Methylphenidate and mortality in children with attention-deficit hyperactivity disorder: population-based cohort study

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Background

Little is known about methylphenidate (MPH) use and mortality outcomes.

Aims

To investigate the association between MPH use and mortality among children with an attention-deficit hyperactivity disorder (ADHD) diagnosis.

Method

This population-based cohort study analysed data from Taiwan's National Health Insurance Research Database (NHIRD). A total of 68 096 children and adolescents aged 4–17 years with an ADHD diagnosis and prescribed MPH between 2000 and 2010 were compared with 68 096 without an MPH prescription, matched on age, gender and year of first ADHD diagnosis. All participants were followed to death, migration, withdrawal from the National Health Insurance programme or 31 December 2013. MPH prescriptions were measured on a yearly basis during the study period, and the association between MPH use and mortality was analysed using a repeated-measures time-dependent Cox regression model. The outcome measures included all-cause, unnatural-cause (including suicide, accident and homicide) and natural-cause mortality, obtained from linkage to the National Mortality Register in Taiwan.

Results

The MPH group had lower unadjusted all-cause, natural-, unnatural- and accident-cause mortality than the comparison group. After controlling for potential confounders, MPH use was associated with a significantly lower all-cause mortality (adjusted hazard ratio AHR = 0.81, 95% CI 0.67–0.98, $P = 0.027$), delayed use of MPH was associated with higher mortality (AHR = 1.05, 95% CI 1.01–1.09) and longer MPH use was associated with lower mortality (AHR = 0.83, 95% CI 0.70–0.98).

Conclusions

MPH use is associated with a reduced overall mortality in children with ADHD in this cohort study, but unmeasured confounding cannot be excluded absolutely.

Keywords

Methylphenidate; attention deficit hyperactivity disorder; all cause; natural; unnatural mortality.

Copyright and usage

With an estimated prevalence of 2.6–4.5%, attention-deficit hyperactivity disorder (ADHD) is one of the most common mental disorders among children and adolescents.[1] Characterised by hyperactivity, impulsivity and attention deficit, ADHD affects not only those under age 18; symptoms of ADHD often persist into adult life.[2,3] Increased risk of mood disorder, conduct disorder and substance use disorder have been found in children with ADHD,[4] as well as increased risk of suicide,[5] accidents,[6–8] traffic violations and road injuries.[9,10] Higher premature mortality has consequently been found, with accidents, trauma or suicide as main causes of death.[11–14] Core ADHD symptoms of inattention, distractibility and impulsivity,[15,16] as well as comorbidity with depression, oppositional defiant disorder and/or conduct disorder may partly account for these risks.[9]

Debate regarding risk of mortality and medication for ADHD

The debate concerning beneficial and adverse effects of stimulant treatment for ADHD is still ongoing. Treatment guidelines for ADHD suggest stimulants as a first-line intervention, and these have been reported as effective in reducing ADHD symptoms in more than 70% of childhood cases,[17,18] as well as more specific reports of reduced trauma-related emergency service utilisation[19–22] and suicidal behaviours.[23,24] One recent meta-analysis of double-blind randomised controlled trials supported stimulants as preferred first-choice medications for the short-term treatment of ADHD,[25] and a recent meta-analysis concluded that people with ADHD treated with stimulants had lower risk of unintentional injuries (OR = 0.838–0.922) than those not receiving treatment.[22] In addition, a population-based study found that longer duration of stimulant use (more than 90 days) was associated with reduced suicide risk.[24] However, stimulants are recognised to have adverse effects of anorexia, sleep problems, stomach-ache and headache,[26] and a large longitudinal nationwide cohort study reported an increased risk of cardiovascular events in children with ADHD receiving stimulants relative to general population and unmedicated children with ADHD as comparators (adjusted hazard ratios AHR = 1.83–2.20).[27] On the other hand, a meta-analysis concluded that stimulant use was not associated with increased risks of sudden death or stroke.[28] A recent qualitative systematic review of studies based on within-individual analyses, which control for time-independent confounders, suggested short-term beneficial effects of ADHD medication on injuries, motor vehicle accidents, education and substance use disorder.[29]

With rising stimulant prescriptions (e.g. a more than 1.5-fold increase in the past decade[30]) and the long-term pharmacotherapy implicated (nearly 50% of patients were found to continue medication use for at least 2–3 years after initiating drug treatment[31]), it is important to investigate associations of stimulants with adverse outcomes, including mortality, given the evidence (albeit conflicting) cited above. Previous investigations have resulted in inconsistent findings on excess mortality in children with ADHD compared with healthy children[11–13] and investigations of associations with

stimulant therapy are even more scant. McCarthy et al reported that receipt of stimulants or atomoxetine was not associated with a raised standardised mortality ratio (SMR) for sudden death; however, they did find increased associated suicide mortality in patients aged 11–14 years (SMR = 161.9, 95% CI 19.6–584.9).[32] Another longitudinal study using within-patient comparisons found a 19% reduction in suicide-related events, including suicide mortality, during periods of stimulant treatment.[33] It is therefore still unclear whether stimulant use is associated with an increased or decreased mortality in children and adolescents with ADHD; furthermore, there has been no study to date investigating associations with all-cause, natural-cause and unnatural-cause mortality simultaneously. In the present study, we assembled a nationwide population-based cohort study to investigate associations of MPH use, the only licensed stimulant for ADHD in Taiwan, with all-cause, natural-cause and unnatural-cause mortality in children with ADHD. We also investigated patterns of MPH prescription in relation to mortality.

Method

Data source

The National Health Insurance (NHI) programme in Taiwan is a single-payer insurance system operated by the government. This system was established in 1995 to support health nationwide and prevent social problems caused by poverty and disease. By December 2010, over 23 million people were enrolled nationwide, with a coverage of 99.6%. The Bureau of National Health Insurance gathered information on medical service utilisation, prescribed drugs and procedures from out-patient, emergency room visits or hospital admissions, and assembled the National Health Insurance Research Database (NHIRD) for research use.[34] The NHIRD includes claims data from 183 480 insured children aged 4–17 years newly diagnosed with ADHD (ICD-9: 314.xx) during the period 2000–2010. The reason for choosing this age group for data extraction was that ADHD was rarely diagnosed outside this range. The focus of the analysis was on methylphenidate (MPH) treatment. In Taiwan, MPH is the only stimulant approved for treatment of ADHD. Atomoxetine, a non-stimulant, received regulatory approval and was made available in Taiwan in 2007; however, atomoxetine has a much lower rate of prescription compared with MPH (4% of all ADHD patients).[35] From this cohort we found 68 096 children who had received MPH treatment between 1 January 2000 and 31 December 2010. This exposed group were compared with 68 096 children with ADHD who had not received MPH treatment during that period and who were matched for gender, age at ADHD first diagnosis (within 1 year) and year of ADHD first diagnosis. The date of first MPH prescription for those children receiving it was defined as the index date for both MHP-receiving and comparison participants. Both the exposure and comparison cohorts were followed up from the index date until death, migration or the end-point of 31 December 2013 (Fig. 1). Linked information from the Mortality Register from 2000 to 2013 was provided by the Department of Health, the Executive Yuan (executive branch of the government) of Taiwan.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by the Institutional Review Board (IRB) of the National Taiwan Normal University (reference: 201703HM006). Written consent from the study participants was not required because the contents of the NHIRD and the Mortality Register are de-identified and anonymised for research purposes. The IRB gave a formal written waiver of the need for informed consent.

Outcome variables and covariates

Our MPH-receiving and comparison participants were evaluated for all-cause mortality within the follow-up period. Unnatural-cause mortality was defined on the basis of ICD-9 External Causes of Death codes for suicide (ICD-9 codes: E950–E959, E980–E989), accidents (E800–E949) and homicide (E960–E969). Natural-cause mortality was defined as all other causes. The coding system for mortality in Taiwan during the study period registered only a primary cause of death code to be entered for each death.

Our covariates included age (at ADHD diagnosis), gender, urban versus rural residence, recorded insurance premium, frequency of recent out-patient visits and the presence or not of each of the following diagnoses before the ADHD diagnosis: congenital anomaly or birth defects (ICD-9: 740–759), intellectual disability (317–319), depressive disorder (296.2, 296.3, 300.4, 311), autism (299), substance use disorder (303–304), conduct disorder or oppositional defiant disorder (ODD) (312, 313.81). National health insurance premiums are levied in Taiwan according to the individual's monthly income (here, the main caregiver paid the premiums), and consequently served as an indicator of the family's economic status for this analysis, classified into three categories: monthly income ≤NT\$20 000, NT\$20 000–39 999 and ≥NT\$40 000 (US\$1 = NT\$32.1 in 2010). The number of outpatient visits (medical claims past 1 year of first diagnosis date of ADHD) served as an indicator of medical service utilisation, and was classified into three categories: 0–10, 11–20 and ≥21. Finally, we extracted data on time from first ADHD diagnosis to first MPH prescription, and defined a covariate representing MPH dose per 100 days. Incident ADHD cases from 2000–2010 were children without ADHD diagnosis from 1998 to the first ADHD medical claim in our database. Children who received MPH before this first ADHD diagnosis date were excluded. Information on prescription of MPH was fully covered by the health insurance data-set throughout the study period owing to the requirement to register controlled medication in Taiwan.

Statistical analysis

The study design that we used has fixed time points where each person has observations at which MPH is measured. Such a study design is common for longitudinal studies. In particular, a time-varying covariate (MPH) is measured in each individual at each time interval and all intervals are of the same length (in our study, 1 year). In this context, the regression coefficients represent the association between MPH and an event (death) that occurs during the subsequent interval. Using this method each observation interval is considered a mini-follow-up study in which the current risk factors are updated to predict events in the interval. Once an individual has an event in a particular interval, all subsequent intervals for that individual are excluded from the analysis.[36] MPH prescription was measured each year during the study period. Annual average days of MPH prescriptions served as the main exposure variable. The event was considered as censored if no death occurs in that follow-up year. The risk of mortality during the follow-up period was calculated through repeated- measures time-dependent Cox regression. Repeated-measures time-dependent Cox regression models adjusted for competing risk were used to estimate associations of MPH with mortality outcomes, considering other causes of mortality aside from the target cause as competing risk events for each participant. Although the participants were matched by gender and age at ADHD diagnosis, the analysis unit was the follow-up period (1 year) not the participant. Therefore, we also adjusted for gender and age in the regression analysis. Cumulative incidences were calculated and results of log-rank tests were obtained using the Fine and Gray method.[37,38] The model was analysed first
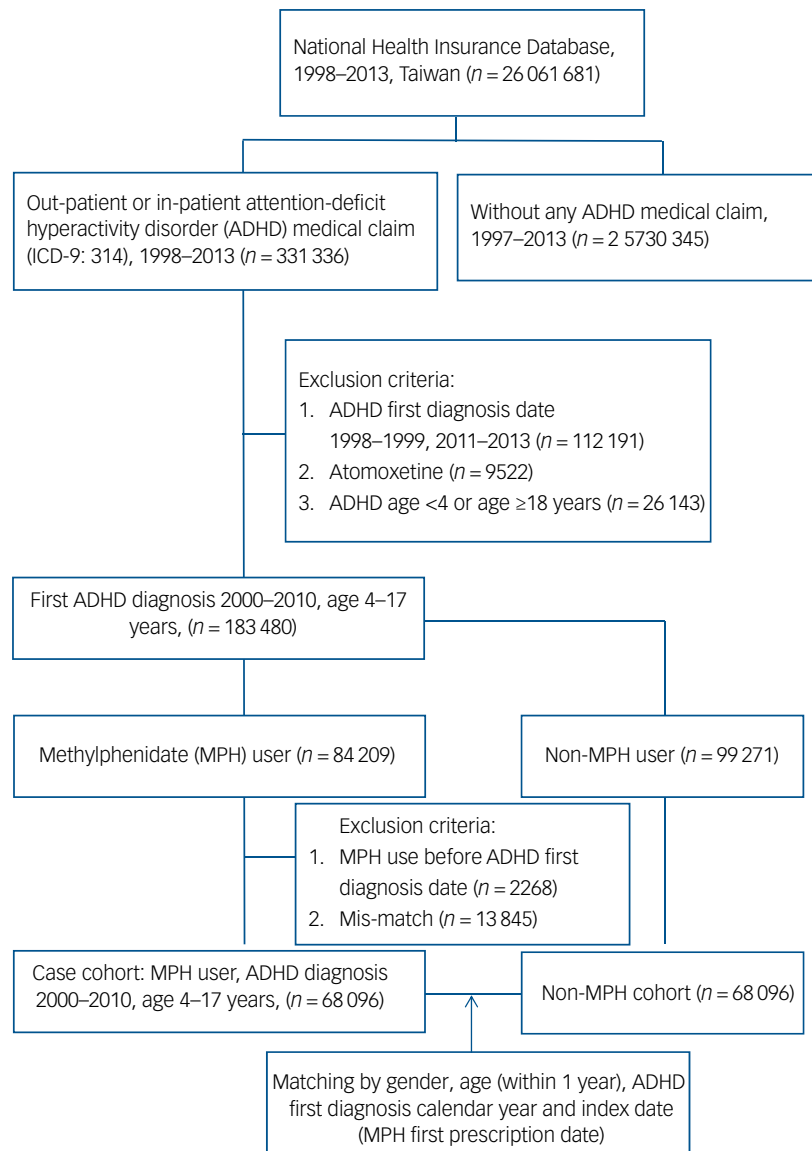
Fig. 1 Flow chart of data collection in this study.

with all samples. Subsequently, stratified analyses by gender and age groups (age 4–11 years and 12–17 years) were performed.

Several multivariate adjusted models were calculated. Model 1 incorporated gender, age, levels of urbanisation and income, and out-patient visits (medical claims past 1 year of first diagnosis date of ADHD). Model 2 incorporated further adjustments for congenital anomaly or birth defect, intellectual disability, depressive disorder, autism, substance use disorder, and conduct disorder or ODD, diagnosed before the index date. A further subanalysis was performed to investigate the effect of duration between the first ADHD diagnosis and the first MPH prescription on mortality in the MPH-treated subgroup. Data management was performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Cumulative incidences and the Cox model in the competing-risk analysis were calculated using the R package.[39]

Results

As described, a total of 68 096 MPH-treated children and 68 096 matched comparison children with no MPH treatment were

included in our analysis. As summarised in Table 1, gender, age at first diagnosis and the year in which ADHD was first diagnosed were matched effectively between groups. Levels of urbanisation were also similar between the two groups. Higher proportions of comorbid intellectual disability, depressive disorder, autism, substance use disorder and conduct disorder/ODD were noted in MPH-treated children than in those without MPH treatment.

Results of univariate repeated-measures time-dependent analyses showed that MPH treatment was associated with significantly lower all-cause mortality (HR = 0.48, 95% CI 0.34–0.69), natural-cause mortality (HR = 0.58, 95% CI 0.37–0.89), unnatural-cause mortality (HR = 0.35, 95% CI 0.18–0.66) and mortality due to accidents (HR: 0.45, 95% CI 0.23–0.89) than in non-MPH-treated counterparts (Table 2; and supplementary Fig. 1, available at https://doi.org/10.1192/bjp.2020.129). There was only 1 death by suicide in the MPH-treated follow-up year (incidence 0.06 per 10 000 person-years) compared with 32 in the comparison follow-up year (incidence 0.42 per 10 000 person-years). No homicide deaths occurred in the MPH-treated follow-up year, compared with 7 in the comparison follow-up year (incidence 0.09 per 10 000 person-years). Stratified analysis by gender or age showed that reductions in

Table 1 Demographic and clinical characteristics[a] of the methylphenidate-receiving and comparison cohorts of children/adolescents with attention-deficit hyperactivity disorder

Characteristic	MPH, n = 68 096 (%)	Non-MPH, n = 68 096 (%)	P
Gender			
Male	53 150 (78.05)	53 150 (78.05)	>0.99
Female	14 946 (21.95)	14 946 (21.95)	
Age at ADHD diagnosis, years			
4–11	59 625 (87.56)	59 625 (87.56)	>0.99
12–17	8471 (12.44)	8471 (12.44)	
Year of ADHD first diagnosis			
2000	3683 (5.41)	3683 (5.41)	>0.99
2001	3986 (5.85)	3986 (5.85)	
2002	4793 (7.04)	4793 (7.04)	
2003	4632 (6.8)	4632 (6.8)	
2004	5773 (8.48)	5773 (8.48)	
2005	6054 (8.89)	6054 (8.89)	
2006	6500 (9.55)	6500 (9.55)	
2007	7726 (11.35)	7726 (11.35)	
2008	8300 (12.19)	8300 (12.19)	
2009	8214 (12.06)	8214 (12.06)	
2010	8435 (12.39)	8435 (12.39)	
Residence			
Rural	10 424 (15.31)	10 305 (15.13)	0.369
Urban	57 672 (84.69)	57 791 (84.87)	
Insurance premium of main caregiver			
Less than NT$20 000[b]	22 046 (32.37)	20 133 (29.57)	<0.001
NT$20 000–39 999	33 096 (48.6)	32 530 (47.77)	
NT$40 000 or more	12 954 (19.02)	15 433 (22.66)	
Birth defect			
Yes	1127 (1.66)	1130 (1.66)	0.949
No	66 969 (98.34)	66 966 (97.83)	
Intellectual disability			
Yes	2193 (3.22)	1479 (2.17)	<0.001
No	65 903 (96.78)	66 617 (97.83)	
Depressive disorder			
Yes	164 (0.24)	98 (0.14)	<0.001
No	67 932 (99.76)	67 998 (99.86)	
Autism			
Yes	1413 (2.08)	1041 (1.53)	<0.001
No	66 683 (97.92)	67 055 (98.47)	
Substance use disorder			
Yes	579 (0.85)	449 (0.66)	<0.001
No	67 517 (99.15)	67 647 (99.34)	
Conduct disorder or ODD			
Yes	158 (0.23)	101 (0.15)	<0.001
No	67 938 (99.77)	67 995 (99.85)	
All-cause mortality			
Yes	163 (0.24)	184 (0.27)	0.259
No	67 933 (99.76)	67 912 (99.73)	
Natural-cause mortality			
Yes	89 (0.13)	117 (0.17)	0.051
No	68 007 (99.87)	67 979 (99.83)	
Unnatural-cause mortality			
Yes	74 (0.11)	67 (0.10)	0.555
No	68 022 (99.89)	68 029 (99.90)	
Suicide mortality			
Yes	17 (0.02)	16 (0.02)	0.868
No	68 079 (99.98)	68 080 (99.98)	
Accident mortality			
Yes	53 (0.08)	48 (0.07)	0.619
No	68 043 (99.92)	68 048 (99.93)	
Homicide mortality			
Yes	4 (0.01)	3 (0.00)	0.705
No	68 092 (99.99)	68 093 (100.00)	
Out-patient visits,[c] n			
0–10	18 279 (26.84)	16 909 (24.83)	<0.001
11–20	21 170 (31.09)	20 750 (30.47)	
≥21	28 647 (42.07)	30 437 (44.7)	

MPH, methylphenidate; ADHD, attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder.
a. Pre-existing diagnoses: congenital anomaly or birth defect (ICD-9: 740–759); intellectual disability (ICD-9: 317–319); depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311); autism (ICD-9: 299); substance use disorder (ICD-9: 303–304); conduct disorder or ODD (ICD-9: 312, 313.81).
b. 1 US$ = 32.1 New Taiwan dollars (NT$) in 2010.
c. Medical claims past 1 year of first diagnosis date of ADHD.

Table 2 Univariate analysis of the association between methylphenidate and mortality outcomes in children/adolescents with attention deficit hyperactivity disorder

Subgroup	Outcome[a]	MPH[b]			Non-MPH[b]			HR[c] (95% CI)	P
		Deaths, n	Person-years	Rate[c]	Deaths, n	Person-years	Rate[d]		
Total	All-cause	33	164 697	2.00	314	754 837	4.16	0.48 (0.34–0.69)	<0.001
	Natural-cause	23	164 697	1.40	183	754 837	2.42	0.58 (0.37–0.89)	0.012
	Unnatural-cause	10	164 697	0.61	131	754 837	1.74	0.35 (0.18–0.66)	0.001
	Suicide	1	164 697	0.06	32	754 837	0.42	0.14 (0.02–1.05)	0.055
	Accident	9	164 697	0.55	92	754 837	1.22	0.45 (0.23–0.89)	0.021
	Homicide	0	164 697	0.00	7	754 837	0.09	n.a.	n.a.
Male	All-cause	24	13 2316	1.81	251	58 6659	4.28	0.42 (0.28–0.64)	<0.001
	Natural-cause	18	132 316	1.36	138	586 659	2.35	0.58 (0.35–0.94)	0.029
	Unnatural-cause	6	132 316	0.45	113	586 659	1.93	0.23 (0.10–0.53)	0.001
	Suicide	0	132 316	0.00	24	586 659	0.41	n.a.	n.a.
	Accident	6	132 316	0.45	82	586 659	1.40	0.32 (0.14–0.74)	0.008
	Homicide	0	132 316	0.00	7	586 659	0.12	n.a.	n.a.
Female	All-cause	9	32 381	2.78	63	168 178	3.75	0.74 (0.37–1.49)	0.402
	Natural-cause	5	32 381	1.54	45	168 178	2.68	0.58 (0.23–1.45)	0.243
	Unnatural-cause	4	32 381	1.24	18	16 8178	1.07	1.15 (0.39–3.40)	0.797
	Suicide	1	32 381	0.31	8	168 178	0.48	0.65 (0.08–5.13)	0.679
	Accident	3	32 381	0.93	10	168 178	0.60	1.56 (0.43–5.68)	0.499
	Homicide	0	32 381	0.00	0	168 178	0.00	n.a.	n.a.
Age 4–11 years	All-cause	26	149 866	1.74	220	648 308	3.39	0.51 (0.34–0.77)	0.001
	Natural-cause	20	149 866	1.34	141	648 308	2.18	0.61 (0.38–0.98)	0.041
	Unnatural-cause	6	149 866	0.40	79	648 308	1.22	0.33 (0.14–0.75)	0.008
	Suicide	1	149 866	0.07	16	648 308	0.25	0.27 (0.04–2.02)	0.201
	Accident	5	149 866	0.33	59	648 308	0.91	0.37 (0.15–0.91)	0.031
	Homicide	0	149 866	0.00	4	648 308	0.06	n.a.	n.a.
Age 12–17 years	All-cause	7	14 832	4.72	94	106 529	8.82	0.53 (0.25–1.15)	0.110
	Natural-cause	3	14 832	2.02	42	106 529	3.94	0.51 (0.16–1.65)	0.264
	Unnatural-cause	4	14 832	2.70	52	106 529	4.88	0.55 (0.20–1.53)	0.252
	Suicide	0	14 832	0.00	16	106 529	1.50	n.a.	n.a.
	Accident	4	14 832	2.70	33	106 529	3.10	0.86 (0.30–2.44)	0.780
	Homicide	0	14 832	0.00	3	10 6529	0.28	n.a.	n.a.

MPH, methylphenidate; ADHD, attention-deficit hyperactivity disorder; HR, hazard ratio; n.a., no available owing to zero deaths among the MPH cohort.
a. Causes of death: suicide, ICD-9: E950–E959, E980–E989; accident, ICD-9: E800–E949; homicide, ICD-9: E960–E969; unnatural-cause (suicide, accident and homicide), natural-cause (all-cause mortality excluded suicide, Accident and homicide).
b. Time-dependent repeated measures analysis, MPH measured each year during the study follow-up.
c. All-cause mortality analysed by log-rank test, specific-cause mortality analysed by modifying log-rank test using the Fine and Gray method.
d. Per 10 000 person-years.

mortality associated with MPH use were only statistically significant in males and those diagnosed at a younger age (aged 4–11 years), although coefficients did not differ substantially between age groups.

After adjusting for listed potential confounders, although the effect attenuated, MPH use was still associated with a significantly lower risk of all-cause mortality (AHR = 0.81, 95% CI 0.67–0.98) (Table 3). This association also remained statistically significant in the subgroups who were male or aged 4–11 years.

Analyses presented in Table 4 describe factors associated with all-cause mortality in the MPH-receiving cohort, specifically investigating timing and duration of MPH prescription as predictors. The mean interval from ADHD first diagnosis to MPH first prescription was 307.4 days (s.d. = 594.9 days). Higher all-cause mortality was found in those with a longer time between diagnosis of ADHD and MPH commencement (AHR = 1.05, 95% CI 1.01–1.09), and lower all-cause mortality was found in those with a longer duration of treatment (AHR = 0.83, 95% CI 0.70–0.98).

Discussion

To our knowledge, this is the first study to investigate associations of MPH use in ADHD with all-cause, natural and unnatural mortality. Our primary finding was that MPH use was associated with significantly lower all-cause mortality. Within the group receiving MPH, a

longer interval between diagnosis and first treatment was associated with an increased risk of mortality, whereas longer treatment duration was associated with lowered risk.

MPH and decreased risk of mortality

Our findings showed that the adjusted hazard ratio for all-cause mortality was significantly lower in the MPH-receiving group than in the comparison group, and that no significant differences were found in natural-cause mortality in adjusted analyses. Recently, a concern was reported that cardiovascular events are increased two-fold in MPH users,[27] although other self-controlled and population-based cohort studies have not found associations with risk of cardiac events.[40–42] Previous studies have also reported no increase in the standardised mortality ratio for sudden death in patients receiving MPH.[28,32] Our findings thus add to the evidence that MPH use is not associated with an increased risk of natural-cause mortality.

Unnatural-cause and suicide mortality

Our findings that MPH use was associated with decreased hazard ratios for both natural and unnatural causes of mortality in univariate analyses are in agreement with previous studies.[16,21,24,43,44] However, after adjusting for demographic variables and comorbidities, these protective effects remained statistically significant only for all-cause mortality as an outcome. It should be borne in mind that mortality events were very rare and statistical power was thus

Table 3 Multivariate analysis of the association between methylphenidate and mortality outcomes in children/adolescents with attention deficit hyperactivity disorder

Subgroup	Outcome	Adjusted model 1[a]		Adjusted model 2[b]	
		HR[c] (95% CI)	P	HR[c] (95% CI)	P
Total	All-cause	0.82 (0.68–0.99)	0.038	0.81 (0.67–0.98)	0.027
	Natural-cause[d]	0.87 (0.70–1.08)	0.205	0.85 (0.68–1.05)	0.138
	Unnatural-cause[d]	0.71 (0.49–1.04)	0.081	0.72 (0.49–1.05)	0.086
	Suicide[d]	0.64 (0.22–1.85)	0.411	0.64 (0.22–1.86)	0.415
	Accident[d]	0.69 (0.44–1.08)	0.104	0.69 (0.44–1.08)	0.106
Male	All-cause	0.82 (0.66–1.01)	0.059	0.80 (0.65–0.99)	0.043
	Natural-cause[d]	0.88 (0.69–1.12)	0.313	0.86 (0.67–1.09)	0.217
	Unnatural-cause[d]	0.68 (0.44–1.05)	0.085	0.69 (0.44–1.06)	0.090
	Suicide[d]	n.a.	n.a.	n.a.	n.a.
	Accident[d]	0.69 (0.42–1.12)	0.130	0.69 (0.43–1.12)	0.134
Female	All-cause	0.83 (0.55–1.26)	0.389	0.83 (0.55–1.25)	0.369
	Natural-cause[d]	0.83 (0.51–1.35)	0.457	0.82 (0.51–1.34)	0.437
	Unnatural-cause[d]	0.83 (0.39–1.80)	0.643	0.83 (0.38–1.78)	0.630
	Suicide[d]	1.08 (0.40–2.88)	0.881	1.09 (0.41–2.94)	0.861
	Accident[d]	0.67 (0.19–2.29)	0.520	0.66 (0.19–2.26)	0.511
Age 4–11 years	All-cause	0.81 (0.66–0.99)	0.044	0.80 (0.65–0.98)	0.032
	Natural-cause[d]	0.85 (0.67–1.08)	0.186	0.83 (0.66–1.06)	0.133
	Unnatural-cause[d]	0.70 (0.45–1.09)	0.111	0.70 (0.45–1.10)	0.119
	Suicide[d]	0.72 (0.25–2.03)	0.529	0.73 (0.26–2.05)	0.545
	Accident[d]	0.63 (0.36–1.12)	0.119	0.64 (0.36–1.13)	0.125
Age 12–17 years	All-cause	0.94 (0.62–1.42)	0.758	0.93 (0.61–1.41)	0.725
	Natural-cause[d]	1.06 (0.62–1.81)	0.844	1.02 (0.60–1.75)	0.930
	Unnatural-cause[d]	0.82 (0.42–1.60)	0.562	0.82 (0.42–1.60)	0.563
	Suicide[d]	n.a.	n.a.	n.a.	n.a.
	Accident[d]	0.84 (0.41–1.72)	0.635	0.83 (0.41–1.71)	0.621

ODD, oppositional defiant disorder; HR, hazard ratio; CI, confidence interval; n.a., Non-available due to zero deaths among MPH cohort.
a. Model 1: adjusted for gender, age, residence, insurance premium and out-patient visits (medical claims past 1 year of first diagnosis date of ADHD).
b. Model 2: Model 1, further adjusted for pre-existing diagnoses and causes of death. Pre-existing diagnoses: congenital anomaly or birth defect (ICD-9: 740–759); intellectual disability (ICD-9: 317–319); depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311); autism (ICD-9: 299); substance use disorder (ICD-9: 303–304); conduct disorder or ODD (ICD-9: 312, 313.81). Causes of death: suicide, ICD-9: E950–E959, E980–E989; accident, ICD-9: E800–E949; homicide, ICD-9: E960–E969; unnatural-cause (suicide, accident and homicide), natural-cause (all-cause mortality excluded suicide, Accident and homicide).
c. Unit: per 100 days of MPH use.
d. Adjusted for other-cause mortality by competing-risk-adjusted Cox regression.

limited for detecting these specific cause-of-death subgroups. Of note, in the fully adjusted models, the significant hazard ratio of 0.81 for all-cause mortality associated with MPH use was more strongly accounted for by the hazard ratio of 0.72 for its unnatural-cause component (141 deaths) than by the 0.85 for natural-cause mortality. Furthermore, accident-related deaths ($n = 101$) were the principal component of unnatural mortality, so are likely to be responsible for a high component of the all-cause reduction, despite not being statistically significant as a specific cause of death.

Age and gender differences

Our findings indicated that the association of MPH with reduced mortality was more prominent in the younger age group. The results extended previous findings that people diagnosed with ADHD in childhood and adolescence have a lower risk of mortality than those diagnosed in adulthood.[12] It is unclear why the association of MPH with reduced all-cause mortality varies with age at first ADHD diagnosis; however, it has been reported that initiating MPH at an earlier age (aged 6–7) is associated with a lower lifetime risk of non-alcohol substance use disorder than later initiation (aged 8–12).[45] Since substance misuse can result in higher risk of mortality in the general population,[46] earlier identification and initiation of MPH treatment in children with ADHD may also be able to decrease the excessive mortality. In addition, greater comorbidity in the MPH-treatment group implies that higher severity/complexity of difficulties is associated with greater prescription and/or uptake of prescriptions. Greater comorbidity encompassing depression, conduct disorder and substance misuse elements suggests that

a higher level of mortality from unnatural causes (accidents, assaults, suicide, etc.) might be expected in the MPH-receiving group, which makes the observed reduction detected all the more striking. Receipt of a diagnosis at a younger age might also relate to greater severity of difficulties and could be a subject for further research in clinical samples.

Although MPH treatment was also associated with a significantly lower risk of mortality in male but not female participants, the effect sizes were similar and the differences may reflect differences in sample size and event numbers. The lack of a statistically significant effect for females compared with males may be due to the smaller stratum size and insufficient statistical power since ADHD diagnoses, referral for treatment, medication for ADHD, and mortality are all lower among females.[47,48]

Earlier and continuous treatment

This is the first study reporting that a longer interval between first ADHD diagnosis and first prescription of MPH is associated with a higher risk of all-cause mortality. In addition, we also found that participants receiving longer-duration MPH treatment had lower risk of all-cause mortality. It has been reported that people diagnosed with ADHD in adulthood have a higher risk of mortality than those diagnosed in childhood and adolescence.[12] Combined with our results, an implication is that receiving a diagnosis earlier and receiving medication earlier may reduce the risk of later adverse consequences. As described, one possible reason for this may be benefits of MPH treatment in reducing rates of accident-related causes of death.[19,21,49] Of relevance, Mannuzza et al described a higher risk of developing substance use disorder

Table 4 Multivariate analysis[a] of factors predicting all-cause mortality in children and adolescents receiving methylphenidate prescription (n = 68 096)

Variable	HR (95% CI)	P
Period of MPH prescription since diagnosis[b]	1.05 (1.01–1.09)	0.009
Duration of MPH prescription, per 100 prescription days/year	0.83 (0.70–0.98)	0.031
Gender		
Male	1.00	
Female	1.37 (0.91–2.08)	0.131
Age, years)	1.15 (1.11–1.19)	<0.001
Residence		
Rural	1.00	
Urban	1.29 (0.85–1.95)	0.234
Insurance premium of main caregiver		
Less than NT$20 000[c]	1.00	0.004
NT$20 000–39 999	0.23 (0.15–0.34)	<0.001
NT$40 000 or more	0.16 (0.08–0.32)	<0.001
Out-patient visits,[d] n		
0–10	1.00	
11–20	1.07 (0.72–1.59)	0.725
≥21	1.21 (0.83–1.77)	0.321
Congenital anomaly or birth defect[e]	1.75 (0.99–3.10)	0.055
Intellectual disability	1.44 (0.76–2.72)	0.263
Depressive disorder	2.47 (0.77–7.89)	0.128
Autism	3.14 (1.54–6.39)	0.002
Substance use disorder	0.59 (0.15–2.38)	0.456
Conduct disorder or ODD	1.64 (0.23–11.93)	0.624

MPH, methylphenidate; HR, hazard ratio; ODD, oppositional defiant disorder.
a. Factors entered simultaneously as covariates.
b. Period between attention-deficit hyperactivity disorder first diagnosis date and the MPH first prescription date, unit: per 100 days.
c. 1 US $ = 32.1 New Taiwan dollars (NT$) in 2010.
d. Medical claims past 1 year of first diagnosis date of ADHD.
e. Pre-existing diagnoses: congenital anomaly or birth defect (ICD-9: 740–759); intellectual disability (ICD-9: 317–319); depressive disorder (ICD-9:296.2, 296.3, 300.4, 311); autism (ICD-9: 299); substance use disorder (ICD-9: 303–304); conduct disorder or ODD (ICD-9: 312, 313.81).

associated with MPH initiation at a later age[45] and substance misuse may link to worse outcomes. For longer-duration MPH treatment, survival bias needs to be considered: i.e. early mortality reducing the length of time over which treatment is recorded. However, since the analysis was based on a repeated-measures time-dependent Cox regression model, the number of deaths was too few to generate this reverse effect.

Strengths and limitations

Strengths of this study included the population-based cohort design, which minimised the likelihood of selection and recall bias. The linkage to the National Mortality Register allowed us to investigate the association of MPH use and mortality, and we were able to adjust for a wide range of demographic factors and comorbidities. The competing-risk model we applied also enhanced our precision for target causes of death.

Notwithstanding, there are several limitations that should be borne in mind when drawing inferences from our findings. First, diagnoses obtained from the NHIRD were based on physicians' clinical judgements rather than structured research-quality interviews. Second, this is an observational study using data from the population in Taiwan, and generalisability to other populations needs to be established. Third, although we adjusted for multiple covariates, information lacking in the database precluded the measurement of other possible confounders, such as family history, psychosocial stressors, effect of behavioural therapy or severity of comorbidities. Therefore, as with all observational data, it is not possible to be conclusive about whether the association with lower mortality is related to an effect of MPH treatment itself or whether other characteristics of the children receiving MPH may account for the lower risk (i.e. confounding by indication). Finally, although the cohort sizes were large, the number of deaths was small and this limited statistical power, particularly for investigation of cause-specific mortality and of subgroup differences. Because of the relatively low number of deaths and limited follow-up duration, longer-term studies with larger samples are warranted to delineate further associations with specific causes of death and intervening causal pathways. To generalise the findings, similar population-based cohort studies from other countries are warranted.

Implications

Our finding that MPH use was associated with a reduced overall mortality among people with ADHD, especially those treated earlier after diagnosis and with longer treatment duration, adds to a growing observational literature drawing on administrative data and should reassure families that methylphenidate does not at least appear to be related to increased mortality.

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Supplementary material

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Data availability

The data that support the findings of this study are available from the National Health Insurance Research Database provided by the Central Bureau of National Health Insurance, the Department of Health, and managed by the Taiwan National Health Research Institutes, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

Declaration of interest

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Psychiatry in history

Neuroanatomical explorations of the human mind: the legacy of Albert W. Adamkiewicz (1850–1921)

Fabian-Alexander Tietze iD, **Marcin Orzechowski** iD and **Florian Steger** iD

Albert Wojciech Adamkiewicz, born on 11 August 1850, was a Polish physician whose pioneering research in neuroanatomy made him the eponym of the great anterior radiculomedullary artery. Despite his notable achievements in neurology, his critical engagement with psychodynamic theories of mental states and disorders is commonly ignored in research. This year we commemorate the 100th anniversary of his death.

Fig. 1 Albert Wojciech Adamkiewicz (1850–1921). Reprinted from Skalski JH, Zembala M. Albert Wojciech Adamkiewicz: the discoverer of the variable vascularity of the spinal cord. *Annals of Thoracic Surgery* 2005; **80**: 1971–5. © Elsevier 2005, reproduced with permission.

Adamkiewicz studied medicine in Königsberg, Breslau and Würzburg and became full professor at the Jagiellonian University in Cracow in 1879. Following a controversy about his claim to have discovered an antiserum against a carcinogenic parasite, for which he could not provide sufficient evidence, he resigned his professorship and left Cracow for Vienna in 1891. Little is known about his work as chief physician at the Clinic for Neurology at the Rothschild Hospital in Vienna, as most biographical studies on Adamkiewicz concentrate on his achievements in neuroanatomy. Until the end of his career, Adamkiewicz remained a controversial figure in the medical profession and published polemic articles against Viennese medical society. Interestingly, he also critically engaged with the newly established theory of psychoanalysis and tried to set a naturalistic exploration of human thought against the psychodynamic approach developed by Sigmund Freud (1856–1939). A neurological case study that Adamkiewicz published in 1887 received a sarcastic review by Freud, who tried to explain the case's casuistry using his own theory of hysteria. During his time in Vienna, Adamkiewicz elaborated a theory of human thought in which he tried to synthesise his findings from neuroanatomy with central theorems of psychoanalysis, such as psychosis and the unconscious. In 1902 he conceived a neurophysiological theory of unconscious thought in which he distinguished between neuroanatomical correlates of the unconscious and consciousness. Adamkiewicz held that if normally inactive, and therefore unconscious, cortical areas did not regulate their own neural activity, psychotic states can follow and voices might be perceived without external stimulation. His hypothesis was an early anticipation of present explanations of intrinsic neural activity in states of perceptual hallucinations.

The oeuvre of Adamkiewicz includes around 90 research articles and 10 monographs, which he published in Polish, German, French and even Latin. His late work has been overshadowed by scientific controversy but deserves renewed attention. It shows his efforts to provide a neuroanatomical grounding for mental disorders, making him an undervalued precursor of neuropsychiatry. Adamkiewicz died in Vienna on 31 October 1921, aged 71.