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# BMJ Open

## INCREASED MORTALITY ASSOCIATED WITH METHYLPHENIDATE IN ADULTS

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057303
Article Type:	Original research
Date Submitted by the Author:	14-Sep-2021
Complete List of Authors:	Stricker, Bruno; Erasmus Medical Center, Epidemiology Cheung, Kiki; Erasmus Medical Center, Epidemiology Verhamme, Katia; Erasmus Medical Center, Medical Informatics
Keywords:	Suicide & self-harm < PSYCHIATRY, Adverse events < THERAPEUTICS, EPIDEMIOLOGY

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12 ***INCREASED MORTALITY ASSOCIATED WITH METHYLPHENIDATE IN ADULTS***  
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43 word count [body of text]: 3194

44 key words: methylphenidate, psychostimulants, pharmacoepidemiology, pharmacovigilance,  
45 psychiatric adverse events, mortality, suicide  
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## Abstract

### Objectives

Methylphenidate is a 'prescription only' drug against attention disorders which is increasingly used by adults. We investigated whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt, and overall mortality.

### Design

A population-based matched cohort design.

### Setting

The IPCI system, an automated general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants.

### Participants

During the study period between 1<sup>st</sup> June 1996 and 1<sup>st</sup> January 2018, 8905 adults started methylphenidate and were matched to 10 non-users on sex, age, GP practice, and prescription date. The total study population consisted of 97,198 participants.

### Main outcome measures

Serious psychiatric events such as depression and suicide attempts, and overall mortality.

### Analyses

Risks of development of each event during use of methylphenidate were expressed as hazard ratios (HR) with 95% confidence limits (CI), adjusted for relevant confounders with methylphenidate as a time-dependent determinant. Additional adjustment was performed for the intervention ['intention-to-treat'].

### Results

Although during follow-up the unadjusted risks of depression, and suicide attempt were strongly increased in users, depression and psychosis became non-significant after adjustment for alcohol- and substance abuse and psychiatric disease in the medical history and after adjustment for 'intention-to-treat'. However, the risk of suicide attempts remained significantly increased after full adjustment [HR 2.0; 95%CI 1.1-3.6], and was highest in women and in participants within the age-group of 18 to 40 years. The unadjusted risk of overall mortality was strongly increased but this lowered to a significant 30% risk increase [HR 1.3; 95%CI 1.1-1.6] after full adjustment.

### Conclusion

There is an increased risk of suicide attempts in adults up to 40 years of age after starting methylphenidate and this risk should be carefully considered before prescribing to this group.

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3 Strengths and limitations  
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5 Population-based study with GP medical records  
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7 Large sample size  
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- 9
- 10 • Population-based study with GP medical records with diagnoses and prescriptions
  - 11 • Large sample size
  - 12 • Medical records with free text for validation
  - 13 • No data 'over-the-counter' medicines or illicit drug use
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## INTRODUCTION

Methylphenidate is a psychostimulant which is pharmacologically related to amphetamines and which was already registered more than 50 years ago for the treatment of children with a hyperkinetic syndrome, later named 'attention deficit hyperactivity disorder' (ADHD) [1, 2]. In patients with 'attention deficit disorder' (ADD) or ADHD they improve the balance between concentration and distraction and decrease hyperactivity [4]. Over the past years, these 'prescription only' drugs were increasingly used 'off label' in adults for a variety of indications. In 2018, methylphenidate was registered in the Netherlands for use in adults. Until April 2017, approximately 1,200 reports of mostly serious adverse events attributed to methylphenidate were notified to the national Dutch Pharmacovigilance Center, of which 542 (45.2%) in adults [5]. Psychiatric adverse events were frequent among these reported events but also cardiovascular events were reported.

Longitudinal studies have shown that ADHD in childhood is itself a risk factor for a diagnosis of psychosis in adult life [6-8]. Research indicates that these disorders share common genetic [9] and environmental aetiologies [6, 10]. A potential mediator of the association between ADHD and psychosis is the prescription of central stimulants for ADHD, which causes considerable concern for several clinicians [11, 12]. Central stimulants act as indirect dopamine agonists and are presumed to amplify neuronal signaling by prompting a marked increase in the extracellular concentration of neurotransmitters in the prefrontal cortex of the brain [13]. Methylphenidate blocks the transporters of dopamine and noradrenaline, inhibits their presynaptic reuptake and has stimulant properties [3]. Increased concentrations of synaptic dopamine have also been implicated in the generation of psychotic symptoms [14]. Hence, the pharmacological mechanism of central stimulant medication can be viewed by clinicians as having the potential to induce psychotic symptoms and disorders [8, 15].

Therefore, the current study was performed to investigate whether the use of methylphenidate was associated with an increased risk of psychiatric adverse events such as depression, psychosis, or suicide attempts in adults. We also investigated whether there was an increased risk of overall mortality in methylphenidate users.

## METHODS

### Setting

The source population consisted of all patients who were registered with one of the general practitioners (GPs) who contribute information to the Integrated Primary Care Information (IPCI) database, which was established in 1992 [16]. IPCI is a longitudinal observational database with data from computer-based patient records retrieved from a selected group of GPs throughout the Netherlands, who voluntarily supply data to the database. In the Netherlands, the GP plays a central role in the health care system and acts as a gatekeeper by referring patients to other medical disciplines for out- or inpatient care and as a central receiver of information from secondary or

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3 tertiary care. Data from the GP computer system are downloaded on a monthly basis and sent to  
4 the IPCI gatekeeper who anonymizes all information before further access is provided to the  
5 researchers. It is a dynamic cohort because over time, people may enter the population as new  
6 patients, or leave because of removal or death. Details of the database have been described  
7 elsewhere [16, 17]. Currently, more than 600 GPs are providing data to the database which has  
8 expanded to now more than 2,500,000 patients. The database is representative of the Dutch  
9 population regarding age and sex. The IPCI database complies with European Union guidelines  
10 on the use of medical data for medical research and has been proven valid for pharmaco-  
11 epidemiological studies. For the use of IPCI for this study, permission has been granted by the  
12 IPCI review board [RvT 7/2017]. The investigators had complete access to all completely  
13 anonymized patient records, including free text, in a stand alone password protected dataset in a  
14 locked room. There was no restriction to using all available data. There was no patient and/or public  
15 involvement in this study.  
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## 20 Source population

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22 The source population consisted of 2,546,082 individuals with at least one year of medical history  
23 within the IPCI database with an average follow-up time of slightly more than four years. Start of  
24 the follow-up period was 1<sup>st</sup> June 1996 or 1 year after enrolment with the GP practice when starting  
25 after 1<sup>st</sup> June 1996 [most practices], and the end of follow-up was death, removal, or end of the  
26 study on 1<sup>st</sup> January 2018, whichever came first.  
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## 29 Design and Study population

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31 For this matched cohort design, we selected only starters with methylphenidate of 18 years or  
32 older. Out of 51,603 starters ['first ever use'] with methylphenidate, 20,596 [40%] started during  
33 adulthood of whom 8,905 during the study period [11,691 started as adult but before their practice  
34 participated in IPCI]. Because methylphenidate was mainly prescribed to relatively young male  
35 adults, we sampled up to 10 non-users without history of methylphenidate for each of these 8,905  
36 starters whom were matched on sex, age [less than 1-year difference], and GP-practice. This  
37 resulted in a total study population of 97,198 subjects [see flow diagram Figure 1]. For each  
38 matched set of 1 user and [mostly] 10 nonusers, follow-up started at the day of first prescription  
39 of methylphenidate and this date was also allocated to the 10 non-users. All participants were  
40 eligible for GP healthcare during the study period.  
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## 44 Outcomes

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46 All registered diagnoses and problem codes during the study period were gathered, as coded  
47 according to the International Classification of Primary Care [ICPC] coding thesaurus [18]. Apart  
48 from overall mortality, the following psychiatric outcomes were studied: psychosis [ICPC P71-  
49 P73, P98]; anxiety [P74]; hypochondria [P75]; depression [P76]; suicide/suicidal attempt [P77];  
50 neurasthenia/burnout [P78, P79]; personality disorder [P80]; and other psychiatric illness [P99].  
51 For each diagnosis, those with a prevalent code before the index date were excluded from the  
52 follow-up analyses in order to study the association between methylphenidate and incident  
53 psychiatric outcomes. All mortality is registered in the IPCI database. For every deceased  
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individual, month and year are registered. For the precise day of the month, the original medical record was studied.

## Medication exposure

All medications prescribed by the general practitioners are automatically stored. For each prescription, the prescribed daily number, the strength, the total number of prescribed units [tablets, capsules], and route of administration [oral, parenteral, topical, etc.] are registered. Specialist medication is only included if the general practitioner continues prescribing, for instance, if medication is chronic.

For each prescription of methylphenidate, we calculated the prescription length by dividing the total number of prescribed units by the prescribed daily number. To calculate the 'medication possession ratio' for each individual, we summed the total number of days of exposure [according to the prescription] and divided this by the calendar time in days between the first day of the first prescription and the last day of the last prescription of methylphenidate. For other drugs used in this study, such as antidepressants and antipsychotics, exposure was calculated in the same way.

## Co-factors

As potential confounders of the association between methylphenidate and psychiatric events, we considered the following independent risk factors: sex, age, smoking, body mass index (BMI), alcohol abuse/intoxication [ICPC P15], medication abuse [P18], tobacco abuse [, drug abuse [P19], psychosis [P71-P73, P98], depression [P76], anxiety [P74], or neuroses in history [P78, P79], personality disorder [P80], other psychiatric disease [P99], and use of antidepressants (ATC code N06A), antipsychotics (N05A), anxiolytics (N05B), and sedatives (N05C). For the endpoint overall mortality, we considered independent risk factors, notably body mass index [BMI], smoking, diabetes mellitus, hypertension, hypercholesterolemia, and history of stroke, heart failure, or arrhythmia. Smoking was distinguished into 'current', 'past', and 'never'. Diabetes mellitus was defined as a diagnosis or problem code before the index date, if the patient had a prescription for a hypoglycemic agent [ATC code 'A10'], or if the patient had a fasting glucose level > 7.0 mmol/l. Hypertension was considered as present if any of the ICPC codes K85, K86, or K87 was given as a diagnosis or problem code before the index date, or if the patient used an antihypertensive before the index date. As there were often multiple measurements for each co-factor, the one which was closest to the event date was chosen.

## Statistics

Comparison between baseline variables in methylphenidate users and non-users were expressed as proportion ratios with 95% confidence limits to show the magnitude and significance of each variable. We calculated hazard ratios with 95% CI in the cohort analysis in which users/non-users were followed for the occurrence of the above-mentioned psychiatric disease outcomes with a Cox proportional hazards model. In this model, methylphenidate was defined as a time-dependent risk factor and adjustment was performed for the co-factors listed above which were treated as confounders if they changed the point estimate by 10 percent or more. Because the percentage of missing data was sometimes large, i.e. for smoking and BMI, we decided not to impute these

values but rather to adjust with missing status as a separate dummy variable in a categorical set of values to investigate whether missing status was a confounder. Furthermore, we adjusted for the likelihood of being treated [adjustment for intention-to-treat]. Lastly, all 168 cases with a notification of suicide [attempt] were validated by reference to the medical patient records, as well as all 1,027 deaths.

## RESULTS

### *General characteristics*

On average, the 8,905 starters on methylphenidate received 10 prescriptions with an average total duration of 370 days. The mean starting dose of the first prescription was 30 mg per day, while the mean dosage of the last prescription during the study period was 35 mg per day. Eighty-four percent of the prescribers of the first prescription was a general practitioner. Further general characteristics of the study population are given in Table 1. Fifty-four percent was male and 64 percent was in the age category of 18-40 years. Methylphenidate users had a significantly higher prevalence of tobacco, alcohol, and other substance abuse, as well as of a history of psychiatric comorbidity.

### *Incident psychiatric adverse events*

There were significantly increased risks of incident organic psychosis [delirium], affective psychosis, anxiety, depression, burnout, other neuroses, personality disorder, and other psychotic and other psychiatric disorders in methylphenidate users. There was a significantly increased risk of suicide attempts in users of methylphenidate. Increased risks were observed in smokers and people with a history of a variety of psychiatric diseases in the medical history. Further adjustment for smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, and psychiatric events in history reduced the risk estimates in table 2. However, adjustment for the intervention/intention-to-treat abolished almost all statistically significant relative risks in table 2. This means that with the exception of overall mortality and suicide [attempts], all significantly increased risks in table 2 were confounded by the intention-to-treat itself.

All 168 cases with a notification of suicide [attempt] were validated by reference to the medical patient records. Out of these 168 cases, 117 were suicide attempts of which 16 successful while the remaining 51 cases were notification of suicidal ideation, or phantasies/tendencies. A further 19 cases of successful suicide came from the validation of all 1,027 cases of death. Restricting the analyses to these 136 cases of whom 6 were excluded because of a history of suicidal ideation/attempts before the index date, yielded an unadjusted relative risk of suicide in methylphenidate users of 5.5 [95%CI: 3.5-8.6]. After additional adjustment for the intervention, the relative risk went down to 2.0 [95%CI: 1.1-3.6] for current use of methylphenidate but remained statistically significant. In table 3A, these risks were stratified according to sex and age-groups. The majority of suicide [attempts] were in the age group from 18 through 40 years. The risk of suicide [attempts] was highest in women. As one can see from figure 2, the suicide [attempt]

occurs especially in the early period of follow-up in users whereas it is spread over a longer period of follow-up in non-users.

### *Overall mortality*

Because the cause of death was not specifically coded in the GP database, we took overall mortality as an endpoint. Especially age, hypertension, diabetes mellitus, and decreased renal function were associated with an increased risk of death.

We performed a validation of all 1,027 cases of death to check the precise date of death, and to distinguish its causes – where possible - by going through the patient history. Thirty percent of all death occurred within 80 days after starting with methylphenidate. After restricting the analyses to cases in which the precise date of death could be verified [n=946], the unadjusted risk of all-cause mortality in users of methylphenidate was 7.5 [95%CI 6.3-8.9] but reduced to 1.3 [95%CI 1.1-1.6] after full adjustment. Apart from suicide, there was a large and significant risk increase in those who died during methylphenidate in palliative care with a risk of 12.7 [95%CI 9.5-16.9]. As the pharmacologic effect of methylphenidate is immediate, we did not study duration-effect relationships. In extra analysis, we further adjusted all relative risks for dosage but this did not substantially change the risk estimates. Finally, we studied effect modification by sex- and age category [table 3B]. The risk of mortality in the intervention group was significantly increased in women only. Furthermore, the risk was significantly increased by 60% in the age category 61 to 80 years of age. As one can see from figure 3, overall mortality peaked especially in the early period of follow-up in users but not in non-users.

## **DISCUSSION**

From this study, we can conclude that although there was a strongly increased risk of psychiatric events in users of methylphenidate, most part of it was explained by confounding by intervention ['intention-to-treat']. However, even after adjusting for the intervention, a significantly increased risk of suicide [attempts] after starting methylphenidate remained.

Especially the strong association with death in our study is striking. The risk increase of death was genuine but mainly explained by confounding by the indication palliative care because from validation of the medical records, it became clear that this risk increase was largely explained by starting methylphenidate in depressed or extremely tired patients in their latest phase of life. Because regular antidepressants take 6-8 weeks before they exert their therapeutic effects, they may be too late for treating depression in the last weeks of life and then psychostimulants may help. This is in line with British and Dutch guidelines [20].

Similar to Dutch reports, data from the British Yellow Card scheme showed that, of 1,335 adverse drug reaction reports regarding methylphenidate, 663 adverse reactions were psychiatric disorders, making these disorders the most frequently reported class of adverse drug reactions of methylphenidate [Vigilance and Intelligence Research Group; <http://www.mhra.gov.uk/drug->

analysis-prints/drug-analysis-prints-a-z/index.htm]. Among these reports, 105 (15.8%) patients reported hallucinations, psychosis or psychotic disorders. Moreover, in an FDA review [21] of data from 49 randomised controlled clinical trials investigating the effects of central stimulant medication in children, 11 adverse events related to psychosis or mania were observed during 743 person-years of follow-up in 5,717 individuals, versus no events reported with placebo, giving a number needed to harm of 526 patients. Given these reports of treatment-emergent psychotic events with central stimulant medication, clinicians have been concerned that methylphenidate and other psychostimulants might provoke psychosis [8, 11]. In literature, use of stimulant ADHD medication is considered as relatively contraindicated in patients with a history of psychosis [12]. However, clinicians face a therapeutic dilemma without clear evidence to guide them when balancing the potential risk of psychotic events with the benefits of stimulants that are the first-line treatment for ADHD in adolescent and adult patients [22]. Some observational studies [12, 23] that reported an increased risk of psychotic events associated with methylphenidate might be affected by confounding by indication; that is, patients who receive stimulant medication for ADHD are inherently different from those who do not and could have a greater risk of psychotic events independently of stimulant prescription. This type of confounding also played a role in our IPCI-study but by adjusting for independent risk factors and for the intervention we were able to deal with it. In a study in 2016 that tried to adjust for confounding by indication, Man and colleagues [24] used a within-individual case series design in a population of children and adolescents, and did not find an increased risk of psychotic events during methylphenidate treatment. In a direct comparison in the USA, methylphenidate was associated with a significantly lower risk of psychosis than amphetamine [25].

### ***Strengths and limitations***

One of the major strengths is the population-based design of this study, as in the Netherlands everybody is designated to only one general practitioner. Therefore, selection bias is highly unlikely. As the information on diseases is prospectively gathered and prescriptions are automatically and completely stored in the computer of the general practice, information bias is also highly unlikely. A limitation may be the fact that not every patient fills his prescription at the pharmacy. According to an earlier study, some 10% of prescriptions from the general practitioner is not filled, and even if filled, patients may decide not to use their medicines [19].

However, chronic medication requires regular prescriptions and if patients get repeated prescriptions, it is more likely that these are really filled. But which product is ultimately filled, remains unknown in a GP database and this means that we could not adjust for regular or slow-release methylphenidate. Also, medication obtained via hospitals or outpatient clinics is missing, as well as illegal drug use. Usually, these types of exposure misclassification lead to an underestimation of the true risk.

We adjusted for confounding by multivariable adjustment of the risk estimates by all known risk factors. Unfortunately, for some confounders there were missing data [for instance, smoking and BMI]. Because the percentage of missing data was sometimes large, we decided not to impute these values but rather to adjust with missing status as a separate dummy variable in a categorical set of values. In this way, we were able to investigate whether the missing status acted as a

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3 confounder but there was almost no confounding by missing status. An important potential  
4 confounder in any observation study in which the consequences of an intervention are studied, is  
5 the indication. Confounding by indication played a role in palliative care in which methylphenidate  
6 is used 'off label' as a psychostimulant. Also, as ADHD/ADD in childhood is a risk factor for a  
7 diagnosis of psychosis in adult life [6-8], confounding by indication will inevitably have played a  
8 role in the increased risk of psychosis which was found in this study although it disappeared after  
9 adjustment for the intervention. Although this might also partly explain the increased risk of  
10 suicide, an independent risk for methylphenidate remained and an adverse role of methylphenidate  
11 seems plausible because of its stimulant properties in a population of patients receiving  
12 methylphenidate despite psychiatric contraindications.  
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16 In conclusion, in this large population-based study with data from general practitioners  
17 encompassing almost 100,000 people, methylphenidate was associated with a significantly  
18 increased risk of mortality, partly explained by 'off label' use as a psychostimulant in palliative  
19 care. There was a significantly increased risk of psychosis, and depression but this was probably  
20 confounded by intervention. However, there was also an increased risk of suicide in current users  
21 of methylphenidate, even after adjustment for the intervention. Considering the population-based  
22 nature of our studies, we think that our results are generalizable to many western countries. All in  
23 all, it seems that a cautious approach to prescribing methylphenidate in adults is warranted,  
24 especially in those with a history of suicidal ideation.  
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## Funding

This study was funded with an unconditional grant by the Health and Youth Care Inspectorate of the Netherlands [2018-16]. The funder had no influence on performance of the study or drafting the report.

## Conflict of interest declaration

Bruno Stricker and Kiki Cheung have no conflict of interest regarding this paper. Katia Verhamme works for a research department who received/receives unconditional research grants from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, GSK, Chiesi, Amgen, UCB, Astra Zeneca and J&J, none of which are related to the content of this manuscript.

## Ethics statement

For the use of IPCI for this study, permission has been granted by the IPCI review board [RvT 7/2017]. The investigators had complete access to all completely anonymized patient records, including free text, in a stand alone password protected dataset in a locked room. There was no restriction to use all available data.

## Patient and public involvement

No patients involved.

## Data sharing

No additional data available.

## Contributorship statement

KV and BHS were responsible for the conception, design, analysis, conduct and reporting of this study. KC was responsible for analysis, interpretation, and reporting of this study.

## LITERATURE

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Table 1 Characteristics of the study population [\*]

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Sex			
Men	4,839 [54.3%]	47,907 [54.3%]	1.0 [reference]
Women	4,066 [45.7%]	40,386 [45.7%]	1.0 [0.9-1.1]
Age	36.5 years	36.3 years	
18-40 yr	5,737 [64.4%]	56,888 [64.4%]	1.0 [reference]
41-60 yr	2,584 [29.0%]	25,847 [29.2%]	1.0 [0.9-1.1]
61-80 yr	476 [ 5.3%]	4,718 [ 5.3%]	1.0 [0.9-1.1]
> 80 yr	108 [ 1.3%]	840 [0.01%]	<b>1.3 [1.1-1.6]</b>
Follow-up [days]	1943 days	1944 days	
BMI [*]			
<25	864 [9.7%]	5617 [6.4%]	1.0 [reference]
25-30	717 [8.1%]	5,746 [6.5%]	<b>0.8 [0.7-0.9]</b>
>30	629 [7.1%]	4,702 [5.3%]	<b>0.9 [0.8-1.0]</b>
Smoking [*]			
Never	2,111 [23.7%]	21,629 [24.5%]	1.0 [reference]
Past	723 [ 8.1%]	4634 [ 5.2%]	<b>1.6 [1.5-1.8]</b>
Current	2,292 [25.7%]	13,111 [14.8%]	<b>1.8 [1.7-1.9]</b>
Alcohol abuse	352 [3.9%]	878 [1.0%]	<b>4.1 [3.6-4.7]</b>
Acute alcohol intoxication	105 [1.2%]	398 [0.5%]	<b>2.6 [2.1-3.3]</b>
Tobacco abuse	810 [9.1%]	3,930 [4.5%]	<b>2.2 [2.0-2.3]</b>
Medicines abuse	87 [0.9%]	230 [0.3%]	<b>3.8 [3.0-4.8]</b>
Drug abuse	525 [5.9%]	859 [1.0%]	<b>6.4 [5.7-7.1]</b>
History of:			
Organic psychosis [delier]	37 [0.4%]	157 [0.2%]	<b>2.3 [1.6-3.3]</b>
Schizophrenia	36 [0.4%]	282 [0.3%]	1.3 [0.9-1.8]
Affective psychosis	82 [0.9%]	245 [0.3%]	<b>3.3 [2.6-4.3]</b>
Anxiety	922 [10.4%]	3602 [4.1%]	<b>2.8 [2.6-3.0]</b>
Hypochondria/hysteria	55 [0.6%]	392 [0.4%]	<b>1.4 [1.1-1.9]</b>
Depression	1,772 [19.9%]	5252 [5.9%]	<b>4.3 [4.0-4.6]</b>
Suicide [attempt]	161 [1.8%]	410 [0.5%]	<b>4.0 [3.3-4.8]</b>
Burnout/overstrain	886 [9.9%]	3962 [4.5%]	<b>2.6 [2.4-2.8]</b>
Other neuroses	169 [1.9%]	674 [0.7%]	<b>2.5 [2.1-3.0]</b>
Personality disorder	479 [5.4%]	822 [0.9%]	<b>6.3 [5.6-7.0]</b>
Other non-specified psychotic disorder	80 [0.9%]	372 [0.4%]	<b>2.2 [1.7-2.8]</b>

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Other psychiatric disorder	541 [6.1%]	1100 [1.2%]	<b>5.3 [4.7-5.9]</b>
Total psychiatric	3729 [41.9%]	13549 [115.3%]	<b>4.5 [4.3-4.7]</b>
Previous or current use of:			
Antipsychotics	835 [9.4%]	1,884 [2.1%]	<b>4.8 [4.4-5.2]</b>
Antidepressants	3,037 [34.1%]	10,213 [11.6%]	<b>4.0 [3.8-4.2]</b>
Anxiolytics	3,338 [37.5%]	16,390 [18.6%]	<b>2.6 [2.5-2.8]</b>
Sedatives	2,498 [28.1%]	10,201 [11.6%]	<b>3.0 [2.8-3.1]</b>

[\*] Values were missing for BMI [n=78,923], smoking [n=52,698]

Table 2 Number of cases and referents per psychiatric disease code/overall mortality occurring during follow-up and the risk [hazard ratio] to develop such a disease in users of methylphenidate in comparison to non-users

Outcome	Case	Referents	HR [95%-CI] [*]	HR [95%-CI] [**]
Organic psychosis [delier]	154	96,850	<b>8.3 [5.2-13.0]</b>	1.7 [0.9-3.0]
Schizophrenia	50	96,830	1.6 [0.4-6.7]	0.9 [0.2-4.3]
Affective psychosis	64	96,807	3.5 [1.4-6.9]	1.2 [0.4-3.6]
Anxiety	1374	91,300	1.8 [1.4-2.4]	0.8 [0.6-1.1]
Hypochondria/hysteria	109	96,642	1.5 [0.5-4.0]	0.8 [0.3-2.6]
Depression	1468	88,706	<b>2.7 [2.1-3.3]</b>	1.0 [0.8-1.3]
Suicide/suicide attempt	129	96,498	<b>5.5 [3.5-8.6]</b>	<b>2.0 [1.1-3.6]</b>
Burnout/overstrain	1583	90,767	1.4 [1.0-1.8]	1.0 [0.7-1.4]
Other neuroses	183	96,172	2.0 [1.0-3.9]	0.7 [0.4-1.6]
Personality disorder	412	95,485	6.0 [4.5-7.9]	1.2 [0.8-1.6]
Other non-specified psychotic disorder	162	96,584	3.2 [1.8-5.7]	0.9 [0.5-1.8]
Other psychiatric disorder	538	95,019	4.9 [3.8-6.5]	1.4 [0.9-1.8]
Any psychosis	347	95,727	4.8 [3.4-6.8]	1.3 [0.9-2.0]
Death [***]	946	96,252	<b>7.5 [6.3-8.9]</b>	<b>1.3 [1.1-1.6]</b>

[\*] All hazard ratios [HR] are adjusted for sex, and age by matching

[\*\*] All HR are adjusted for sex, age, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and for 'intention-to-treat'

[\*\*\*] Additionally are adjusted for hypertension, diabetes mellitus, hypercholesterolemia, and decreased renal function.

Table 3A; Age and sex specific risks of suicide, suicidal attempts/ideation during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	64/44,043	3.9 [1.5-10.2]
Men	65/52,294	1.1 [0.4-2.6]
18-40 yrs. of age	84/62,196	2.4 [1.2-4.9]
41-60 yrs. of age	38/28,108	1.3 [0.4-4.9]
61-80 yrs. of age	4/4,543	1.6 [0.0-∞]
>80 yrs. of age	3/836	- [*]

All hazard ratios [HR] are adjusted for sex, age, intervention, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and ‘intention-to-treat’

[\*] No cases exposed to methylphenidate

Table 3B; Age and sex-specific risks of all-cause mortality during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	375/44,077	1.7 [1.2-2.5]
Men	571/52,154	1.1 [0.8-1.5]
18-40 yrs. of age	67/62,478	1.2 [0.4-3.5]
41-60 yrs. of age	240/28,191	1.1 [0.7-1.8]
61-80 yrs. of age	412/4,781	1.6 [1.2-2.2]
>80 yrs. of age	227/721	1.2 [0.7-2.0]

[\*] All hazard ratios [HR] are adjusted for sex, age, smoking, hypertension, diabetes mellitus, BMI, hypercholesterolemia, decreased renal function, and ‘intention-to-treat’

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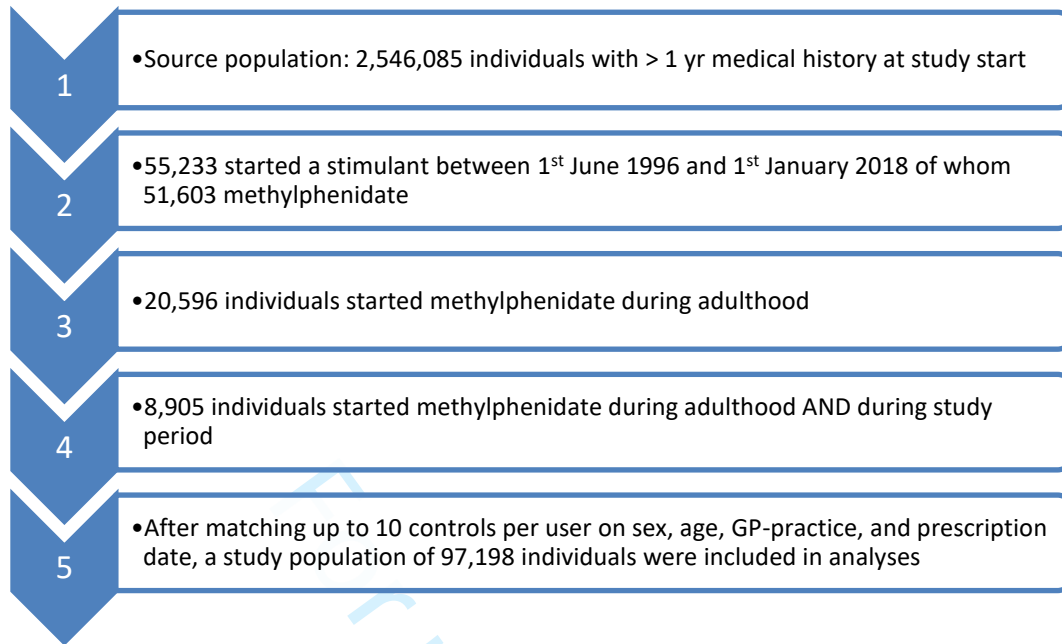
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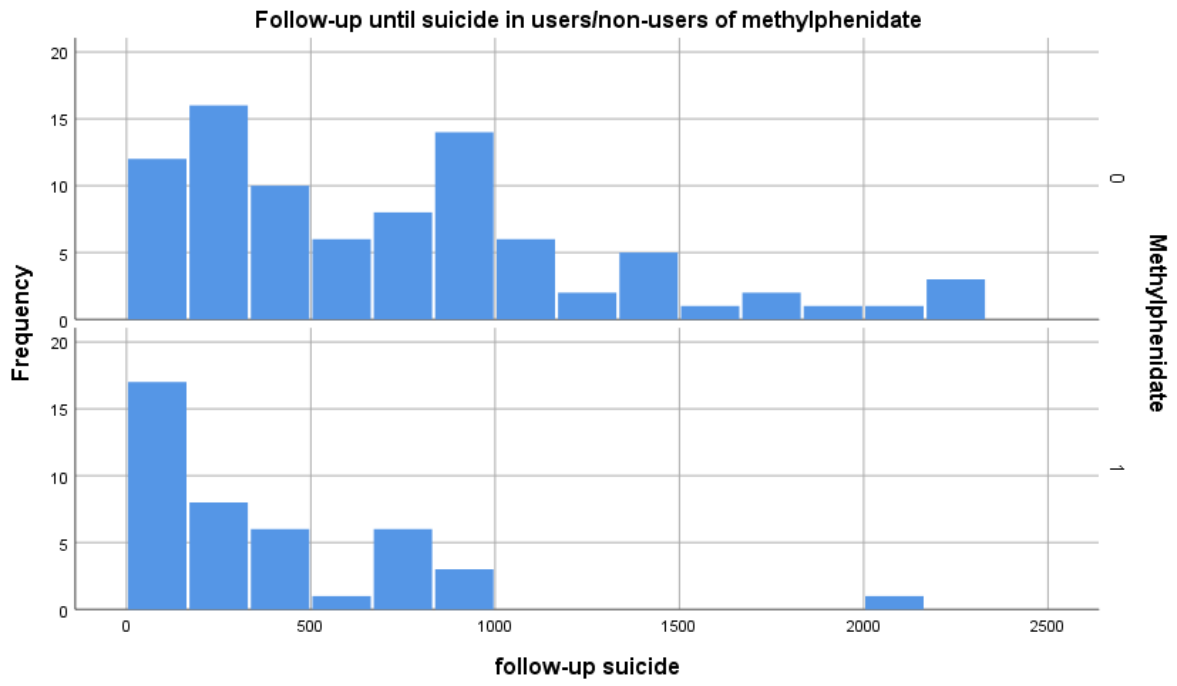
18 Figure 1 Time delay between 1st intake of methylphenidate and suicide [attempt]. In non-users  
19 with the same reference date as users [upper part of figure 2], this delay is spread over several  
20 years whereas it is focused in the early weeks of intake in users [lower part of figure 2].  
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29 Figure 3 Time delay between 1st intake of methylphenidate and death. In non-users with the  
30 same reference date as users [upper part of figure 3], this delay is spread over several years  
31 whereas it is focused in the early weeks of intake in users [lower part of figure 3].  
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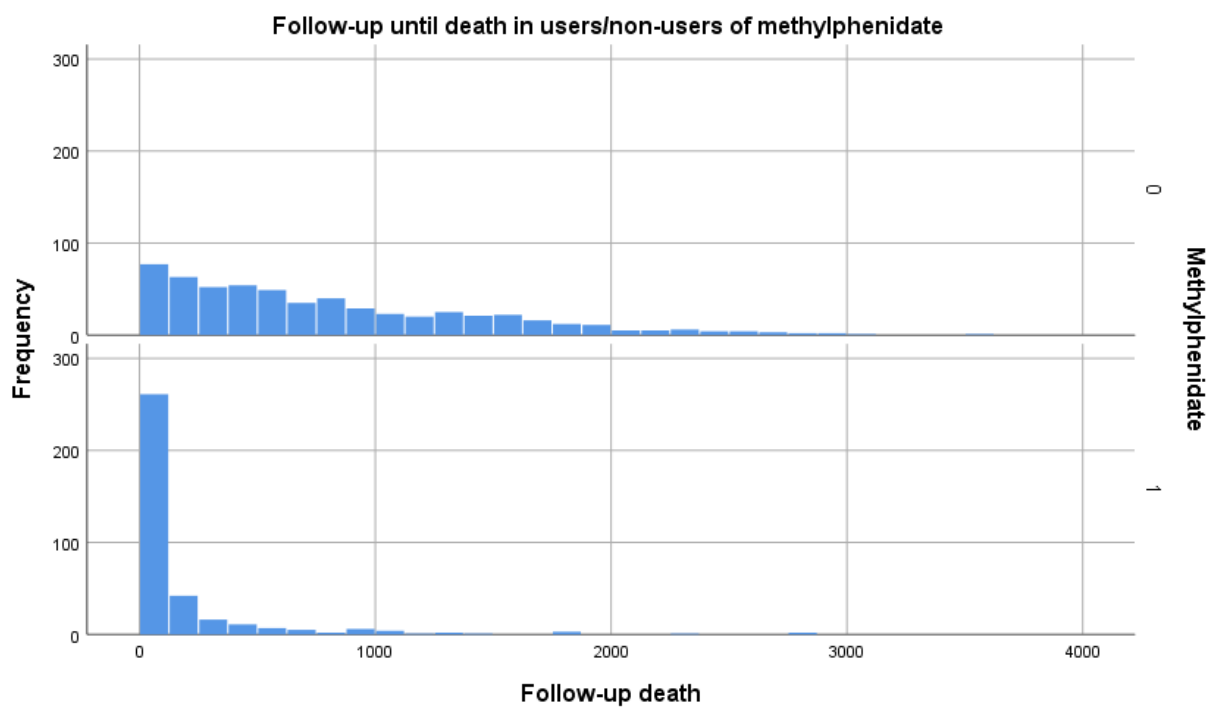


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**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.  RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.  RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P. 2
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			P. 3
Objectives	3	State specific objectives, including any prespecified hypotheses			P. 3
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper			P. 3/4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			A. 4

Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>		<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	<p>4/5</p> <p>N/A</p> <p>N/A</p>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	4/5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			4/5

1 2 3 4 5 6 7 8 9	Bias	9	Describe any efforts to address potential sources of bias			P. 2/9
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Study size	10	Explain how the study size was arrived at			P. 4
33 34 35 36 37 38 39 40 41 42 43 44 45 46	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			P. 5-7
	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			P. 5-7
	Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	P. 4

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	W/A
<b>Results</b>					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	P. 4
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)			P. 14
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure			A. 6/7

		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			P. 6/7
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses			P. 7
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives			P. 7/8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	P. 8
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			P. 9

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			p. 9
<b>Other Information</b>					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			p. 10
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# BMJ Open

## METHYLPHENIDATE IN ADULTS ASSOCIATED WITH INCREASED MORALITY. A COHORT STUDY IN A GENERAL PRACTICE DATABASE

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057303.R1
Article Type:	Original research
Date Submitted by the Author:	15-Feb-2022
Complete List of Authors:	Stricker, Bruno; Erasmus Medical Center, Epidemiology Cheung, Kiki; Erasmus Medical Center, Epidemiology Verhamme, Katia; Erasmus Medical Center, Medical Informatics
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Suicide & self-harm < PSYCHIATRY, Adverse events < THERAPEUTICS, EPIDEMIOLOGY

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12 ***METHYLPHENIDATE IN ADULTS ASSOCIATED WITH INCREASED MORALITY. A***  
13 ***COHORT STUDY IN A GENERAL PRACTICE DATABASE***  
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17 Bruno H Stricker [1,2], Kiki C Cheung [2], Katia MC Verhamme [3]  
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44 word count [body of text]: 3384  
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46 key words: methylphenidate, psychostimulants, pharmacoepidemiology, pharmacovigilance,  
47 psychiatric adverse events, mortality, suicide  
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## Abstract

### Objectives

Methylphenidate is a 'prescription only' drug against attention disorders which is increasingly used by adults. We investigated whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt, and overall mortality.

### Design

A population-based matched cohort design.

### Setting

The IPCI system, a general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants.

### Participants

During the study period between 1<sup>st</sup> June 1996 and 1<sup>st</sup> January 2018, 8905 adults started methylphenidate and were matched to 10 non-users on sex, age, GP practice, and prescription date. The total study population consisted of 97,198 participants.

### Main outcome measures

Serious psychiatric events such as depression and suicide attempts, and overall mortality.

### Analyses

Risks of development of each event during use of methylphenidate were expressed as hazard ratios (HR) with 95% confidence limits (CI), adjusted for relevant confounders with methylphenidate as a time-dependent determinant. Additional adjustment was performed for the intervention ['intention-to-treat'].

### Results

Although during follow-up the unadjusted risks of depression, and suicide attempt were strongly increased in users, depression and psychosis became non-significant after adjustment for alcohol- and substance abuse and psychiatric disease in the medical history and after adjustment for 'intention-to-treat'. However, the risk of suicide attempts remained significantly increased after full adjustment [HR 2.0; 95%CI 1.1-3.6], and was highest in women and in participants within the age-group of 18 to 40 years. The unadjusted risk of overall mortality was strongly increased but this lowered to a significant 30% risk increase [HR 1.3; 95%CI 1.1-1.6] after full adjustment.

### Conclusion

There is an increased risk of suicide attempts in adults up to 40 years of age after starting methylphenidate and this risk should be carefully considered before prescribing to this group.

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3 Strengths and limitations  
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- 5 • Prospective population-based controlled cohort study
  - 6 • No selection- or information bias
  - 7 • Complete GP records
  - 8 • No drug dispensing data
  - 9 • No in-hospital drug data
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For peer review only

## INTRODUCTION

Methylphenidate is a psychostimulant which is pharmacologically related to amphetamines and which was already registered more than 50 years ago for the treatment of children with a hyperkinetic syndrome, later named 'attention deficit hyperactivity disorder' (ADHD). Methylphenidate is increasingly used in children in many countries [1-3]. Attention deficit hyperactivity disorder (ADHD) is defined as a mental health disability, which usually begins before 12 years of age, and is characterized by three main symptoms: inattention, impulsivity, and hyperactivity [without hyperactivity, the term 'attention deficit disorder' (ADD) may be used]. The intensity of the symptoms tends to decrease with ageing, but in 40% to 50% of people diagnosed with ADHD in childhood, symptoms may persist during adolescence and adulthood [4,5]. Therefore, methylphenidate is also increasingly used in adults [4], which was considered as an 'off-label' group for several years. In patients with ADD or ADHD methylphenidate improves the balance between concentration and distraction and decrease hyperactivity [6]. Over the past years, these 'prescription only' drugs were increasingly used 'off label' in adults for a variety of indications. In 2018, methylphenidate was registered in the Netherlands for use in adults. Until April 2017, approximately 1,200 reports of mostly serious adverse events attributed to methylphenidate were notified to the national Dutch Pharmacovigilance Center, of which 542 (45.2%) in adults [7]. Psychiatric adverse events were frequent among these reported events but also cardiovascular events were reported.

Longitudinal studies have shown that ADHD in childhood is itself a risk factor for a diagnosis of psychosis in adult life [8-10]. Research indicates that these disorders share common genetic [11] and environmental aetiologies [8, 12]. A potential mediator of the association between ADHD and psychosis is the prescription of central stimulants for ADHD, which causes considerable concern for several clinicians [13-15]. Central stimulants act as indirect dopamine agonists and are presumed to amplify neuronal signaling by prompting a marked increase in the extracellular concentration of neurotransmitters in the prefrontal cortex of the brain [15]. Methylphenidate blocks the transporters of dopamine and noradrenaline, inhibits their presynaptic reuptake and has stimulant properties [6]. Increased concentrations of synaptic dopamine have also been implicated in the generation of psychotic symptoms [16]. Hence, the pharmacological mechanism of central stimulant medication can be viewed by clinicians as having the potential to induce psychotic symptoms and disorders [10, 17].

Therefore, the current study was performed to investigate whether the use of methylphenidate was associated with an increased risk of psychiatric adverse events such as depression, psychosis, or suicide attempts in adults. We also investigated whether there was an increased risk of overall mortality in methylphenidate users.

## METHODS

## Setting

The source population consisted of all patients who were registered with one of the general practitioners (GPs) who contribute information to the Integrated Primary Care Information (IPCI) database, which was established in 1992 [18]. IPCI is a longitudinal observational database with data from computer-based patient records retrieved from a selected group of GPs throughout the Netherlands, who voluntarily supply data to the database. In the Netherlands, the GP plays a central role in the health care system and acts as a gatekeeper by referring patients to other medical disciplines for out- or inpatient care and as a central receiver of information from secondary or tertiary care. Data from the GP computer system are downloaded on a monthly basis and sent to the IPCI gatekeeper who anonymizes all information before further access is provided to the researchers. It is a dynamic cohort because over time, people may enter the population as new patients, or leave because of removal or death. Details of the database have been described elsewhere [18, 19]. Currently, more than 600 GPs are providing data to the database which has expanded to now more than 2,500,000 patients. The database is representative of the Dutch population regarding age and sex. The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological studies. For the use of IPCI for this study, permission and ethical approval was granted by the IPCI review board [RvT 7/2017].

## Source population

The source population consisted of 2,546,082 individuals with at least one year of medical history within the IPCI database with an average follow-up time of slightly more than four years. Start of the follow-up period was 1<sup>st</sup> June 1996 or 1 year after enrolment with the GP practice when starting after 1<sup>st</sup> June 1996 [most practices], and the end of follow-up was death, removal, or end of the study on 1<sup>st</sup> January 2018, whichever came first.

## Design and Study population

For this matched cohort design, we selected only starters with methylphenidate of 18 years or older. Out of 51,603 starters ['first ever use'] with methylphenidate, 20,596 [40%] started during adulthood of whom 8,905 during the study period [11,691 started as adult but before their practice participated in IPCI]. Because methylphenidate was mainly prescribed to relatively young male adults, we sampled up to 10 non-users without history of methylphenidate for each of these 8,905 starters whom were matched on sex, age [less than 1-year difference], and GP-practice. This resulted in a total study population of 97,198 subjects [see flow scheme Figure 1]. For each matched set of 1 user and [mostly] 10 nonusers during the study period, follow-up started at the day of first prescription of methylphenidate and this date was also allocated to the 10 non-users. All participants were eligible for GP healthcare during the study period.

## Outcomes

All registered diagnoses and problem codes during the study period were gathered, as coded according to the International Classification of Primary Care [ICPC] coding thesaurus [20]. Apart from overall mortality, the following psychiatric outcomes were studied: psychosis [ICPC P71-

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3 P73, P98]; anxiety [P74]; hypochondria [P75]; depression [P76]; suicide/suicidal attempt [P77];  
4 neurasthenia/burnout [P78, P79]; personality disorder [P80]; and other psychiatric illness [P99].  
5 For each diagnosis, those with a prevalent code before the index date were excluded from the  
6 follow-up analyses in order to study the association between methylphenidate and incident  
7 psychiatric outcomes. All mortality is registered in the IPCI database. For every deceased  
8 individual, month and year are registered. For the precise day of the month, the original medical  
9 record was studied.  
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## 12 Medication exposure

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14 All medications prescribed by the general practitioners are automatically stored. For each  
15 prescription, the prescribed daily number, the strength, the total number of prescribed units  
16 [tablets, capsules], and route of administration [oral, parenteral, topical, etc.] are registered.  
17 Specialist medication is only included if the general practitioner continues prescribing, for  
18 instance, if medication is chronic.  
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21 For each prescription of methylphenidate, we calculated the prescription length by dividing the  
22 total number of prescribed units by the prescribed daily number. For other drugs used in this study,  
23 such as antidepressants and antipsychotics, exposure was calculated in the same way.  
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## 26 Co-factors

27 As potential confounders of the association between methylphenidate and psychiatric events, we  
28 considered the following independent risk factors: sex, age, smoking, body mass index (BMI),  
29 alcohol abuse/intoxication [ICPC P15], medication abuse [P18], tobacco abuse [, drug abuse [P19],  
30 psychosis [P71-P73, P98], depression [P76], anxiety [P74], or neuroses in history [P78, P79],  
31 personality disorder [P80], other psychiatric disease [P99], and use of antidepressants (ATC code  
32 N06A), antipsychotics (N05A), anxiolytics (N05B), and sedatives (N05C). For the endpoint  
33 overall mortality, we considered independent risk factors, notably body mass index [BMI],  
34 smoking, diabetes mellitus, hypertension, hypercholesterolemia, and history of stroke, heart  
35 failure, or arrhythmia. Smoking was distinguished into 'current', 'past', and 'never'. Diabetes  
36 mellitus was defined as a diagnosis or problem code before the index date, if the patient had a  
37 prescription for a hypoglycemic agent [ATC code 'A10'], or if the patient had a fasting glucose  
38 level > 7.0 mmol/l. Hypertension was considered as present if any of the ICPC codes K85, K86,  
39 or K87 was given as a diagnosis or problem code before the index date, or if the patient used an  
40 antihypertensive before the index date. As there were often multiple measurements for each co-  
41 factor, the one which was closest to the event date was chosen.  
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## 47 Statistics

48 Comparison between baseline variables in methylphenidate users and non-users were expressed  
49 as proportion ratios with 95% confidence limits to show the magnitude and significance of each  
50 variable. We calculated hazard ratios with 95% CI in the cohort analysis in which users/non-users  
51 were followed for the occurrence of the above-mentioned psychiatric disease outcomes with a Cox  
52 proportional hazards model. In this model, methylphenidate was defined as a time-dependent risk  
53 factor and adjustment was performed for the co-factors listed above which were treated as  
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3 confounders if they changed the point estimate by 10 percent or more. Because the percentage of  
4 missing data was sometimes large, i.e. for smoking and BMI, we decided not to impute these  
5 values but rather to adjust with missing status as a separate dummy variable in a categorical set of  
6 values to investigate whether missing status was a confounder. Furthermore, we adjusted for the  
7 likelihood of being treated [adjustment for intention-to-treat]. Lastly, all 168 cases with a  
8 notification of suicide [attempt] were validated by reference to the medical patient records, as well  
9 as all 1,027 deaths.  
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## 12 Patient and Public involvement

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14 There was no public or patient involvement. Only completely anonymized general practice data were used.  
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## 17 18 19 RESULTS

### 20 21 *General characteristics*

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23 On average, the 8,905 starters on methylphenidate received 10 prescriptions with an average total  
24 duration of 370 days. The mean starting dose of the first prescription was 30 mg per day, while the  
25 mean dosage of the last prescription during the study period was 35 mg per day. Eighty-four  
26 percent of the prescribers of the first prescription was a general practitioner. Further general  
27 characteristics of the study population are given in Table 1. Fifty-four percent was male and 64  
28 percent was in the age category of 18-40 years. Methylphenidate users had a significantly higher  
29 prevalence of tobacco, alcohol, and other substance abuse, as well as of a history of psychiatric  
30 comorbidity.  
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### 33 34 *Incident psychiatric adverse events*

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36 There were significantly increased risks of incident organic psychosis [delirium], affective psychosis,  
37 anxiety, depression, burnout, other neuroses, personality disorder, and other psychotic and other  
38 psychiatric disorders in methylphenidate users. There was a significantly increased risk of suicide  
39 attempts in users of methylphenidate. Increased risks were observed in smokers and people with a  
40 history of a variety of psychiatric diseases in the medical history. Further adjustment for smoking,  
41 BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, and  
42 psychiatric events in history reduced the risk estimates in table 2. However, adjustment for the  
43 intervention/intention-to-treat abolished almost all statistically significant relative risks in table 2.  
44 This means that with the exception of overall mortality and suicide [attempts], all significantly  
45 increased risks in table 2 were confounded by the intention-to-treat itself.  
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49 All 168 cases with a notification of suicide [attempt] were validated by reference to the medical  
50 patient records. Out of these 168 cases, 117 were suicide attempts of which 16 successful while  
51 the remaining 51 cases were notification of suicidal ideation, or phantasies/tendencies. A further  
52 19 cases of successful suicide came from the validation of all 1,027 cases of death. Restricting the  
53 analyses to these 136 cases of whom 6 were excluded because of a history of suicidal  
54 ideation/attempts before the index date, yielded an unadjusted relative risk of suicide in  
55 methylphenidate users of 5.5 [95%CI: 3.5-8.6]. After additional adjustment for the intervention,  
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3 the relative risk went down to 2.0 [95%CI: 1.1-3.6] for current use of methylphenidate but  
4 remained statistically significant. In table 3A, these risks were stratified according to sex and age-  
5 groups. The majority of suicide [attempts] were in the age group from 18 through 40 years. The  
6 risk of suicide [attempts] was highest in women. As one can see from figure 2, the suicide [attempt]  
7 occurs especially in the early period of follow-up in users whereas it is spread over a longer period  
8 of follow-up in non-users.  
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### 11 *Overall mortality*

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13 Because the cause of death was not specifically coded in the GP database, we took overall mortality  
14 as an endpoint. Especially age, hypertension, diabetes mellitus, and decreased renal function were  
15 associated with an increased risk of death.  
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17 We performed a validation of all 1,027 cases of death to check the precise date of death, and to  
18 distinguish its causes – where possible - by going through the patient history. Thirty percent of all  
19 death occurred within 80 days after starting with methylphenidate. After restricting the analyses  
20 to cases in which the precise date of death could be verified [n=946], the unadjusted risk of all-  
21 cause mortality in users of methylphenidate was 7.5 [95%CI 6.3-8.9] but reduced to 1.3 [95%CI  
22 1.1-1.6] after full adjustment. Apart from suicide, there was a large and significant risk increase in  
23 those who died during methylphenidate in palliative care with a risk of 12.7 [95%CI 9.5-16.9]. As  
24 the pharmacologic effect of methylphenidate is immediate, we did not study duration-effect  
25 relationships. In extra analysis, we further adjusted all relative risks for dosage but this did not  
26 substantially change the risk estimates. Finally, we studied effect modification by sex- and age  
27 category [table 3B]. The risk of mortality in the intervention group was significantly increased in  
28 women only. Furthermore, the risk was significantly increased by 60% in the age category 61 to  
29 80 years of age. As one can see from figure 3, death occurred especially in the early period of  
30 follow-up in users whereas it is spread over a longer period of follow-up in non-users.  
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## 40 **DISCUSSION**

41 From this study, we can conclude that although there was a strongly increased risk of psychiatric  
42 events in users of methylphenidate, most part of it was explained by confounding by intervention  
43 ['intention-to-treat']. However, even after adjusting for the intervention, a significantly increased  
44 risk of suicide [attempts] after starting methylphenidate remained.  
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47 Especially the strong association with death in our study is striking. The risk increase of death was  
48 genuine but mainly explained by confounding by the indication palliative care because from  
49 validation of the medical records, it became clear that this risk increase was largely explained by  
50 starting methylphenidate in depressed or extremely tired patients in their latest phase of life.  
51 Because regular antidepressants take 6-8 weeks before they exert their therapeutic effects, they  
52 may be too late for treating depression in the last weeks of life and then psychostimulants may  
53 help. This is in line with British and Dutch guidelines [21].  
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3 Similar to Dutch reports, data from the British Yellow Card scheme showed that, of 1,335 adverse  
4 drug reaction reports regarding methylphenidate, 663 adverse reactions were psychiatric disorders,  
5 making these disorders the most frequently reported class of adverse drug reactions of  
6 methylphenidate [Vigilance and Intelligence Research Group; [http://www.mhra.gov.uk/drug-  
7 analysis-prints/drug-analysis-prints-a-z/index.htm](http://www.mhra.gov.uk/drug-analysis-prints/drug-analysis-prints-a-z/index.htm)]. Among these reports, 105 (15.8%) patients  
8 reported hallucinations, psychosis or psychotic disorders. Moreover, in an FDA review [22] of  
9 data from 49 randomised controlled clinical trials investigating the effects of central stimulant  
10 medication in children, 11 adverse events related to psychosis or mania were observed during 743  
11 person-years of follow-up in 5,717 individuals, versus no events reported with placebo, giving a  
12 number needed to harm of 526 patients. Given these reports of treatment-emergent psychotic  
13 events with central stimulant medication, clinicians have been concerned that methylphenidate and  
14 other psychostimulants might provoke psychosis [10, 13]. In literature, use of stimulant ADHD  
15 medication is considered as relatively contraindicated in patients with a history of psychosis [14].  
16 However, clinicians face a therapeutic dilemma without clear evidence to guide them when  
17 balancing the potential risk of psychotic events with the benefits of stimulants that are the first-  
18 line treatment for ADHD in adolescent and adult patients [23]. Some observational studies [14,  
19 24] that reported an increased risk of psychotic events associated with methylphenidate might be  
20 affected by confounding by indication; that is, patients who receive stimulant medication for  
21 ADHD are inherently different from those who do not and could have a greater risk of psychotic  
22 events independently of stimulant prescription. This type of confounding also played a role in our  
23 IPCI-study but by adjusting for independent risk factors and for the intervention we were able to  
24 deal with it. In a study in 2016 that tried to adjust for confounding by indication, Man and  
25 colleagues [25] used a within-individual case series design in a population of children and  
26 adolescents, and did not find an increased risk of psychotic events during methylphenidate  
27 treatment. In a direct comparison in the USA, methylphenidate was associated with a significantly  
28 lower risk of psychosis than amphetamine [26].

### 36 *Strengths and limitations*

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38 One of the major strengths is the population-based design of this study, as in the Netherlands  
39 everybody is designated to only one general practitioner. Therefore, selection bias is highly  
40 unlikely. As the information on diseases is prospectively gathered and prescriptions are  
41 automatically and completely stored in the computer of the general practice, information bias is  
42 also highly unlikely. A limitation may be the fact that not every patient fills his prescription at  
43 the pharmacy. According to an earlier study, some 10% of prescriptions from the general  
44 practitioner is not filled, and even if filled, patients may decide not to use their medicines [27].  
45 Also, we might have missed the most severe cases of ADHD/ADD, initially treated by the  
46 psychiatrist. However, in the majority of patients the continuation of methylphenidate treatment goes  
47 through the GP. Therefore, we think that we will have enrolled also most of the severe cases,  
48 albeit somewhat later in their treatment course. And even if we miss some of the most severe  
49 cases, it is likely that this has led to conservative instead of inflated estimates.

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55 However, chronic medication requires regular prescriptions and if patients get repeated  
56 prescriptions, it is more likely that these are really filled. But which product is ultimately filled,  
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3 remains unknown in a GP database and this means that we could not adjust for regular or slow-  
4 release methylphenidate. Also, medication obtained via hospitals or outpatient clinics is missing,  
5 as well as illegal drug use. Usually, these types of exposure misclassification lead to an  
6 underestimation of the true risk because the group of non-exposed actually includes exposed  
7 individuals [28].  
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10 We adjusted for confounding by multivariable adjustment of the risk estimates by all known risk  
11 factors. Unfortunately, for some confounders there were missing data [for instance, smoking and  
12 BMI]. Because the percentage of missing data was sometimes large, we decided not to impute  
13 these values but rather to adjust with missing status as a separate dummy variable in a categorical  
14 set of values. In this way, we were able to investigate whether the missing status acted as a  
15 confounder but there was almost no confounding by missing status. An important potential  
16 confounder in any observation study in which the consequences of an intervention are studied, is  
17 the indication. Confounding by indication played a role in palliative care in which methylphenidate  
18 is used 'off label' as a psychostimulant. Also, as ADHD/ADD in childhood is a risk factor for a  
19 diagnosis of psychosis in adult life [6-8], confounding by indication will inevitably have played a  
20 role in the increased risk of psychosis which was found in this study although it disappeared after  
21 adjustment for the intervention. Although this might also partly explain the increased risk of  
22 suicide, an independent risk for methylphenidate remained and an adverse role of methylphenidate  
23 seems plausible because of its stimulant properties in a population of patients receiving  
24 methylphenidate despite psychiatric contraindications.  
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29 In conclusion, in this large population-based study with data from general practitioners  
30 encompassing almost 100,000 people, methylphenidate was associated with a significantly  
31 increased risk of mortality, partly explained by 'off label' use as a psychostimulant in palliative  
32 care. There was a significantly increased risk of psychosis, and depression but this was probably  
33 confounded by intervention. However, there was also an increased risk of suicide in current users  
34 of methylphenidate, even after adjustment for the intervention. All in all, it seems that a cautious  
35 approach to prescribing methylphenidate in adults is warranted, especially in those with a history  
36 of suicidal ideation.  
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3 Contributorship statement  
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5 Bruno Stricker and Kiki Cheung designed the study. Data gathering was performed by Bruno  
6 Stricker and Katia Verhamme. All contributed to analysis and writing of the manuscript.  
7

8 Funding  
9

10 This study was funded by the Health and Youth Care Inspectorate of the Netherlands.  
11

12 Competing interest declaration  
13

14 Bruno Stricker and Kiki Cheung have no competing interest regarding this paper. Katia  
15 Verhamme works for a research department who received/receives unconditional research grants  
16 from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, GSK, Chiesi, Amgen, UCB, Astra  
17 Zeneca and J&J, none of which are related to the content of this manuscript.  
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20 Data sharing agreement  
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22 No additional data available.  
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## LITERATURE

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-

Table 1 Characteristics of the study population [\*]

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Sex			
Men	4,839 [54.3%]	47,907 [54.3%]	1.0 [reference]
Women	4,066 [45.7%]	40,386 [45.7%]	1.0 [0.9-1.1]
Age	36.5 years	36.3 years	
18-40 yr	5,737 [64.4%]	56,888 [64.4%]	1.0 [reference]
41-60 yr	2,584 [29.0%]	25,847 [29.2%]	1.0 [0.9-1.1]
61-80 yr	476 [5.3%]	4,718 [5.3%]	1.0 [0.9-1.1]
> 80 yr	108 [1.3%]	840 [0.01%]	<b>1.3 [1.1-1.6]</b>
Follow-up [days]	1943 days	1944 days	
BMI [*]			
<25	864 [9.7%]	5617 [6.4%]	1.0 [reference]
25-30	717 [8.1%]	5,746 [6.5%]	<b>0.8 [0.7-0.9]</b>
>30	629 [7.1%]	4,702 [5.3%]	<b>0.9 [0.8-1.0]</b>
Smoking [*]			
Never	2,111 [23.7%]	21,629 [24.5%]	1.0 [reference]
Past	723 [8.1%]	4634 [5.2%]	<b>1.6 [1.5-1.8]</b>
Current	2,292 [25.7%]	13,111 [14.8%]	<b>1.8 [1.7-1.9]</b>
Alcohol abuse	352 [3.9%]	878 [1.0%]	<b>4.1 [3.6-4.7]</b>
Acute alcohol intoxication	105 [1.2%]	398 [0.5%]	<b>2.6 [2.1-3.3]</b>
Tobacco abuse	810 [9.1%]	3,930 [4.5%]	<b>2.2 [2.0-2.3]</b>
Medicines abuse	87 [0.9%]	230 [0.3%]	<b>3.8 [3.0-4.8]</b>
Drug abuse	525 [5.9%]	859 [1.0%]	<b>6.4 [5.7-7.1]</b>
History of:			
Organic psychosis [delier]	37 [0.4%]	157 [0.2%]	<b>2.3 [1.6-3.3]</b>
Schizophrenia	36 [0.4%]	282 [0.3%]	1.3 [0.9-1.8]
Affective psychosis	82 [0.9%]	245 [0.3%]	<b>3.3 [2.6-4.3]</b>
Anxiety	922 [10.4%]	3602 [4.1%]	<b>2.8 [2.6-3.0]</b>
Hypochondria/hysteria	55 [0.6%]	392 [0.4%]	<b>1.4 [1.1-1.9]</b>
Depression	1,772 [19.9%]	5252 [5.9%]	<b>4.3 [4.0-4.6]</b>
Suicide [attempt]	161 [1.8%]	410 [0.5%]	<b>4.0 [3.3-4.8]</b>
Burnout/overstrain	886 [9.9%]	3962 [4.5%]	<b>2.6 [2.4-2.8]</b>
Other neuroses	169 [1.9%]	674 [0.7%]	<b>2.5 [2.1-3.0]</b>
Personality disorder	479 [5.4%]	822 [0.9%]	<b>6.3 [5.6-7.0]</b>
Other non-specified psychotic disorder	80 [0.9%]	372 [0.4%]	<b>2.2 [1.7-2.8]</b>
Other psychiatric disorder	541 [6.1%]	1100 [1.2%]	<b>5.3 [4.7-5.9]</b>

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Total psychiatric	3729 [41.9%]	13549 [115.3%]	<b>4.5 [4.3-4.7]</b>
Previous or current use of:			
Antipsychotics	835 [9.4%]	1,884 [2.1%]	<b>4.8 [4.4-5.2]</b>
Antidepressants	3,037 [34.1%]	10,213 [11.6%]	<b>4.0 [3.8-4.2]</b>
Anxiolytics	3,338 [37.5%]	16,390 [18.6%]	<b>2.6 [2.5-2.8]</b>
Sedatives	2,498 [28.1%]	10,201 [11.6%]	<b>3.0 [2.8-3.1]</b>

[\*] Values were missing for BMI [n=78,923], smoking [n=52,698]

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Table 2 Number of cases and referents per psychiatric disease code/overall mortality occurring during follow-up and the risk [hazard ratio] to develop such a disease in users of methylphenidate in comparison to non-users

Outcome	Case	Referents	HR [95%-CI] [*]	HR [95%-CI] [**]
Organic psychosis [delir]	154	96,850	<b>8.3 [5.2-13.0]</b>	1.7 [0.9-3.0]
Schizophrenia	50	96,830	1.6 [0.4-6.7]	0.9 [0.2-4.3]
Affective psychosis	64	96,807	3.5 [1.4-6.9]	1.2 [0.4-3.6]
Anxiety	1374	91,300	1.8 [1.4-2.4]	0.8 [0.6-1.1]
Hypochondria/hysteria	109	96,642	1.5 [0.5-4.0]	0.8 [0.3-2.6]
Depression	1468	88,706	<b>2.7 [2.1-3.3]</b>	1.0 [0.8-1.3]
Suicide/suicide attempt	129	96,498	<b>5.5 [3.5-8.6]</b>	<b>2.0 [1.1-3.6]</b>
Burnout/overstrain	1583	90,767	1.4 [1.0-1.8]	1.0 [0.7-1.4]
Other neuroses	183	96,172	2.0 [1.0-3.9]	0.7 [0.4-1.6]
Personality disorder	412	95,485	6.0 [4.5-7.9]	1.2 [0.8-1.6]
Other non-specified psychotic disorder	162	96,584	3.2 [1.8-5.7]	0.9 [0.5-1.8]
Other psychiatric disorder	538	95,019	4.9 [3.8-6.5]	1.4 [0.9-1.8]
Any psychosis	347	95,727	4.8 [3.4-6.8]	1.3 [0.9-2.0]
Death [***]	946	96,252	<b>7.5 [6.3-8.9]</b>	<b>1.3 [1.1-1.6]</b>

[\*] All hazard ratios [HR] are adjusted for sex, and age by matching

[\*\*] All HR are adjusted for sex, age, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and for 'intention-to-treat'

[\*\*\*] Additionally are adjusted for hypertension, diabetes mellitus, hypercholesterolemia, and decreased renal function.



Table 3A; Age and sex specific risks of suicide, suicidal attempts/ideation during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	64/44,043	3.9 [1.5-10.2]
Men	65/52,294	1.1 [0.4-2.6]
18-40 yrs. of age	84/62,196	2.4 [1.2-4.9]
41-60 yrs. of age	38/28,108	1.3 [0.4-4.9]
61-80 yrs. of age	4/4,543	1.6 [0.0-∞]
>80 yrs. of age	3/836	- [*]

All hazard ratios [HR] are adjusted for sex, age, intervention, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and ‘intention-to-treat’

[\*] No cases exposed to methylphenidate

Table 3B; Age and sex-specific risks of all-cause mortality during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	375/44,077	1.7 [1.2-2.5]
Men	571/52,154	1.1 [0.8-1.5]
18-40 yrs. of age	67/62,478	1.2 [0.4-3.5]
41-60 yrs. of age	240/28,191	1.1 [0.7-1.8]
61-80 yrs. of age	412/4,781	1.6 [1.2-2.2]
>80 yrs. of age	227/721	1.2 [0.7-2.0]

[\*] All hazard ratios [HR] are adjusted for sex, age, smoking, hypertension, diabetes mellitus, BMI, hypercholesterolemia, decreased renal function, and ‘intention-to-treat’

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## Figure legends

### Figure 1

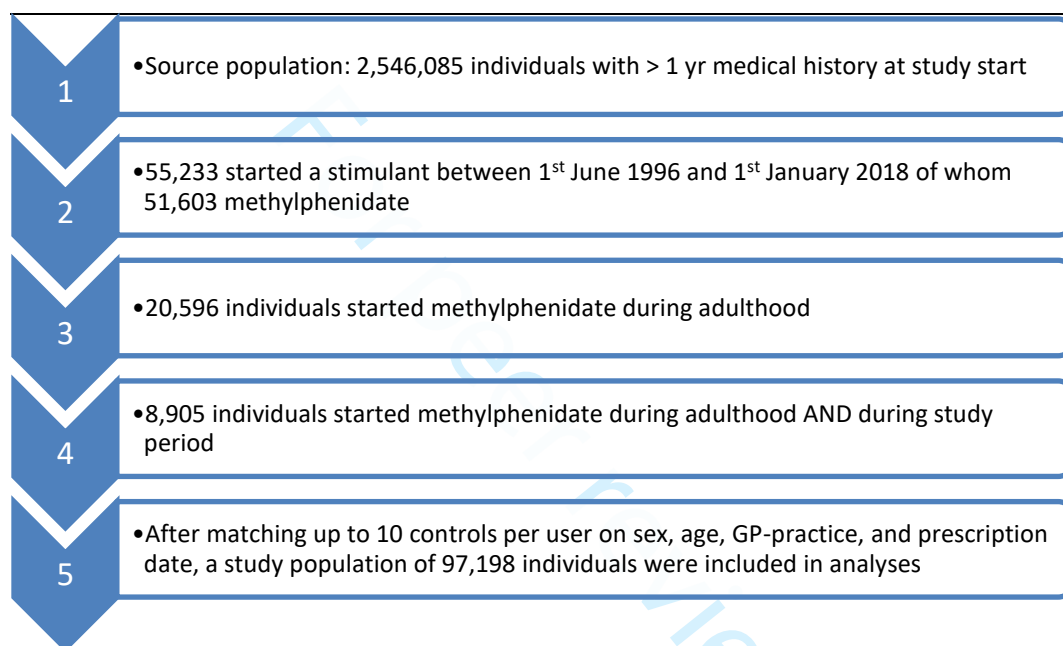
Flow scheme from source population to study population

### Figure 2

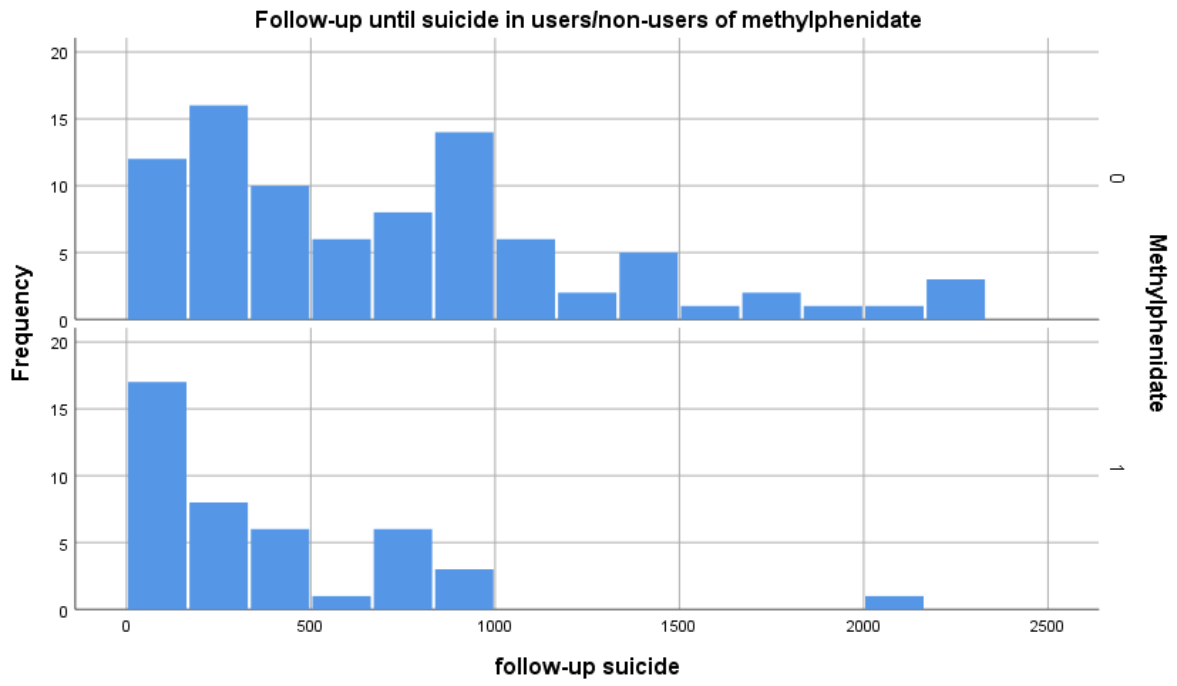
Time delay in follow-up days between 1st intake of methylphenidate and suicide [attempt]. On the y-axis, the number of cases of suicide [attempt] are given while the x-axis represents the number of days of follow-up. In non-users with the same reference date as users [upper part of figure 2], this delay is spread over several years whereas it is focused in the early weeks of intake in users [lower part of figure 2].

### Figure 3

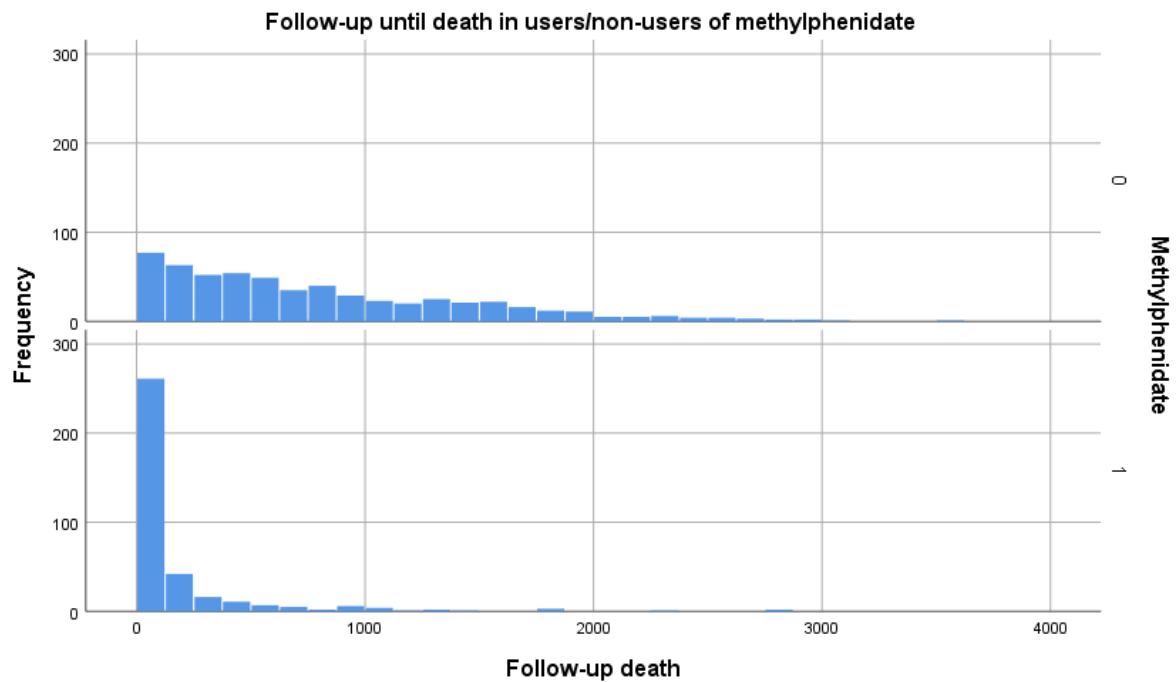
Time delay in follow-up days between 1st intake of methylphenidate and death. On the y-axis, the number of cases of death are given while the x-axis represents the number of days of follow-up. In non-users with the same reference date as users [upper part of figure 3], this delay is spread over several years whereas it is focused in the early weeks of intake in users [lower part of figure 3].



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**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.  RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.  RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P. 2
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			P. 3
Objectives	3	State specific objectives, including any prespecified hypotheses			P. 3
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper			P. 3/4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			A. 4

Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>		<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	<p>4/5</p> <p>N/A</p> <p>N/A</p>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	4/5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			4/5

1 2 3 4 5 6 7 8 9	Bias	9	Describe any efforts to address potential sources of bias			P. 2/9
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Study size	10	Explain how the study size was arrived at			P. 4
33 34 35 36 37 38 39 40 41 42 43 44 45 46	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			P. 5-7
	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			P. 5-7
	Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	P. 4



				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	W/A
<b>Results</b>					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	P. 4
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)			P. 14
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure			A. 6/7

		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			P. 6/7
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses			P. 7
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives			P. 7/8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	P. 8
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			P. 9

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		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			p. 9
<b>Other Information</b>					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			p. 10
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# BMJ Open

## A COHORT STUDY IN A GENERAL PRACTICE DATABASE ON MORTALITY IN ADULTS ON METHYLPHENIDATE

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057303.R2
Article Type:	Original research
Date Submitted by the Author:	12-May-2022
Complete List of Authors:	Stricker, Bruno; Erasmus Medical Center, Epidemiology Cheung, Kiki; Erasmus Medical Center, Epidemiology Verhamme, Katia; Erasmus Medical Center, Medical Informatics
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Suicide & self-harm < PSYCHIATRY, Adverse events < THERAPEUTICS, EPIDEMIOLOGY

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12 ***A COHORT STUDY IN A GENERAL PRACTICE DATABASE ON MORTALITY IN***  
13 ***ADULTS ON METHYLPHENIDATE***  
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44 word count [body of text]: 3384  
45

46 key words: methylphenidate, psychostimulants, pharmacoepidemiology, pharmacovigilance,  
47 psychiatric adverse events, mortality, suicide  
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## Abstract

### Objectives

Methylphenidate is a 'prescription only' drug against attention disorders which is increasingly used by adults. We investigated whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt, and overall mortality.

### Design

A population-based matched cohort design.

### Setting

The Integrated Primary Care Information (IPCI) system, a general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants.

### Participants

During the study period between 1<sup>st</sup> June 1996 and 1<sup>st</sup> January 2018, 8905 adults started methylphenidate and were matched to 10 non-users on sex, age, GP practice, and prescription date. The total study population consisted of 97,198 participants.

### Main outcome measures

Serious psychiatric events such as depression and suicide attempts, and overall mortality.

### Analyses

Risks of development of each event during use of methylphenidate were expressed as hazard ratios (HR) with 95% confidence limits (CI), adjusted for relevant confounders with methylphenidate as a time-dependent determinant. Additional adjustment was performed for the intervention ['intention-to-treat'].

### Results

Although during follow-up the unadjusted risks of depression, and suicide attempt were strongly increased in users, depression and psychosis became non-significant after adjustment for alcohol- and substance abuse and psychiatric disease in the medical history and after adjustment for 'intention-to-treat'. However, the risk of suicide attempts remained significantly increased after full adjustment [HR 2.0; 95%CI 1.1-3.6], and was highest in women and in participants within the age-group of 18 to 40 years. The unadjusted risk of overall mortality was strongly increased but this lowered to a significant 30% risk increase [HR 1.3; 95%CI 1.1-1.6] after full adjustment.

### Conclusion

There is an increased risk of suicide attempts in adults up to 40 years of age after starting methylphenidate and this risk should be carefully considered before prescribing to this group.

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3 Strengths and limitations  
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- 5 • It consists of a prospective population-based controlled cohort study with limited chance  
6 of selection- or information bias
- 7 • The use of complete GP records in a healthcare system with a central role of the GP is a  
8 strength
- 9 • Limitations are that there are prescription but not dispensing data and that there are no in-  
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## INTRODUCTION

Methylphenidate is a psychostimulant which is pharmacologically related to amphetamines and which was already registered more than 50 years ago for the treatment of children with a hyperkinetic syndrome, later named 'attention deficit hyperactivity disorder' (ADHD). Methylphenidate is increasingly used in children in many countries [1-3]. Attention deficit hyperactivity disorder (ADHD) is defined as a mental health disability, which usually begins before 12 years of age, and is characterized by three main symptoms: inattention, impulsivity, and hyperactivity [without hyperactivity, the term 'attention deficit disorder' (ADD) may be used]. The intensity of the symptoms tends to decrease with ageing, but in 40% to 50% of people diagnosed with ADHD in childhood, symptoms may persist during adolescence and adulthood [4,5]. Therefore, methylphenidate is also increasingly used in adults [4], which was considered as an 'off-label' group for several years. In patients with ADD or ADHD methylphenidate improves the balance between concentration and distraction and decrease hyperactivity [6]. Over the past years, these 'prescription only' drugs were increasingly used 'off label' in adults for a variety of indications. In 2018, methylphenidate was registered in the Netherlands for use in adults. Until April 2017, approximately 1,200 reports of mostly serious adverse events attributed to methylphenidate were notified to the national Dutch Pharmacovigilance Center, of which 542 (45.2%) in adults [7]. Psychiatric adverse events were frequent among these reported events but also cardiovascular events were reported.

Longitudinal studies have shown that ADHD in childhood is itself a risk factor for a diagnosis of psychosis in adult life [8-10]. Research indicates that these disorders share common genetic [11] and environmental aetiologies [8, 12]. A potential mediator of the association between ADHD and psychosis is the prescription of central stimulants for ADHD, which causes considerable concern for several clinicians [13, 15]. Central stimulants act as indirect dopamine agonists and are presumed to amplify neuronal signaling by prompting a marked increase in the extracellular concentration of neurotransmitters in the prefrontal cortex of the brain [15]. Methylphenidate blocks the transporters of dopamine and noradrenaline, inhibits their presynaptic reuptake and has stimulant properties [6]. Increased concentrations of synaptic dopamine have also been implicated in the generation of psychotic symptoms [16]. Hence, the pharmacological mechanism of central stimulant medication can be viewed by clinicians as having the potential to induce psychotic symptoms and disorders [10, 17].

Therefore, the current study was performed to investigate whether the use of methylphenidate was associated with an increased risk of psychiatric adverse events such as depression, psychosis, or suicide attempts in adults. We also investigated whether there was an increased risk of overall mortality in methylphenidate users.

## METHODS

## Setting

The source population consisted of all patients who were registered with one of the general practitioners (GPs) who contribute information to the Integrated Primary Care Information (IPCI) database, which was established in 1992 [18]. IPCI is a longitudinal observational database with data from computer-based patient records retrieved from a selected group of GPs throughout the Netherlands, who voluntarily supply data to the database. In the Netherlands, the GP plays a central role in the health care system and acts as a gatekeeper by referring patients to other medical disciplines for out- or inpatient care and as a central receiver of information from secondary or tertiary care. Data from the GP computer system are downloaded on a monthly basis and sent to the IPCI gatekeeper who anonymizes all information before further access is provided to the researchers. It is a dynamic cohort because over time, people may enter the population as new patients, or leave because of removal or death. Details of the database have been described elsewhere [18, 19]. Currently, more than 600 GPs are providing data to the database which has expanded to now more than 2,500,000 patients. The database is representative of the Dutch population regarding age and sex. The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological studies. For the use of IPCI for this study, permission has been granted by the IPCI review board [RvT 7/2017].

## Source population

The source population consisted of 2,546,082 individuals with at least one year of medical history within the IPCI database with an average follow-up time of slightly more than four years. Start of the follow-up period was 1<sup>st</sup> June 1996 or 1 year after enrolment with the GP practice when starting after 1<sup>st</sup> June 1996 [most practices], and the end of follow-up was death, removal, or end of the study on 1<sup>st</sup> January 2018, whichever came first.

## Design and Study population

For this matched cohort design, we selected only starters with methylphenidate of 18 years or older. Out of 51,603 starters ['first ever use'] with methylphenidate, 20,596 [40%] started during adulthood of whom 8,905 during the study period [11,691 started as adult but before their practice participated in IPCI]. Because methylphenidate was mainly prescribed to relatively young male adults, we sampled up to 10 non-users without history of methylphenidate for each of these 8,905 starters whom were matched on sex, age [less than 1-year difference], and GP-practice. This resulted in a total study population of 97,198 subjects [see flow diagram Figure 1]. For each matched set of 1 user and [mostly] 10 nonusers during the study period, follow-up started at the day of first prescription of methylphenidate and this date was also allocated to the 10 non-users. All participants were eligible for GP healthcare during the study period.

## Outcomes

All registered diagnoses and problem codes during the study period were gathered, as coded according to the International Classification of Primary Care [ICPC] coding thesaurus [20]. Apart from overall mortality, the following psychiatric outcomes were studied: psychosis [ICPC P71-

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3 P73, P98]; anxiety [P74]; hypochondria [P75]; depression [P76]; suicide/suicidal attempt [P77];  
4 neurasthenia/burnout [P78, P79]; personality disorder [P80]; and other psychiatric illness [P99].  
5 For each diagnosis, those with a prevalent code before the index date were excluded from the  
6 follow-up analyses in order to study the association between methylphenidate and incident  
7 psychiatric outcomes. All mortality is registered in the IPCI database. For every deceased  
8 individual, month and year are registered. For the precise day of the month, the original medical  
9 record was studied.  
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## 12 Medication exposure

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14 All medications prescribed by the general practitioners are automatically stored. For each  
15 prescription, the prescribed daily number, the strength, the total number of prescribed units  
16 [tablets, capsules], and route of administration [oral, parenteral, topical, etc.] are registered.  
17 Specialist medication is only included if the general practitioner continues prescribing, for  
18 instance, if medication is chronic.  
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21 For each prescription of methylphenidate, we calculated the prescription length by dividing the  
22 total number of prescribed units by the prescribed daily number. For other drugs used in this study,  
23 such as antidepressants and antipsychotics, exposure was calculated in the same way.  
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## 26 Co-factors

27 As potential confounders of the association between methylphenidate and psychiatric events, we  
28 considered the following independent risk factors: sex, age, smoking, body mass index (BMI),  
29 alcohol abuse/intoxication [ICPC P15], medication abuse [P18], tobacco abuse [, drug abuse [P19],  
30 psychosis [P71-P73, P98], depression [P76], anxiety [P74], or neuroses in history [P78, P79],  
31 personality disorder [P80], other psychiatric disease [P99], and use of antidepressants (ATC code  
32 N06A), antipsychotics (N05A), anxiolytics (N05B), and sedatives (N05C). For the endpoint  
33 overall mortality, we considered independent risk factors, notably body mass index [BMI],  
34 smoking, diabetes mellitus, hypertension, hypercholesterolemia, and history of stroke, heart  
35 failure, or arrhythmia. Smoking was distinguished into 'current', 'past', and 'never'. Diabetes  
36 mellitus was defined as a diagnosis or problem code before the index date, if the patient had a  
37 prescription for a hypoglycemic agent [ATC code 'A10'], or if the patient had a fasting glucose  
38 level > 7.0 mmol/l. Hypertension was considered as present if any of the ICPC codes K85, K86,  
39 or K87 was given as a diagnosis or problem code before the index date, or if the patient used an  
40 antihypertensive before the index date. As there were often multiple measurements for each co-  
41 factor, the one which was closest to the event date was chosen.  
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## 47 Statistics

48 Comparison between baseline variables in methylphenidate users and non-users were expressed  
49 as proportion ratios with 95% confidence limits to show the magnitude and significance of each  
50 variable. We calculated hazard ratios with 95% CI in the cohort analysis in which users/non-users  
51 were followed for the occurrence of the above-mentioned psychiatric disease outcomes with a Cox  
52 proportional hazards model. In this model, methylphenidate was defined as a time-dependent risk  
53 factor and adjustment was performed for the co-factors listed above which were treated as  
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3 confounders if they changed the point estimate by 10 percent or more. Because the percentage of  
4 missing data was sometimes large, i.e. for smoking and BMI, we decided not to impute these  
5 values but rather to adjust with missing status as a separate dummy variable in a categorical set of  
6 values to investigate whether missing status was a confounder. Furthermore, we adjusted for the  
7 likelihood of being treated [adjustment for intention-to-treat]. Lastly, all 168 cases with a  
8 notification of suicide [attempt] were validated by reference to the medical patient records, as well  
9 as all 1,027 deaths.  
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## 12 Patient and Public involvement

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14 There was no public or patient involvement. Only completely anonymized general practice data were used.  
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## 17 18 19 RESULTS

### 20 21 *General characteristics*

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23 On average, the 8,905 starters on methylphenidate received 10 prescriptions with an average total  
24 duration of 370 days. The mean starting dose of the first prescription was 30 mg per day, while the  
25 mean dosage of the last prescription during the study period was 35 mg per day. Eighty-four  
26 percent of the prescribers of the first prescription was a general practitioner. Further general  
27 characteristics of the study population are given in Table 1. Fifty-four percent was male and 64  
28 percent was in the age category of 18-40 years. Methylphenidate users had a significantly higher  
29 prevalence of tobacco, alcohol, and other substance abuse, as well as of a history of psychiatric  
30 comorbidity.  
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### 33 34 *Incident psychiatric adverse events*

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36 There were significantly increased risks of incident organic psychosis [delirium], affective psychosis,  
37 anxiety, depression, burnout, other neuroses, personality disorder, and other psychotic and other  
38 psychiatric disorders in methylphenidate users. There was a significantly increased risk of suicide  
39 attempts in users of methylphenidate. Increased risks were observed in smokers and people with a  
40 history of a variety of psychiatric diseases in the medical history. Further adjustment for smoking,  
41 BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, and  
42 psychiatric events in history reduced the risk estimates in table 2. However, adjustment for the  
43 intervention/intention-to-treat abolished almost all statistically significant relative risks in table 2.  
44 This means that with the exception of overall mortality and suicide [attempts], all significantly  
45 increased risks in table 2 were confounded by the intention-to-treat itself.  
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49 All 168 cases with a notification of suicide [attempt] were validated by reference to the medical  
50 patient records. Out of these 168 cases, 117 were suicide attempts of which 16 successful while  
51 the remaining 51 cases were notification of suicidal ideation, or phantasies/tendencies. A further  
52 19 cases of successful suicide came from the validation of all 1,027 cases of death. Restricting the  
53 analyses to these 136 cases of whom 6 were excluded because of a history of suicidal  
54 ideation/attempts before the index date, yielded an unadjusted relative risk of suicide in  
55 methylphenidate users of 5.5 [95%CI: 3.5-8.6]. After additional adjustment for the intervention,  
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3 the relative risk went down to 2.0 [95%CI: 1.1-3.6] for current use of methylphenidate but  
4 remained statistically significant. In table 3A, these risks were stratified according to sex and age-  
5 groups. The majority of suicide [attempts] were in the age group from 18 through 40 years. The  
6 risk of suicide [attempts] was highest in women. As one can see from figure 2, the suicide [attempt]  
7 occurs especially in the early period of follow-up in users whereas it is spread over a longer period  
8 of follow-up in non-users.  
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### 11 *Overall mortality*

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13 Because the cause of death was not specifically coded in the GP database, we took overall mortality  
14 as an endpoint. Especially age, hypertension, diabetes mellitus, and decreased renal function were  
15 associated with an increased risk of death.  
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17 We performed a validation of all 1,027 cases of death to check the precise date of death, and to  
18 distinguish its causes – where possible - by going through the patient history. Thirty percent of all  
19 death occurred within 80 days after starting with methylphenidate. After restricting the analyses  
20 to cases in which the precise date of death could be verified [n=946], the unadjusted risk of all-  
21 cause mortality in users of methylphenidate was 7.5 [95%CI 6.3-8.9] but reduced to 1.3 [95%CI  
22 1.1-1.6] after full adjustment. Apart from suicide, there was a large and significant risk increase in  
23 those who died during methylphenidate in palliative care with a risk of 12.7 [95%CI 9.5-16.9]. As  
24 the pharmacologic effect of methylphenidate is immediate, we did not study duration-effect  
25 relationships. In extra analysis, we further adjusted all relative risks for dosage but this did not  
26 substantially change the risk estimates. Finally, we studied effect modification by sex- and age  
27 category [table 3B]. The risk of mortality in the intervention group was significantly increased in  
28 women only. Furthermore, the risk was significantly increased by 60% in the age category 61 to  
29 80 years of age. As one can see from figure 3, death occurred especially in the early period of  
30 follow-up in users whereas it is spread over a longer period of follow-up in non-users.  
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## 40 **DISCUSSION**

41 From this study, we can conclude that although there was a strongly increased risk of psychiatric  
42 events in users of methylphenidate, most part of it was explained by confounding by intervention  
43 ['intention-to-treat']. However, even after adjusting for the intervention, a significantly increased  
44 risk of suicide [attempts] after starting methylphenidate remained.  
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47 Especially the strong association with death in our study is striking. The risk increase of death was  
48 genuine but mainly explained by confounding by the indication palliative care because from  
49 validation of the medical records, it became clear that this risk increase was largely explained by  
50 starting methylphenidate in depressed or extremely tired patients in their latest phase of life.  
51 Because regular antidepressants take 6-8 weeks before they exert their therapeutic effects, they  
52 may be too late for treating depression in the last weeks of life and then psychostimulants may  
53 help. This is in line with British and Dutch guidelines [21].  
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3 Similar to Dutch reports, data from the British Yellow Card scheme showed that, of 1,335 adverse  
4 drug reaction reports regarding methylphenidate, 663 adverse reactions were psychiatric disorders,  
5 making these disorders the most frequently reported class of adverse drug reactions of  
6 methylphenidate [Vigilance and Intelligence Research Group; [http://www.mhra.gov.uk/drug-  
7 analysis-prints/drug-analysis-prints-a-z/index.htm](http://www.mhra.gov.uk/drug-analysis-prints/drug-analysis-prints-a-z/index.htm)]. Among these reports, 105 (15.8%) patients  
8 reported hallucinations, psychosis or psychotic disorders. Moreover, in an FDA review [22] of  
9 data from 49 randomised controlled clinical trials investigating the effects of central stimulant  
10 medication in children, 11 adverse events related to psychosis or mania were observed during 743  
11 person-years of follow-up in 5,717 individuals, versus no events reported with placebo, giving a  
12 number needed to harm of 526 patients. Given these reports of treatment-emergent psychotic  
13 events with central stimulant medication, clinicians have been concerned that methylphenidate and  
14 other psychostimulants might provoke psychosis [10, 13]. In literature, use of stimulant ADHD  
15 medication is considered as relatively contraindicated in patients with a history of psychosis [14].  
16 However, clinicians face a therapeutic dilemma without clear evidence to guide them when  
17 balancing the potential risk of psychotic events with the benefits of stimulants that are the first-  
18 line treatment for ADHD in adolescent and adult patients [23]. Some observational studies [14,  
19 24] that reported an increased risk of psychotic events associated with methylphenidate might be  
20 affected by confounding by indication; that is, patients who receive stimulant medication for  
21 ADHD are inherently different from those who do not and could have a greater risk of psychotic  
22 events independently of stimulant prescription. This type of confounding also played a role in our  
23 IPCI-study but by adjusting for independent risk factors and for the intervention we were able to  
24 deal with it. In a study in 2016 that tried to adjust for confounding by indication, Man and  
25 colleagues [25] used a within-individual case series design in a population of children and  
26 adolescents, and did not find an increased risk of psychotic events during methylphenidate  
27 treatment. In a direct comparison in the USA, methylphenidate was associated with a significantly  
28 lower risk of psychosis than amphetamine [26].

### 36 *Strengths and limitations*

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38 One of the major strengths is the population-based design of this study, as in the Netherlands  
39 everybody is designated to only one general practitioner. Therefore, selection bias is highly  
40 unlikely. As the information on diseases is prospectively gathered and prescriptions are  
41 automatically and completely stored in the computer of the general practice, information bias is  
42 also highly unlikely. A limitation may be the fact that not every patient fills his prescription at  
43 the pharmacy. According to an earlier study, some 10% of prescriptions from the general  
44 practitioner is not filled, and even if filled, patients may decide not to use their medicines [27].  
45 Also, we might have missed the most severe cases of ADHD/ADD, initially treated by the  
46 psychiatrist. However, in the majority of patients the continuation of methylphenidate treatment  
47 goes through the GP. Therefore, we think that we will have enrolled also most of the severe  
48 cases, albeit somewhat later in their treatment course. And even if we miss some of the most  
49 severe cases, it is likely that this has led to conservative instead of inflated estimates.  
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3 However, chronic medication requires regular prescriptions and if patients get repeated  
4 prescriptions, it is more likely that these are really filled. But which product is ultimately filled,  
5 remains unknown in a GP database and this means that we could not adjust for regular or slow-  
6 release methylphenidate. Also, medication obtained via hospitals or outpatient clinics is missing,  
7 as well as illegal drug use. Usually, these types of exposure misclassification lead to an  
8 underestimation of the true risk because the group of non-exposed actually includes exposed  
9 individuals [28]. Furthermore, although there is a specific guideline for GPs on the diagnosis and  
10 treatment of ADHD/ADD, it is some that there is some misclassification of the diagnosis by  
11 GPs.  
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15 We adjusted for confounding by multivariable adjustment of the risk estimates by all known risk  
16 factors. Unfortunately, for some confounders there were missing data [for instance, smoking and  
17 BMI]. Because the percentage of missing data was sometimes large, we decided not to impute  
18 these values but rather to adjust with missing status as a separate dummy variable in a categorical  
19 set of values. In this way, we were able to investigate whether the missing status acted as a  
20 confounder but there was almost no confounding by missing status. An important potential  
21 confounder in any observation study in which the consequences of an intervention are studied, is  
22 the indication. Confounding by indication played a role in palliative care in which methylphenidate  
23 is used 'off label' as a psychostimulant. Also, as ADHD/ADD in childhood is a risk factor for a  
24 diagnosis of psychosis in adult life [6-8], confounding by indication will inevitably have played a  
25 role in the increased risk of psychosis which was found in this study although it disappeared after  
26 adjustment for the intervention. Although this might also partly explain the increased risk of  
27 suicide, an independent risk for methylphenidate remained and an adverse role of methylphenidate  
28 seems plausible because of its stimulant properties in a population of patients receiving  
29 methylphenidate despite psychiatric contraindications. Obviously, there is collinearity between the  
30 intervention at baseline and actual use during follow-up. People may decide not to fill a  
31 prescription for methylphenidate, fail to use it, stop it early or use it continuously. Although we  
32 adjusted for the intervention at baseline to adjust for non/registered mental co-morbidity, changes  
33 during follow-up might have led to underestimation of the true risk, for instance, because patients  
34 with a lower vulnerability to suicidal thoughts stopped methylphenidate early during follow-up.  
35 Consequently, the risk of suicidal thoughts and attempts may have been underestimated. Therefore,  
36 it is important that our findings must be a starting point for further research.  
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43 In conclusion, in this large population-based study with data from general practitioners  
44 encompassing almost 100,000 people, methylphenidate was associated with a significantly  
45 increased risk of mortality, partly explained by 'off label' use as a psychostimulant in palliative  
46 care. There was a significantly increased risk of psychosis, and depression but this was probably  
47 confounded by intervention. However, there was also an increased risk of suicide in current users  
48 of methylphenidate, even after adjustment for the intervention. All in all, it seems that a cautious  
49 approach to prescribing methylphenidate in adults is warranted, especially in those with a history  
50 of suicidal ideation.  
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3 Contributorship statement  
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5 Bruno Stricker and Kiki Cheung designed the study. Data gathering was performed by Bruno  
6 Stricker and Katia Verhamme. All contributed to analysis and writing of the manuscript.  
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10 Data sharing  
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12 No data are available  
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16 Funding  
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18 This study was funded by the Health and Youth Care Inspectorate of the Netherlands.  
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21 Conflict of interest declaration  
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23 Bruno Stricker and Kiki Cheung have no conflict of interest regarding this paper. Katia  
24 Verhamme works for a research department who received/receives unconditional research grants  
25 from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, GSK, Chiesi, Amgen, UCB, Astra  
26 Zeneca and J&J, none of which are related to the content of this manuscript.  
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## LITERATURE

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Table 1 Characteristics of the study population [\*]

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Sex			
Men	4,839 [54.3%]	47,907 [54.3%]	1.0 [reference]
Women	4,066 [45.7%]	40,386 [45.7%]	1.0 [0.9-1.1]
Age	36.5 years	36.3 years	
18-40 yr	5,737 [64.4%]	56,888 [64.4%]	1.0 [reference]
41-60 yr	2,584 [29.0%]	25,847 [29.2%]	1.0 [0.9-1.1]
61-80 yr	476 [ 5.3%]	4,718 [ 5.3%]	1.0 [0.9-1.1]
> 80 yr	108 [ 1.3%]	840 [0.01%]	<b>1.3 [1.1-1.6]</b>
Follow-up [days]	1943 days	1944 days	
BMI [*]			
<25	864 [9.7%]	5617 [6.4%]	1.0 [reference]
25-30	717 [8.1%]	5,746 [6.5%]	<b>0.8 [0.7-0.9]</b>
>30	629 [7.1%]	4,702 [5.3%]	<b>0.9 [0.8-1.0]</b>
Smoking [*]			
Never	2,111 [23.7%]	21,629 [24.5%]	1.0 [reference]
Past	723 [ 8.1%]	4634 [ 5.2%]	<b>1.6 [1.5-1.8]</b>
Current	2,292 [25.7%]	13,111 [14.8%]	<b>1.8 [1.7-1.9]</b>
Alcohol abuse	352 [3.9%]	878 [1.0%]	<b>4.1 [3.6-4.7]</b>
Acute alcohol intoxication	105 [1.2%]	398 [0.5%]	<b>2.6 [2.1-3.3]</b>
Tobacco abuse	810 [9.1%]	3,930 [4.5%]	<b>2.2 [2.0-2.3]</b>
Medicines abuse	87 [0.9%]	230 [0.3%]	<b>3.8 [3.0-4.8]</b>
Drug abuse	525 [5.9%]	859 [1.0%]	<b>6.4 [5.7-7.1]</b>
History of:			
Organic psychosis [delier]	37 [0.4%]	157 [0.2%]	<b>2.3 [1.6-3.3]</b>
Schizophrenia	36 [0.4%]	282 [0.3%]	1.3 [0.9-1.8]
Affective psychosis	82 [0.9%]	245 [0.3%]	<b>3.3 [2.6-4.3]</b>
Anxiety	922 [10.4%]	3602 [4.1%]	<b>2.8 [2.6-3.0]</b>
Hypochondria/hysteria	55 [0.6%]	392 [0.4%]	<b>1.4 [1.1-1.9]</b>
Depression	1,772 [19.9%]	5252 [5.9%]	<b>4.3 [4.0-4.6]</b>
Suicide [attempt]	161 [1.8%]	410 [0.5%]	<b>4.0 [3.3-4.8]</b>
Burnout/overstrain	886 [9.9%]	3962 [4.5%]	<b>2.6 [2.4-2.8]</b>
Other neuroses	169 [1.9%]	674 [0.7%]	<b>2.5 [2.1-3.0]</b>
Personality disorder	479 [5.4%]	822 [0.9%]	<b>6.3 [5.6-7.0]</b>
Other non-specified psychotic disorder	80 [0.9%]	372 [0.4%]	<b>2.2 [1.7-2.8]</b>
Other psychiatric disorder	541 [6.1%]	1100 [1.2%]	<b>5.3 [4.7-5.9]</b>
Total psychiatric	3729 [41.9%]	13549 [115.3%]	<b>4.5 [4.3-4.7]</b>

Characteristic	Methylphenidate (n=8,905)	No methylphenidate (n=88,293)	Proportion ratio [95%-CI]
Previous or current use of:			
Antipsychotics	835 [9.4%]	1,884 [2.1%]	<b>4.8 [4.4-5.2]</b>
Antidepressants	3,037 [34.1%]	10,213 [11.6%]	<b>4.0 [3.8-4.2]</b>
Anxiolytics	3,338 [37.5%]	16,390 [18.6%]	<b>2.6 [2.5-2.8]</b>
Sedatives	2,498 [28.1%]	10,201 [11.6%]	<b>3.0 [2.8-3.1]</b>

[\*] Values were missing for BMI [n=78,923], smoking [n=52,698]

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Table 2 Number of cases and referents per psychiatric disease code/overall mortality occurring during follow-up and the risk [hazard ratio] to develop such a disease in users of methylphenidate in comparison to non-users

Outcome	Case	Referents	HR [95%-CI] [*]	HR [95%-CI] [**]
Organic psychosis [delier]	154	96,850	<b>8.3 [5.2-13.0]</b>	1.7 [0.9-3.0]
Schizophrenia	50	96,830	1.6 [0.4-6.7]	0.9 [0.2-4.3]
Affective psychosis	64	96,807	3.5 [1.4-6.9]	1.2 [0.4-3.6]
Anxiety	1374	91,300	1.8 [1.4-2.4]	0.8 [0.6-1.1]
Hypochondria/hysteria	109	96,642	1.5 [0.5-4.0]	0.8 [0.3-2.6]
Depression	1468	88,706	<b>2.7 [2.1-3.3]</b>	1.0 [0.8-1.3]
Suicide/suicide attempt	129	96,498	<b>5.5 [3.5-8.6]</b>	<b>2.0 [1.1-3.6]</b>
Burnout/overstrain	1583	90,767	1.4 [1.0-1.8]	1.0 [0.7-1.4]
Other neuroses	183	96,172	2.0 [1.0-3.9]	0.7 [0.4-1.6]
Personality disorder	412	95,485	6.0 [4.5-7.9]	1.2 [0.8-1.6]
Other non-specified psychotic disorder	162	96,584	3.2 [1.8-5.7]	0.9 [0.5-1.8]
Other psychiatric disorder	538	95,019	4.9 [3.8-6.5]	1.4 [0.9-1.8]
Any psychosis	347	95,727	4.8 [3.4-6.8]	1.3 [0.9-2.0]
Death [***]	946	96,252	<b>7.5 [6.3-8.9]</b>	<b>1.3 [1.1-1.6]</b>

[\*] All hazard ratios [HR] are adjusted for sex, and age by matching

[\*\*] All HR are adjusted for sex, age, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and for 'intention-to-treat'

[\*\*\*] Additionally are adjusted for hypertension, diabetes mellitus, hypercholesterolemia, and decreased renal function.

Table 3A; Age and sex specific risks of suicide, suicidal attempts/ideation during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	64/44,043	3.9 [1.5-10.2]
Men	65/52,294	1.1 [0.4-2.6]
18-40 yrs. of age	84/62,196	2.4 [1.2-4.9]
41-60 yrs. of age	38/28,108	1.3 [0.4-4.9]
61-80 yrs. of age	4/4,543	1.6 [0.0-∞]
>80 yrs. of age	3/836	- [*]

All hazard ratios [HR] are adjusted for sex, age, intervention, smoking, BMI, alcohol abuse, acute alcohol intoxication, medicines abuse, tobacco abuse, drug abuse, psychosis in history [for non-psychotic endpoints], depression in history [for non-depressive endpoints], anxiety in history [for non-anxiety endpoints], neuroses in history, personality disorder, other psychiatric disease, and ‘intention-to-treat’

[\*] No cases exposed to methylphenidate

Table 3B; Age and sex-specific risks of all-cause mortality during use of methylphenidate

<i>Characteristic</i>	<i>Cases/controls [n]</i>	<i>HR [95%CI]</i>
Women	375/44,077	1.7 [1.2-2.5]
Men	571/52,154	1.1 [0.8-1.5]
18-40 yrs. of age	67/62,478	1.2 [0.4-3.5]
41-60 yrs. of age	240/28,191	1.1 [0.7-1.8]
61-80 yrs. of age	412/4,781	1.6 [1.2-2.2]
>80 yrs. of age	227/721	1.2 [0.7-2.0]

[\*] All hazard ratios [HR] are adjusted for sex, age, smoking, hypertension, diabetes mellitus, BMI, hypercholesterolemia, decreased renal function, and ‘intention-to-treat’

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5 Figure 1 Flow scheme from source population to study population  
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8 Figure 2 Time delay in follow-up days between 1st intake of methylphenidate and death. On the y-  
9 axis, the number of cases of death are given while the x-axis represents the number of days of follow-  
10 up. In non-users with the same reference date as users [upper part of figure 2], this delay is spread  
11 over several years whereas it is focused in the early weeks of intake in users [lower part of figure 2].  
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11 Figure 31 Time delay in follow-up days between 1st intake of methylphenidate and suicide  
12 [attempt]. On the y-axis, the number of cases of suicide [attempt] are given while the x-axis  
13 represents the number of days of follow-up. In non-users with the same reference date as users  
14 [upper part of figure 3], this delay is spread over several years whereas it is focused in the early  
15 weeks of intake in users [lower part of figure 3].  
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## ***METHYLPHENIDATE IN ADULTS***

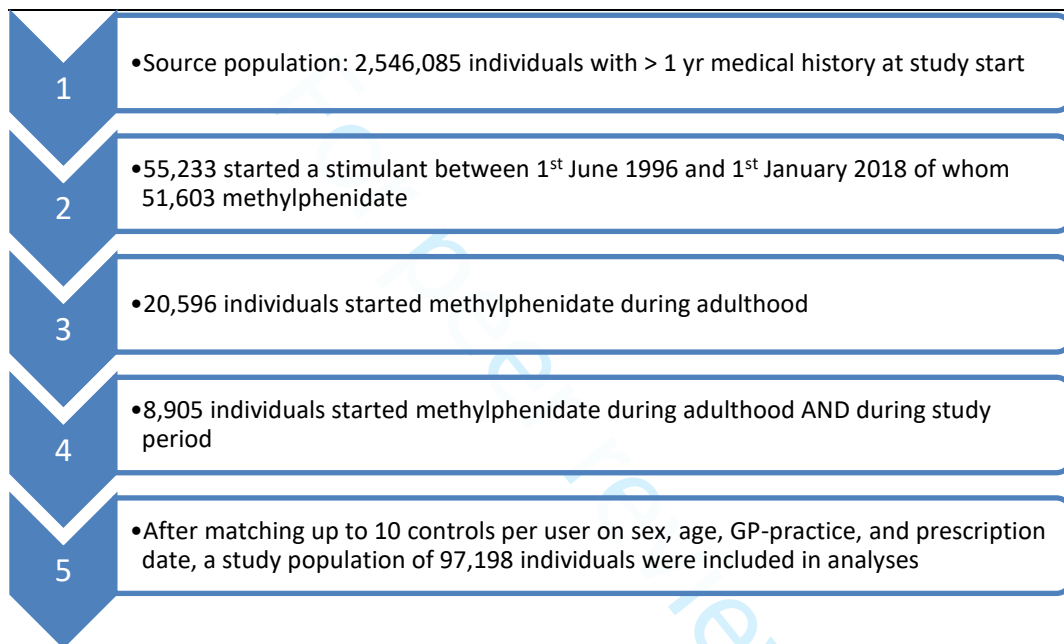


Figure 1 Flow scheme from source population to study population

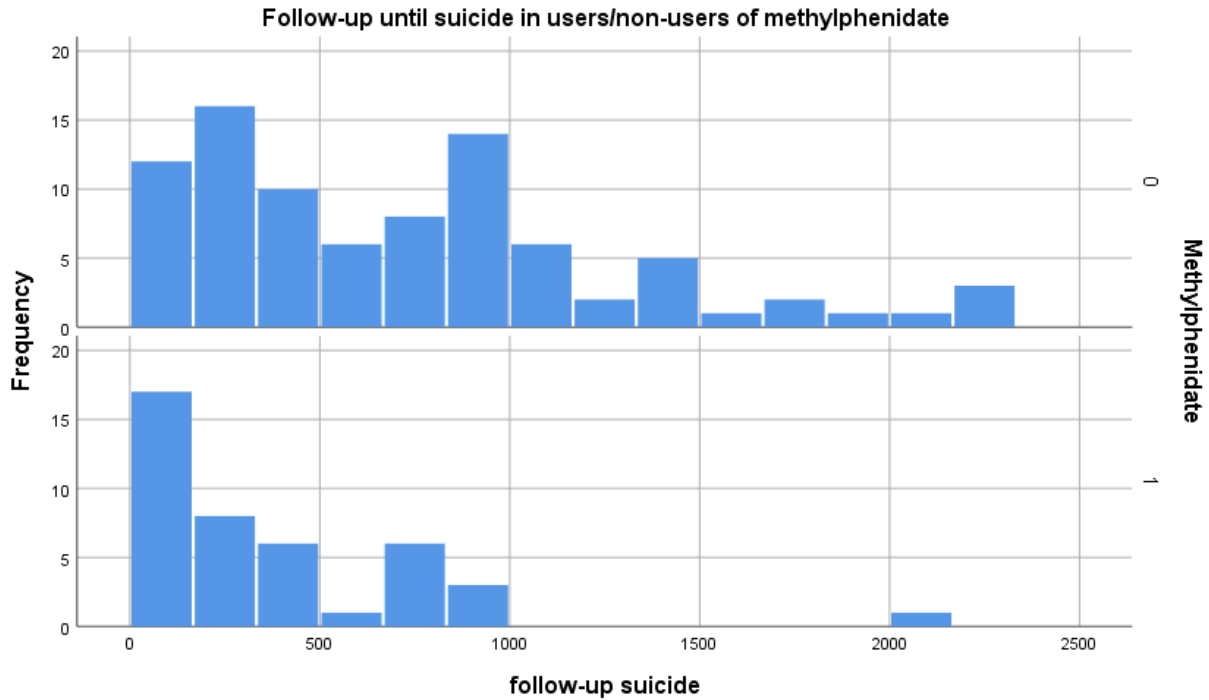


Figure 3 Time delay in follow-up days between 1st intake of methylphenidate and suicide [attempt]. On the y-axis, the number of cases of suicide [attempts] are given while the x-axis represents the number of days of follow-up. In non-users with the same reference date as users [upper part of figure 3], this delay is spread over several years whereas it is focused in the early weeks of intake in users [lower part of figure 3].

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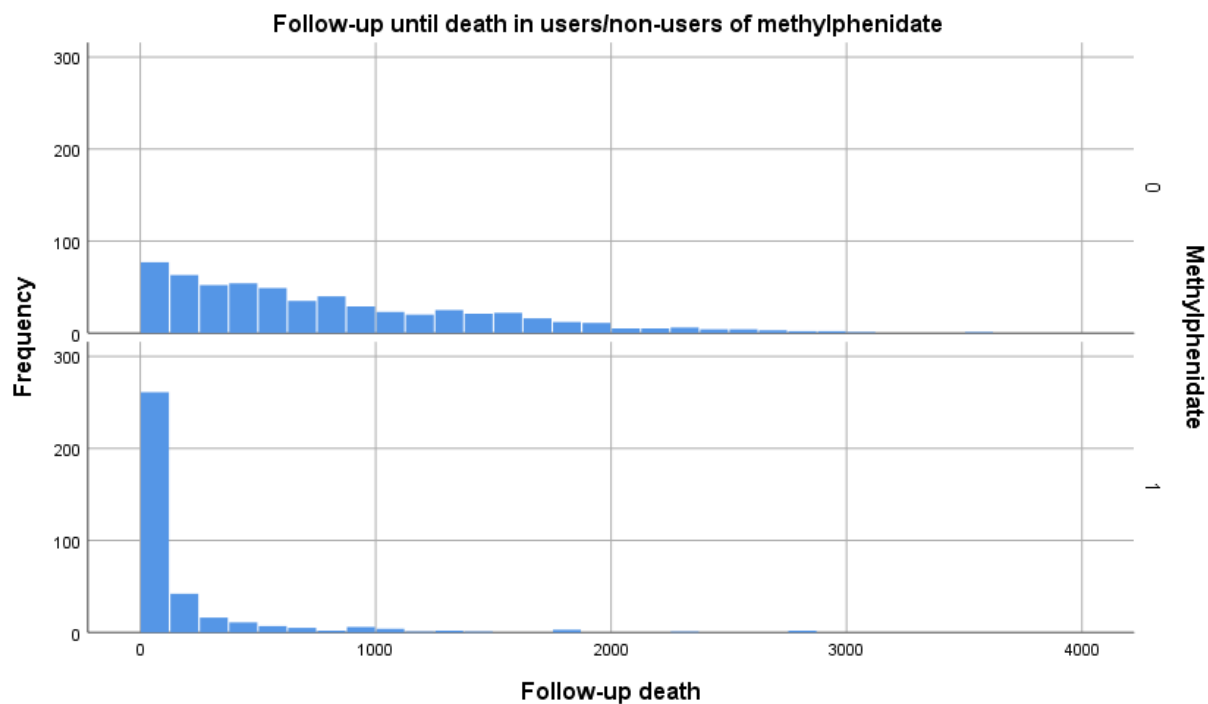


Figure 2 Time delay in follow-up days between 1st intake of methylphenidate and death. On the y-axis, the number of cases of death are given while the x-axis represents the number of days of follow-up. In non-users with the same reference date as users [upper part of figure 2], this delay is spread over several years whereas it is focused in the early weeks of intake in users [lower part of figure 2].

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.  RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.  RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P. 2
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			P. 3
Objectives	3	State specific objectives, including any prespecified hypotheses			P. 3
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper			P. 3/4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			A. 4

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</p> <p>Participants</p>	<p>6</p>	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed  <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>		<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	<p>4/5</p> <p>N/A</p> <p>N/A</p>
<p>27 28 29 30 31 32</p> <p>Variables</p>	<p>7</p>	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.</p>		<p>RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.</p>	<p>4/5</p>
<p>33 34 35 36 37 38 39 40 41 42</p> <p>Data sources/ measurement</p>	<p>8</p>	<p>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</p>			<p>4/5</p>

1 2 3 4 5 6 7 8 9	Bias	9	Describe any efforts to address potential sources of bias			P. 2/9
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Study size	10	Explain how the study size was arrived at			P. 4
33 34 35 36 37 38 39 40 41 42 43 44 45 46	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			P. 5-7
	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			P. 5-7
	Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	P. 4

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	W/A
<b>Results</b>					
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	P. 4
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) Cohort study - summarise follow-up time (e.g., average and total amount)			P. 14
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure			A. 6/7

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		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			P. 6/7
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses			P. 7
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives			P. 7/8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	P. 8
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			P. 9



		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			p. 9
<b>Other Information</b>					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			p. 10
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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