure 1).

Demographic and General Health Characteristics

Among MDD patients who were ASRS-J negative and ASRS-J positive, no significant differences were observed in terms of demographic and general health characteristics except for marital status (44.4% vs 32.1% married or living

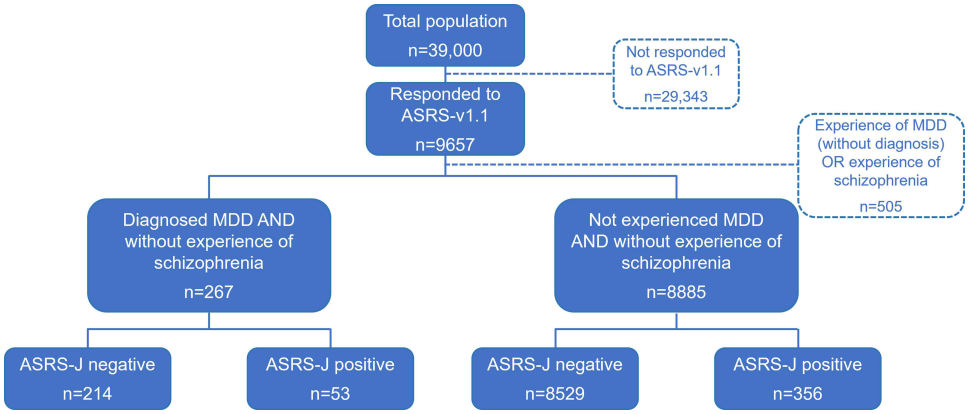

Figure 1 Respondent flow chart (ASRS-J).
Notes: ASRS-J positive/negative respondents were determined based on ASRS-J cut-off score.[28]
Abbreviations: ASRS, Adult ADHD Self-Report Scale; MDD, major depressive disorder.

with partner) and BMI (26.2% vs 39.6% obese) (Table 1). Interestingly, MDD patients who were ASRS-J positive had significantly higher PHQ-9 scores compared to those who were ASRS-J negative ([mean±S.D.] 17.83±7.63 vs 10.64±6.72, $p < 0.001$), indicating that ASRS-J positive MDD patients experienced more severe depressive symptoms.

Non-MDD respondents who were ASRS-J positive were significantly younger than those who were ASRS-J negative (42.15±16.10 vs 51.38±16.25, $p < 0.001$). More ASRS-J positive non-MDD respondents were not married (45.8% vs 65.8% married or living with partner) and currently employed (69.1% vs 61.5%), consumed alcohol no more than once per week (71.3% vs 61.9%), and exercised less than 12 times in past 30 days (85.7% vs 78.6%) than ASRS-J negative respondents (Table 1). Non-MDD respondents with ASRS-J positive had significantly higher PHQ-9 scores compared to

Table 1 Demographic and General Health Characteristics of MDD Patients and Non-MDD Respondents with ASRS-J Negative and ASRS-J Positive in Japan

		MDD Patients					Non-MDD Respondents				
		ASRS-J Positive (n=53)		ASRS-J Negative (n=214)		P-value (ASRS-J Positive vs Negative)	ASRS-J Positive (n=356)		ASRS-J Negative (n=8529)		P-value (ASRS-J Positive vs Negative)
Continuous Variables		**Mean ± S.D.**		**Mean ± S.D.**			**Mean ± S.D.**		**Mean ± S.D.**		
Age		40.15 ± 12.07		43.37 ± 12.19		0.085	42.15 ± 16.10		51.38 ± 16.25		<0.001
Charlson Comorbidity Index		0.40 ± 0.95		0.23 ± 0.57		0.112	0.20 ± 0.71		0.18 ± 0.54		0.431
PHQ-9 Score		17.83 ± 7.63		10.64 ± 6.72		<0.001	11.04 ± 7.52		2.37 ± 3.73		<0.001
Categorical Variables		**Count**	**%**	**Count**	**%**		**Count**	**%**	**Count**	**%**	
Gender	*Male*	28	52.8%	107	50.0%	0.712	198	55.6%	4538	53.2%	0.372
	Female	25	47.2%	107	50.0%		158	44.4%	3991	46.8%	
Marital Status	*Married or living with partner*	17	32.1%	95	44.4%	0.041	163	45.8%	5609	65.8%	<0.001
	Not married	35	66.0%	119	55.6%		184	51.7%	2900	34.0%	
	Decline to answer	1	1.9%	0	0.0%		9	2.5%	20	0.2%	

(*Continued*)

Table 1 (Continued).

		MDD Patients					Non-MDD Respondents				
		ASRS-J Positive (n=53)		ASRS-J Negative (n=214)		P-value (ASRS-J Positive vs Negative)	ASRS-J Positive (n=356)		ASRS-J Negative (n=8529)		P-value (ASRS-J Positive vs Negative)
Level of Education	*Completed university education*	16	30.2%	95	44.4%	0.120	156	43.8%	3878	45.5%	<0.001
	Not completed university education	37	69.8%	117	54.7%		187	52.5%	4580	53.7%	
	Decline to answer	0	0.0%	2	0.9%		13	3.7%	71	0.8%	
Employment Status	*Currently employed*	31	58.5%	142	66.4%	0.283	246	69.1%	5245	61.5%	0.004
	Not currently employed	22	41.5%	72	33.6%		110	30.9%	3284	38.5%	
Household Income	*<¥3,000,000*	19	35.8%	57	26.6%	0.441	67	18.8%	1340	15.7%	0.007
	¥3,000,000 to <¥5,000,000	6	11.3%	47	22.0%		83	23.3%	2089	24.5%	
	¥5,000,000 to <¥8,000,000	11	20.8%	45	21.0%		80	22.5%	2092	24.5%	
	¥8,000,000 or more	10	18.9%	37	17.3%		57	16.0%	1811	21.2%	
	Decline to answer	7	13.2%	28	13.1%		69	19.4%	1197	14.0%	
Body Mass Index (BMI)	*Underweight (BMI<18.5)*	4	7.5%	25	11.7%	0.026	36	10.1%	847	9.9%	<0.001
	Normal (18.5≤BMI<23)	13	24.5%	89	41.6%		166	46.6%	4272	50.1%	
	Pre-obese (23≤BMI<25)	7	13.2%	31	14.5%		45	12.6%	1509	17.7%	
	Overweight (BMI ≥25)	21	39.6%	56	26.2%		67	18.8%	1493	17.5%	
	Decline to answer	8	15.1%	13	6.1%		42	11.8%	408	4.8%	
Smoking Status	*Current*	16	30.2%	60	28.0%	0.748	54	15.2%	1435	16.8%	0.307
	Former	8	15.1%	42	19.6%		85	23.9%	2246	26.3%	
	Never	29	54.7%	112	52.3%		217	61.0%	4848	56.8%	
Alcohol Use	*≤once per week*	41	77.4%	146	68.2%	0.194	254	71.3%	5277	61.9%	<0.001
	≥2–3 times per week	12	22.6%	68	31.8%		102	28.7%	3252	38.1%	
Vigorous Exercise in Past 30 Days	*0–11 times*	44	83.0%	182	85.0%	0.714	305	85.7%	6703	78.6%	0.001
	≥12 times	9	17.0%	32	15.0%		51	14.3%	1826	21.4%	

Note: ASRS-J positive/negative respondents were determined based on ASRS-J cut-off score.[28]
Abbreviations: ASRS, Adult ADHD Self-Report Scale; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire-9; S.D., standard deviation.

those who were ASRS-J negative (11.04±7.52 vs 2.37±3.73, p < 0.001), indicating more severe depressive symptoms despite no experience with MDD.

Similar findings were observed among ASRS-A negative and positive respondents (Supplementary Table 1).

Scatter plot of ASRS-J total scores and PHQ-9 scores was created to further investigate the potential correlation between the PHQ-9 score and ASRS-J status (Supplementary Figure 2). A positive correlation among both MDD patients and non-MDD respondents was demonstrated from the scatter plot and from the correlation coefficient between PHQ-9 score and ASRS-J status.

Proportion of ASRS Positive Among MDD Patients and Non-MDD Respondents

Among MDD patients (n = 267) who were screened using Japanese version of the ASRS-v1.1, 53 (19.9%) were ASRS-J positive and 42 (15.7%) were ASRS-A positive (Table 2). Among the non-MDD respondents (n = 8885) who were screened, only 356 (4.0%) and 220 (2.5%) were ASRS-J and ASRS-A positive, respectively.

Among all 39,000 respondents to the 2016 Japan NHWS, regardless of whether responded to the ASRS-v1.1, 1155 patients self-reported being diagnosed by a physician for MDD and having never experienced schizophrenia before, while 35,800 respondents self-reported that they had never experienced MDD and schizophrenia. Only 32 (2.8%) patients self-reported being diagnosed of ADHD among all MDD patients (n = 1155), and 45 (0.13%) among non-MDD respondents (n = 35,800) (Table 2).

Table 2 Unadjusted and Adjusted Odds Ratio Between MDD Status and ASRS Status

2016 Japan NHWS Respondents Who Responded to the ASRS-v1.1 Symptom Checklist		**ASRS Status**				
		ASRS-J Positive (n=409)	**ASRS-J Negative (n=8743)**	**P-value**	**Crude Odds Ratio**	**Adjusted Odds Ratio***
MDD status	**Diagnosed MDD (n=267)**	53	214	<0.001	5.93 (4.31, 8.16)	4.15 (2.96, 5.82)
	Not experienced MDD (n=8885)	356	8529			
2016 Japan NHWS respondents who responded to the ASRS-v1.1 Symptom Checklist		**ASRS-A positive (n=262)**	**ASRS-A negative (n=8890)**	**P-value**	**Crude odds ratio**	**Adjusted odds ratio**
MDD status	**Diagnosed MDD (n=267)**	42	225	<0.001	7.35 (5.15, 10.49)	5.31 (3.66, 7.70)
	Not experienced MDD (n=8885)	220	8665			
All 2016 Japan NHWS respondents		**ADHD diagnosis status**				
		Diagnosed ADHD (n=77)	**Not diagnosed ADHD (n=36,878)**	**P-value**	**Crude odds ratio**	**Adjusted odds ratio†**
MDD status	**Diagnosed MDD (n=1155)**	32	1123	<0.001	22.64 (14.33, 35.76)	-
	Not experienced MDD (n=35,800)	45	35,755			

Notes: *Adjusted odds ratio derived from logistic regression with MDD status being dependent variable and ASRS status being independent variable. Covariates adjusted were age, gender, marital status, level of education, employment status, household income, BMI, CCI, smoking status, alcohol use, and exercise behaviour. †Adjusted odds ratio was not calculated due to limited sample size. ASRS-J positive/negative respondents were determined based on ASRS-J cut-off score,[28] while ASRS-A positive/negative respondents were determined based on ASRS-A cut-off score.[29]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale; MDD, major depressive disorder; NHWS, National Health and Wellness Survey.

A significant association between MDD status and ASRS-J status was observed, with a crude OR of 5.93 (95% CI: 4.31–8.16) (Table 2). A crude OR of 7.35 (95% CI: 5.15, 10.49) was observed between MDD status and ASRS-A status. In addition, a significant association between MDD status and ADHD diagnosis status was also observed with crude OR of 22.64 (95% CI: 14.33–35.76) (Table 2).

After adjusting for baseline demographic and health characteristics (age, gender, marital status, level of education, employment status, household income, BMI, CCI, smoking status, alcohol use, and exercise behaviour) using logistic regression, respondents who were ASRS-J positive and ASRS-A positive were found to be 4.15 times (95% CI: 2.96–5.82) and 5.31 times (95% CI: 3.66–7.70) more likely to have MDD, compared to respondents who were ASRS-J negative and ASRS-A negative, respectively (Table 2).

Assessment of Health Outcomes Among ASRS Positive and Negative Respondents

Before adjustment, bivariate analysis demonstrated that among MDD patients and non-MDD respondents respectively, patients/respondents screened positive with ASRS-J had significantly lower HRQoL measured by PCS, MCS, SF-6D health utilities and EQ-5D index scores, significantly more absenteeism, presenteeism, total work productivity impairment and total activity impairment, compared to those who screened negative (Supplementary Table 2). No significant difference was observed in terms of the number of HCP visits in the past six months.

After adjusting for all baseline characteristics, MDD patients who were ASRS-J positive experienced significantly decreased PCS ([mean±S.E.] 47.62±1.08 vs 50.12±0.75, $p = 0.017$), MCS (27.41±1.71 vs 36.19±1.18, $p < 0.001$) and EQ-5D index (0.63±0.02 vs 0.73±0.02, $p < 0.001$) scores compared to MDD patients with ASRS-J negative. Higher presenteeism (64.41% vs 37.42%, $p < 0.001$), total activity impairment (64.26% vs 41.65%, $p < 0.001$) and total work productivity impairment (75.14% vs 40.91%, $p < 0.001$) were observed among ASRS-J positive MDD patients than ASRS-J negative MDD patients (Figure 2A and B).

Among non-MDD respondents, after adjusting for all baseline characteristics, respondents screened with ASRS-J positive results experienced significantly decreased PCS (48.55±0.31 vs 53.33±0.10, $p < 0.001$), MCS (39.57±0.46 vs 49.05±0.15, $p < 0.001$) and EQ-5D index (0.75±0.01 vs 0.87±0.00, $p < 0.001$) scores, and higher absenteeism (10.24% vs 2.90%, $p < 0.001$), presenteeism (39.05% vs 16.55%, $p < 0.001$), total work productivity impairment (42.16% vs 17.84%, $p < 0.001$) and total activity impairment (41.21% vs 17.85%, $p < 0.001$), compared to respondents who screened negative (Figure 2C and D).

Similar findings were observed among ASRS-A negative and positive respondents (Supplementary Table 3).

Discussion

In the present study, a significant association between MDD status and ASRS-J/ASRS-A status was observed. More severe depressive symptoms measured by PHQ-9 score were associated with increased ADHD traits independent of MDD status. MDD patients who screened positive on the ASRS-v1.1 had worse HRQoL, higher work productivity impairment and presenteeism compared with patients with MDD and screened negative, even after adjusting for confounders.

In this study, about 4.5% (409/9152) and 2.9% (262/9152) respondents were screened and found to be ASRS-positive as per the ASRS-J-specific[28] and the original ASRS (ASRS-A)-specific[29] cut-off scores, respectively. This prevalence range of ASRS-positive respondents is similar with that reported in previous studies.[37,38] On the contrary, only 0.21% of all respondents in this study (77/36,955) had self-reported to be diagnosed with ADHD, which is about one-eighth of the previously reported prevalence of 1.65% in 2012.[6] These findings raise the possibility of an underestimate of adult ADHD diagnosis in the Japanese community. Of note, while about 2.5–4.0% of non-MDD respondents were ASRS-positive, about 15.7–19.9% of MDD patients were found to be screened as ASRS-positive. This was relatively higher than previous studies describing the prevalence of comorbid ADHD among adult MDD patients, which was around 12.5–12.8% in Europe.[8,39] Taken together with the prevalence of respondents who had self-reported to be diagnosed with ADHD among patients with MDD (2.8%, 32/1155), this further highlights the possible underdiagnosis of adult ADHD, especially in the presence of MDD in Japan.

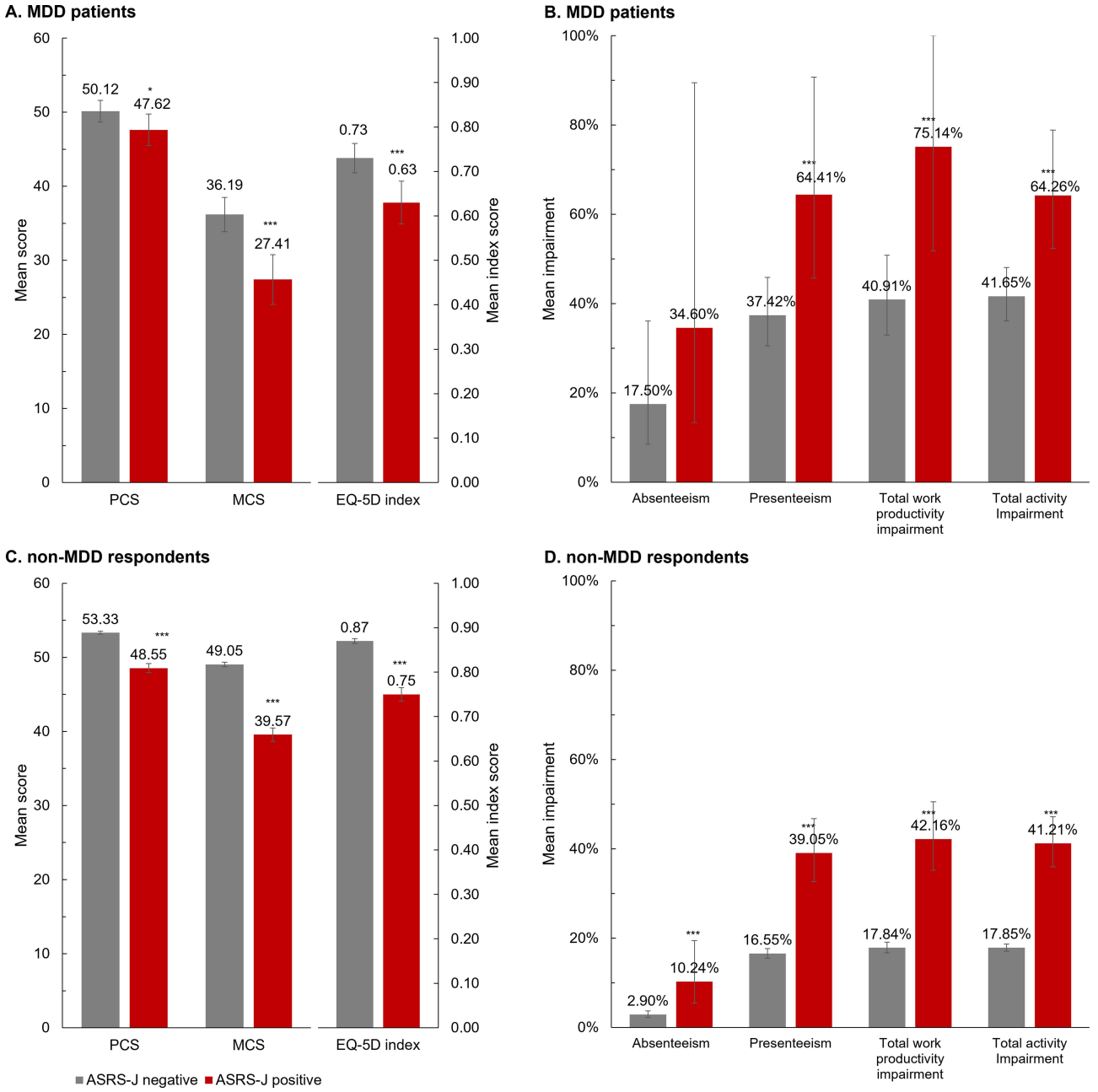

Figure 2 Adjusted means of health outcomes of MDD patients and non-MDD respondents with ASRS-J negative and ASRS-J positive in Japan. (**A**) HRQoL of MDD patients with ASRS-J positive and negative. (**B**) WPAI of MDD patients with ASRS-J positive and negative. (**C**) HRQoL of non-MDD respondents with ASRS-J positive and negative. (**D**) WPAI of non-MDD respondents with ASRS-J positive and negative.
Notes: ASRS-J positive/negative respondents were determined based on ASRS-J cut-off score.[28] Error bar indicates adjusted 95% C.I. *p-value <0.05 ***p-value <0.001.
Abbreviations: ASRS, Adult ADHD Self-Report Scale; EQ-5D, EuroQoL 5-dimention scale; MCS, mental component summary; MDD, major depressive disorder; PCS, physical component summary.

We also observed that MDD patients who screened positive for ADHD traits exhibited more severe depressive symptoms compared to MDD patients without ADHD traits and to non-MDD participants. These results matched those observed in previous studies showing that patients with depressive or anxiety disorder with ADHD comorbidity had reported experiencing greater symptom burden related to distress compared to non-ADHD patients.[13] Moreover, it has been shown that in adults with MDD and controls, the odds of probable ADHD were observed to be higher when depression episodes were longer and when participants reported more severe depressive symptoms.[26]

Compared with individuals with depression alone, individuals with ADHD and depression were found to have higher risk of antidepressant treatment resistance.[25,26] Effective treatment of ADHD along with depression has been shown to improve functioning and associated depression symptoms.[40] Taken together, these findings suggest that coexisting ADHD worsens symptoms in patients with MDD and untreated ADHD can negatively affect outcomes of MDD, which reinforces the importance of the correct medical treatment for both conditions.

A recent study in Japan had reported an association between ASRS score and the severity of depressive condition among adult patients with mood and anxiety disorders.[27] On the other hand, our main focus was on the evaluation of the impact of having ADHD traits in terms of HRQoL and work productivity between the MDD individuals and non-MDD individuals. In our study, individuals with MDD and screened positive for ADHD traits had worse HRQoL, higher work productivity impairment and presenteeism than those who were screened ASRS-negative. This finding is in agreement with previous research suggesting that when ADHD is comorbid with depression, individuals have a higher disease burden and a lower quality of life than those affected by MDD alone.[41] In addition, both MDD and ADHD have previously been associated with functional impairments at work,[42,43] and the results of the current study expand these findings by showing that the co-existence of depressive and ADHD traits also lead to greater humanistic burden than in patients with either depression or ADHD traits only. Therefore, our findings make it imperative to further clarify the co-existence of MDD and ADHD in adults in the general population, since interventions that address ADHD symptoms could improve mood and boost psychosocial functioning and quality of life.

Overall, while the ASRS-v1.1 scale has been suggested to potentially lead to an overestimation of self-perceived ADHD traits, this study provided an estimate of the prevalence and burden of having ADHD traits among adult MDD patients compared with non-MDD individuals in Japan using national population-based NHWS. The study findings suggest that there is possible underdiagnosis of ADHD-related characteristics among adult MDD patients in the general population in Japan. Furthermore, the study having compared the disease burden among MDD patients with or without potential ADHD symptoms showed that these individuals with ADHD generally had higher humanistic burden than adult MDD patients without ADHD traits.

There are several limitations to this study. This is a cross-sectional study based on the Japanese NHWS data which was administered via the Internet. Although the recruitment process of NHWS was designed to reflect the Japanese adult population, the extent to which participants are representative of the general population is unclear. Furthermore, there is a possibility of selection bias as respondents with limited information technology literacy (ie, without access to the Internet or comfort of online administration) may not be well-represented in this web-based study. Furthermore, due to the nature of the NHWS wherein respondents self-reported their diagnoses or responses, validation could not be performed, and recall bias cannot be excluded. No causal relationships between disease diagnoses and health outcomes could be assumed. Our study used existing data from 2016 Japan NHWS because it was the most recent data available at the time of the study design. As a result, subsequent NHWS included the bias of spread of COVID-19. Furthermore, the 2016 data closely coincided with the study periods from previous research,[8,39,44] and it would be of future interest to track the recent prevalence of ADHD traits among adult MDD patients in Japan using data from recent Japan NHWS. Replicating the study in the community and clinical settings where physicians or psychiatrists could validate diagnosis of MDD as well as ADHD symptoms with more appropriate diagnostic methods, including dedicated diagnostic interviews could also be considered for future research. Some of the MDD symptoms may also appear to be inattention symptoms of ADHD, but information related to the duration of ADHD and MDD symptoms was not captured in this study to understand if inattention symptoms were present when not depressed. The current results, however, demonstrated that ASRS positive respondents scored significantly different on both inattention and hyperactive items in ASRS-v1.1 and further studies are warranted to investigate this.

Conclusion

There was a significant association between MDD status and exhibiting ADHD traits. Adult patients with MDD who screened positive using ASRS-v1.1 experienced significantly higher humanistic burden than MDD patients who screened negative. Our results emphasize the importance of ensuring appropriate screening of ADHD and looking out for potentially hidden ADHD symptoms when diagnosing and treating MDD in adulthood.

Data Sharing Statement

Data to support the findings of this study are available from Cerner Enviza, but availability of the data is restricted and was used under license for this study and are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of Cerner Enviza.

Ethics Approval and Informed Consent

The 2016 NHWS Japan was granted exemption status upon review by Pearl International Review Board (Indianapolis, IN, IRB Study Number: 16-KAN-124). All respondents had provided informed online consent prior to participation. The data accessed complied with relevant data protection and privacy regulations.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article; have agreed on the journal to which the article has been submitted; gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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