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Psychotropic medications and hormonal contraception - a nationwide register-based study from Finland

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Abstract

Objectives. To examine whether mental disorders, as indicated by the current and past use of psychotropic medications, are associated with the use and type of hormonal contraception (HC).

Design. Nationwide register-based matched case-control study.

Settings. All fertile-aged women living in Finland in 2017; data from the Medical Birth Register, Population Register Centre, Prescription Centre, Register of Induced Abortions, Care Register of Health Care.

Participants. 294,356 women living in Finland with a redeemed prescription of HC in 2017, and their same-sized control group of non-users (n=294,356) identified through records in the Prescription Centre.

Main outcome measures. Associations between the use of psychotropic medications and the use of HC, and the type of HC tested in logistic regression models.

Results. Altogether 19% of the 588,712 women received at least one prescription for a psychotropic medication in 2017, and 4% and 15% were occasional and regular users of psychotropic medications in 2013–2016, respectively. In multivariable logistic regression models both use of psychotropic medications in 2017, and their occasional or regular use between 2013–2016 were associated with higher odds of HC use, even though with small to very small effect sizes (ORs ranging between 1.37 and 1.06, 95% confidence intervals 1.22 to 1.53, and 1.03 to 1.09, respectively). After adjustment for covariates, when fixed combinations of progestogens and estrogens for systemic use was the reference category, women using almost any class of psychotropic medications had higher odds of using other types of HC (such as hormonal intrauterine device, vaginal ring and progestogens for systemic use).

Conclusions. Fertile-aged women with current and past use of psychotropic medications have higher odds of using HC in Finland, with a specific pattern in the type of contraceptives used, suggesting adequate access to effective contraception for women with psychiatric disorders.

Keywords: women, fertile-age, hormonal contraception, psychotropic medication.

ARTICLE SUMMARY

Strengths and limitations of this study

- The studied population is highly representative of all fertile-aged women in Finland.
- The combination of a cross-sectional and longitudinal retrospective design provides stability to psychiatric prescriptions as predictor of interest.
- Levels of use of psychotropic medications were determined through different approaches.
- Women suffering from and seeking help for their psychiatric disorders, and thus receiving a pharmacological treatment, represent a more conscious and healthy subgroup of this population.
- Misclassification of both psychiatric disorders and HC use as based on drug prescription cannot be ruled out.

INTRODUCTION

The relationship between the use of hormonal contraception (HC) and women's mental health continues to be debated.[1] While ample evidence has been provided showing no associations between the use of contraception and the increased risk of depressive or anxiety disorders,[1-3] findings from recent studies are challenging this view. Recent observations report that women using HC (especially oral contraceptives, OC) have higher odds of depression,[4] and of suicidal behavior,[5,6] with a long-term risk of depression later in adulthood for those who started their OC use during adolescence.[7]

However, while these findings indicate a link between contraceptive use and mental health status, the reverse association is likewise plausible and of public health and clinical relevance. Women suffering from psychiatric disorders seem to have higher risk of unplanned pregnancy and induced abortion, as well as risky sexual behavior including non-use or inconsistent use of contraception,[8-10] or use of less effective contraceptive methods.[11,12] For instance, among teenagers and young women, those with baseline depressive and stress symptoms had higher odds of reporting mood changes, of OC discontinuation, and of inconsistent use of contraception.[13,14] It has been hypothesized that a subgroup of women may be more sensitive to hormonal fluctuations, and thus more prone to develop mood symptoms or disorders in relation to reproductive events (e.g., the premenstrual phase, the postpartum, or the perimenopause),[15] as well as while on contraception.[16] Consequently, women with mental health problems, either because they are more likely to experience mood side effects of HC or to consider their perceived mood changes as caused by HC, are also more likely to discontinue contraception use. In line with these observations, we previously found that a recent care episode for a psychiatric disorder was associated with lower odds of HC use among almost 600,000 women aged 15-49 years in Finland.[17] The study used register records with a psychiatric discharge diagnosis in 2016, thus including only the most severe cases of psychiatric disorders. However, because mild and moderate mental disorders not requiring hospitalization are highly prevalent in the population, the overall relationship between mental health and HC use remains largely unknown. Thus, the aim of this study was to explore the associations between a wide spectrum of psychiatric disorders, as indicated by the current and previous prescriptions of psychotropic medications, and HC use in 2017, in a population inclusive of all fertile-aged women using HC in Finland, and their reference group of non-users. A further aim was to test whether the use of psychotropic medications was associated with the type of HC used.

METHODS

This work is part of a larger register-based study on HC in Finland, described in detail elsewhere.[17] Briefly, the population was selected on the basis of the unique personal identification number given at birth or at immigration to each person permanently residing in Finland. The group of HC users, selected from the Prescription Centre in the Kanta Services,[18] included all fertile-aged women (15–49 years) with at least one redeemed prescription for HC in 2017 (n=294,445). The same-sized control group of HC non-users included women, matched by age and municipality of residence, with no redeemed HC prescriptions in 2017. Altogether 89 women who received a prescription with Anatomical Therapeutic Chemical (ATC) code "G03AD" (i.e., emergency contraception, which is usually available without prescription in Finland), and their matched controls, were excluded, leaving a final population of 588,712 women. As such, the study population included 52% of all fertile-aged women living in Finland in 2017. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Helsinki (3/2018). Because this is a register-based study, no individual consent is needed.

The registers

Information on redeemed medications for each person living in Finland is stored in the Prescription Centre, a centralized database in the Kanta Services. The recorded data include, among others, the product ATC code, date of prescription and of purchase, and the redeemed amount in defined daily dose (DDD). In addition to selection of the study population, the Prescription Centre was used to gather information on redeemed prescriptions for psychotropic medications between 2013 and 2017 for all the study members. Use of psychotropic medications in 2017 was defined as one or more redeemed prescriptions in the same year. Users of psychotropic medications between 2013 and 2016 were divided into occasional and regular users, defined as women with only one vs. two or more redeemed prescriptions of the same class drug.

The examined HC types included intrauterine device (IUD) with progestogen (i.e., the levonorgestrel-releasing intrauterine system, LNG-IUS, ATC code G02BA); vaginal ring with progestogen and estrogen (G02BB); progestogens and estrogens, fixed combinations – including monophasic combined OCs and transdermal patch (G03AA); progestogens and estrogens, sequential preparations for systemic use (G03AB); progestogens for systemic use (G03AC); and cyproterone and estrogen (G03HB01). Psychotropic medications included antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A), psychostimulants (N06B), psycholeptics and psychoanaleptics in combination (N06C).

The Population Register Centre contains basic information of all Finnish citizens and foreign citizens residing permanently in Finland. From this register we obtained information on age, municipality of

residence, civil status, socioeconomic group, highest level of education, and annual income of all the study members on 31 December 2017.

The Medical Birth Register includes data on all live births and stillbirths in Finland since 1987; the Register of Induced Abortions contains data on induced abortions since 1983, and the Register of Sterilizations on all sterilizations since 1987. Based on these registers, we gathered information on pregnancies with birth dates in 2016 and 2017, induced abortions performed in 2016 and 2017, and sterilizations between 1987 and 2016.

The Care Register of Health Care, which includes data on inpatient care in hospitals, health centers, day surgeries and specialized outpatient care, was used to identify women who had received a psychiatric diagnosis (International Classification of Diseases, 10th Revision codes F10–F19 -substance abuse-, F30–F39 -mood disorders-, F40–F48 -anxiety disorders-, F50 -eating disorders- and F60 -personality disorders-) between 2013 and 2016.

Patient and public involvement

Patients and the public were not directly involved in the research process. Because this is a register-based study, no informed consent was needed.

Statistical analyses

The frequency of use of each class of psychotropic medications among HC users and non-users was compared via chi-squared test. We assessed the percentages of women using each type of HC within users of categories of psychotropic medications. Women with redeemed prescriptions of two or more different types of HC in 2017 were classified on the basis of their first redeemed prescription.

Associations between use of each class of psychotropic medications and HC use were tested via univariable (BL-Model 1) and multivariable binary logistic regression models using the "gnm" R-package,[19] which, through the argument "eliminate", allows for handling parameters of stratification factors with a large number of levels (in our case, "municipality of residence"). Separate models were conducted to test the associations with the use of psychotropic medications in 2017, and with occasional or regular use from 2013 to 2016. Multivariable models were progressively adjusted for age group, marital status and education level (BL-Model 2), socioeconomic status and income level (BL-Model 3), and reproductive characteristics (pregnancies in 2017, induced abortions in 2016–2017, and sterilization before 2017) (BL-Model 4). A separate fully adjusted model further tested the interaction between age and use of psychotropic medications; if there was a significant interaction, age-stratified multivariable analyses were performed.

To further confirm the results and take into account a potential "healthcare user bias", sensitivity analyses were conducted utilizing the purchased amount in DDD as indicator of use of psychiatric medications between 2013 and 2016. To this end, the total purchased DDD for each class was divided into tertiles, and groups of low, intermediate and high-level users were created accordingly. Because of the data distribution with duplicate values, only two groups were created for high and low level users of hypnotics/sedatives (cut off at the 50th percentile), and of psycholeptics and psychoanaleptics in combination (cut off at the 60th percentile).

We further examined whether the odds of using distinct types of HC in 2017 differed by occasional or regular use of psychotropic medications between 2013 and 2016. To this end, we conducted univariable (ML-Model 1) and multivariable multinomial logistic regression models among HC users, controlling for age, marital and socioeconomic status, education and income levels (ML-Model 2), and reproductive characteristics (pregnancies or induced abortions in 2016–2017) (ML-Model 3). Because of the relatively small number of women using psychostimulants or psycholeptics and psychoanaleptics in combination, these classes were excluded from these analyses. Sensitivity analyses were additionally performed utilizing groups of users based on the purchased DDD, as described above.

For all the analyses, the two-tailed *p*-values of <0.05 were considered statistically significant. All the analyses were performed with R software version 3.5.1.[20]

RESULTS

A quarter (25.6%, n=294,356) of all fertile-aged women in Finland were using HC in 2017. Their characteristics as well as those of the control women (n=294,356) are described in detail elsewhere.[17] The proportions of different utilized HC types are illustrated in Supplementary Figure 1.

Use of psychotropic medications in 2017

Altogether 110,112 (18.7%) women had redeemed at least one prescription of a psychotropic medication in 2017; of them, 52% (n=57,478) used also HC. The proportions of women using and not using HC who also had one or more prescriptions of psychotropic medications by ATC codes are reported in Table 1.

In univariable logistic regression models the use of psychotropic medications in 2017 was associated with higher odds of HC use (ORs: any medication=1.12; anxiolytics=1.10; hypnotics/sedatives=1.17; antidepressants=1.11; psycholeptics and psychoanaleptics in combination=1.30, p<0.0001). The associations remained after controlling for age group, education and income levels, marital and

socioeconomic status, and reproductive characteristics. Additionally, in partially and fully adjusted models, the use of antipsychotics was also associated with higher odds of being a HC user (ORs=1.10 to 1.09, $p<0.0001$) (Table 2).

There was a significant interaction between age and a recent prescription of psychotropic medications, except for psycholeptics and psychoanaleptics in combination. Regardless of the type of medication, the proportions of HC users among those with a recent psychotropic prescription were consistently higher especially in teenagers but lower in the young age group (20–24 years) as compared to non-users. Among those with a recent psychiatric prescription, the highest rates of using HC were seen for teenagers (varying from 54.6% for antipsychotics to 55.8% for antidepressants, and 57.5% for anxiolytics and sedatives/hypnotics) (Supplementary Figures 2 and 3).

Table 1. Proportions of HC users and non-users receiving one or more prescriptions for psychotropic medications in 2017.

Class of psychotropic medication ATC code, class	**HC users**	**HC non-users**	***p*-value**
Any psychotropic medication	57,478 (19.5%)	52,634 (17.9%)	<0.0001
N05A, antipsychotics	11,136 (3.8%)	11,688 (4.0%)	0.0002
N05B, anxiolytics	17,181 (5.8%)	15,744 (5.4%)	<0.0001
N05C, hypnotics/sedatives	17,829 (6.1%)	15,397 (5.2%)	<0.0001
N06A, antidepressants	40,488 (13.8%)	37,028 (12.6%)	<0.0001
N06B, psychostimulants	1,681 (0.57%)	1,715 (0.58%)	0.570
N06C, psycholeptics and psychoanaleptics (amitriptyline) in combination	1,237 (0.4%)	952 (0.3%)	<0.0001

ATC, Anatomical Therapeutic Chemical; HC, hormonal contraception

Table 2. Associations between prescriptions of psychotropic medications in 2017 and HC use in 2017.

Psychotropic medication.	Model 1			Model 2			Model 3			Model 4		
ATC code, class	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Any psychotropic medication	1.12	1.10 to 1.13	<0.0001	1.15	1.13 to 1.16	<0.0001	1.16	1.14 to 1.17	<0.0001	1.15	1.13 to 1.17	<0.0001
N05A, antipsychotics	0.95	0.93 to 0.98	0.00019	1.02	0.99 to 1.05	0.212	1.10	1.07 to 1.13	<0.0001	1.09	1.06 to 1.12	<0.0001
N05B, anxiolytics	1.10	1.07 to 1.12	<0.0001	1.14	1.12 to 1.17	<0.0001	1.16	1.14 to 1.19	<0.0001	1.16	1.14 to 1.19	<0.0001
N05C, hypnotics/ sedatives	1.17	1.14 to 1.20	<0.0001	1.19	1.16 to 1.21	<0.0001	1.18	1.15 to 1.20	<0.0001	1.17	1.14 to 1.20	<0.0001
N06A, antidepressants	1.11	1.09 to 1.13	<0.0001	1.14	1.12 to 1.15	<0.0001	1.16	1.14 to 1.17	<0.0001	1.15	1.13 to 1.16	<0.0001
N06B, psychostimulants	0.98	0.92 to 1.05	0.56	1.05	0.98 to 1.13	0.142	1.08	1.00 to 1.15	0.039	1.07	1.00 to 1.15	0.057
N06C, psycholeptics and psychoanaleptics	1.30	1.20 to 1.42	<0.0001	1.31	1.20 to 1.42	<0.0001	1.27	1.17 to 1.39	<0.0001	1.26	1.16 to 1.38	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017).

Use of psychotropic medications between 2013 and 2016

A total of 112,609 women of our study population redeemed at least one prescription of a psychotropic medication between 2013 and 2016; of them, 20.8% (n=23,379) received a psychiatric diagnosis in the same period according to the records in the Care Register of Health Care; conversely, 18.5% (n=5,302) of the 28,681 women with a psychiatric diagnosis between 2013 and 2016 had not redeemed any psychiatric prescriptions.

Approximately 15% of the women (n=86,644) were regular users of psychotropic medications in the period 2013–2016, while 4.4% (n=25,965) received only one psychiatric prescription (Table 3, left side).

Higher odds for using HC were predicted by (occasional and regular) use of hypnotics/sedatives and psycholeptics and psychoanaleptics, and by regular use of antidepressants during 2013–2016 in unadjusted logistic regression models. On the contrary, occasional and regular use of antipsychotics and regular use of anxiolytics were associated with lower odds of HC use (Table 4). After adjustment for covariates occasional use of hypnotics/sedatives and psycholeptics and psychoanaleptics, and regular use of almost all the classes of psychiatric medications predicted belonging to the HC user group, although with small to very small effect sizes (ORs ranging between 1.06 and 1.37).

Sensitivity analyses using quantiles of redeemed DDD as indicator of psychotropic drug use (Table 3, right side) substantially confirmed these findings. Specifically, women with higher use (i.e., belonging to the highest levels of redeemed DDD) of all psychotropic medications had higher odds of using HC compared to women with no redeemed medications (i.e., with a DDD of zero for the respective drug class). Lower use of psychotropic medications was generally not associated with HC use (Supplementary Table 1).

There was a significant age*psychotropic medication interaction in predicting HC use for all the medication classes ($p \leq 0.0001$), with the exception of psycholeptics and psychoanaleptics. In detail, among occasional and regular users of psychotropic medications, the odds of HC use tended to be lower (than in non-users of psychotropic medications) in teenagers and young women (20–29 years), but higher in middle-age women (Supplementary Figures 4 and 5).

Table 3. Proportions of HC users and non-users receiving one or more prescriptions of psychotropic medications between 2013 and 2016, as number of prescriptions (left side) or levels of use (based on quantiles of redeemed DDD) (right side).

Class of psychotropic medication	Number of prescriptions	HC users	HC non-users	*p*-value	Level of use*	HC users	HC non-users	*p*-value
Any psychotropic medication				0.0001				
	one prescription	13,269 (4.5%)	12,696 (4.3%)		---	---	---	---
	≥ 2 prescriptions	43,572 (14.8%)	43,072 (14.6%)		---	---	---	---
Antipsychotics				<0.0001	Low	5,445 (1.85%)	5,709 (1.94%)	<0.0001
	one prescription	3,867 (1.5%)	4,273 (1.3%)		Intermediate	4,385 (1.49%)	4,734 (1.61%)	
	≥ 2 prescriptions	10,548 (3.6%)	11,694 (4.0%)		High	4,582 (1.56%)	5,519 (1.88%)	
Anxiolytics				0.011	Low	4,852 (1.65%)	4,650 (1.58%)	0.0013
	one prescription	6,748 (2.3%)	6,564 (2.2%)		Intermediate	4,503 (1.53%)	4,506 (1.53%)	
	≥ 2 prescriptions	6,705 (2.3%)	7,001 (2.4%)		High	4.098 (1.39%)	4,409 (1.50%)	
Hypnotics/	one prescription	6,786 (2.3%)	6,072 (2.1%)	<0.0001	Low	6,865 (2.33%)	6,134 (2.08%)	<0.0001
sedatives	≥ 2 prescriptions	6,321 (2.2%)	5,493 (1.9%)		High	6,232 (2.12%)	5,407 (1.84%)	
Antidepressants				0.053	Low	14,815 (2.52%)	14,867 (2.53%)	0.088
	one prescription	8,395 (2.9%)	8,460 (2.9%)		Intermediate	14,998 (2.55%)	14,689 (2.50%)	
	≥ 2 prescriptions	36,396 (12.4%)	35,793 (12.2%)		High	14,978 (2.54%)	14,697 (2.50%)	
Psychostimulants				0.11	Low	617 (0.21%)	702 (0.24%)	0.052
	one prescription	236 (0.08%)	276 (0.09%)		Intermediate	563 (0.19%)	612 (0.21%)	
	≥ 2 prescriptions	1,604 (0.6%)	1,669 (0.6%)		High	617 (0.21%)	602 (0.21%)	
Psycholeptics-psychoanaleptics	one prescription	809 (0.28%)	673 (0.23%)	<0.0001	Low	804 (0.27%)	658 (0.22%)	<0.0001
in combination	≥ 2 prescriptions	697 (0.24%)	538 (0.18%)		High	702 (0.24%)	553 (0.19%)	

ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose; HC, hormonal contraception.

* Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination).

Table 4. Associations between number of prescriptions of psychotropic medications between 2013 and 2016, and HC use in 2017

Class of psychotropic medication	Number of prescriptions	Model 1			Model 2			Model 3			Model 4		
		OR	95% CI	*p*-value	OR	95% CI	p-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Antipsychotics	one prescription	0.90	0.86 to 0.94	<0.0001	0.95	0.91-1.00	0.0335	0.96	0.92 to 1.01	0.104	0.96	0.92 to 1.00	0.069
	≥ 2 prescriptions	0.90	0.88 to 0.92	<0.0001	0.97	0.94 to 1.00	0.0198	1.06	1.03 to 1.09	0.0001	1.06	1.03 to 1.09	0.0002
Anxiolytics	one prescription	1.03	0.99 to 1.06	0.121	1.04	1.00 to 1.08	0.0295	1.04	1.01 to 1.08	0.0214	1.04	1.00 to 1.07	0.055
	≥ 2 prescriptions	0.96	0.93 to 0.99	0.0117	1.02	0.98 to 1.05	0.309	1.10	1.06 to 1.14	<0.0001	1.10	1.06 to 1.14	<0.0001
Hypnotics/ sedatives	one prescription	1.12	1.09 to 1.16	<0.0001	1.12	1.08 to 1.16	<0.0001	1.09	1.05 to 1.13	<0.0001	1.09	1.05 to 1.13	<0.0001
	≥ 2 prescriptions	1.16	1.12 to 1.20	<0.0001	1.16	1.11 to 1.20	<0.0001	1.18	1.14 to 1.23	<0.0001	1.19	1.15 to 1.24	<0.0001
Antidepressants	one prescription	1.00	0.96 to 1.03	0.724	1.02	0.99 to 1.06	0.165	1.01	0.98 to 1.04	0.479	1.01	0.98 to 1.04	0.575
	≥ 2 prescriptions	1.02	1.00 to 1.04	0.0178	1.04	1.03 to 1.06	<0.0001	1.07	1.06 to 1.09	<0.0001	1.07	1.06 to 1.09	<0.0001
Psychostimulants	one prescription	0.86	0.72 to 1.02	0.077	0.92	0.77 to 1.09	0.323	0.95	0.79 to 1.13	0.535	0.94	0.79 to 1.13	0.510
	≥ 2 prescriptions	0.96	0.90 to 1.03	0.252	1.03	0.96 to 1.10	0.405	1.05	0.98 to 1.12	0.213	1.04	0.97 to 1.12	0.247
Psycholeptics and psychoanaleptics	one prescription	1.20	1.09 to 1.33	0.0004	1.19	1.07 to 1.32	0.0012	1.17	1.06 to 1.30	0.0025	1.18	1.06 to 1.31	0.0024
	≥ 2 prescriptions	1.30	1.16 to 1.45	<0.0001	1.31	1.17 to 1.47	<0.0001	1.35	1.21 to 1.52	<0.0001	1.37	1.22 to 1.53	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017). HC, hormonal contraception.

Psychotropic medications and HC types

Supplementary Figure 6 illustrates the types of HC used in 2017 by occasional and regular users of psychotropic medications between 2013 and 2016.

In univariable and multivariable (adjusted for age group, marital and socioeconomic status, education and income level, recent pregnancy or induced abortion) multinomial logistic regression models, when fixed combinations of progestogens and estrogens for systemic use (ATC: G03AA) was the reference category, women either occasionally (Figure 1) or regularly (Figure 2) using almost any class of psychotropic medications had higher odds of using any other types of HC (such as the LNG-IUS and, to a lesser extent, vaginal ring and progestogens for systemic use). The results were substantially confirmed in unadjusted and, to a lesser extent, adjusted models using quantiles of redeemed DDD (Supplementary Table 2).

DISCUSSION

According to our results, the current as well as past uses of psychotropic medications are associated with higher odds of using HC among Finnish women of fertile age. This association holds also in relation to regular and, although to a lesser extent, occasional use of psychiatric medications during the four previous years. This study additionally indicates that mental disorders, as identified by redeemed prescriptions of psychotropic medications, are associated with the type of contraceptive chosen.

Our study has a number of limitations. First, misclassification of both psychiatric disorders and HC use cannot be ruled out. Because our indicator of psychiatric disorders was a prescription of psychotropic medications, women with mild conditions, who do not need a pharmacological treatment, as well as women with more severe disorders but not yet receiving (or with poor adherence to) a pharmacological treatment, may have been included in the reference group. However, by distinguishing regular vs. occasional past psychiatric prescriptions, and by conducting sensitivity analyses utilizing the amount of purchased drug, we partly took into account these factors. Similarly, because we had no information on contraception use before 2017, it is possible that a number of women in the control group were in fact using HC, especially LARC methods, which may have been prescribed or inserted before 2017. The lack of information on HC use before 2017 further limits the interpretability of the detected prospective associations, which can in fact reflect a more complex path between (unidentified) HC use between 2013–2016, psychiatric problems in the same period, and HC use in 2017. It is also possible that the detected associations in fact result from a selection bias, where unobserved confounding may underlie the choice of using HC, especially in young women.

Additionally, we lacked information on the use of contraceptives that do not require a prescription, such as copper IUD or condoms, or on young women who obtained free contraception as part of municipal programs. We may expect that a proportion of women with psychiatric disorders, being usually high utilizers of healthcare services, may have received free-of-charge (and thus without a prescription) contraception, and thus being erroneously classified as non-users. However, if this were the case, it would even further support our results. Likewise, because more than 20% of women who receive free contraception opt for a LARC method such as the LNG-IUS or contraceptive implants,[33] the same bias may concern the analyses on the HC types.

Among the strengths of the study, our population was highly representative, including more than half of fertile-aged women in Finland. Additional strengths are the use of register data with proven good validity and reliability, and the combination of a cross-sectional and longitudinal retrospective design, which provides stability to our predictor of interest. Our findings are further supported by the use of different approaches to determine levels of use of psychotropic medications.

To the best of our knowledge, this is the first study to examine, on a nationwide scale, the associations between the concurrent and past class-specific use of psychotropic medications and class-specific HC use. The observation of higher odds for HC use among women using psychotropic medications contrasts with large part of the available evidence.[1] [1] In fact, previous studies reported associations between psychiatric disorders and risky sexual behavior, lower contraceptive compliance, contraceptive non-use, unintended pregnancy, and use of less effective methods.[9,11,12,21-28] However, other works showed either no relationships between depressive/anxiety symptoms or psychological distress and inconsistent use of contraception or use of less effective methods, or even higher odds of choosing a more effective method.[29-32]

Although not totally comparable, our findings, supported by the use of both a cross-sectional and a longitudinal design, suggest that women with psychiatric disorders, as indicated by repeated prescriptions of psychotropic medications, have good access to, and are well aware of contraceptive options in Finland. The use of contraception was especially higher among teenagers who used psychiatric medications than in their peers who were not using the same drugs. However, it tended to invert the figure for the young age group (20–24 years), possibly suggesting that the adequate psychiatric and reproductive counselling and education likely offered through the school system may not be completely continued after high school.

The observation of a relationship between the use of psychotropic drugs and the type of contraceptive chosen provides additional information on the reproductive health status of these women. Specifically, the use of psychiatric medications was associated with higher odds of using types of

contraception other than the monophasic OCs, and especially long-acting reversible contraception (LARC) methods such as the LNG-IUS, as well as vaginal ring and progestogens for systemic use including implants. Because the oral preparations in particular require daily motivation, the use of less user-dependent LARC methods may be advisable especially in women who, because of their psychological challenges, may have difficulty with a method necessitating daily remembering.

It could be argued that our findings may be affected by a healthcare user bias. In other words, it is likely that women suffering from and seeking help for their psychiatric disorders, and thus receiving a pharmacological treatment, represent a more conscious and healthy subgroup of this population. As such, they may obtain a better control of their symptoms (as compared to their peers not using psychiatric medications), and thus also of other areas of their lives, including contraception. Moreover, because more likely to visit healthcare services, they may also be more likely to receive and adhere to any medical prescription. Reciprocally, women who use HC are likely to see healthcare providers, and thus to have their psychiatric symptoms diagnosed and pharmacologically treated. This assumption is supported by the observation that the detected associations were substantially consistent for women with either repeated prescriptions or belonging to the highest DDD group, but almost completely non-existent for occasional users or those with the lowest purchased DDD. However, in our sensitivity analyses part of the associations hold also in the group of women with intermediate/low use (e.g., in the case of hypnotic/sedatives, antidepressants, psycholeptics and psychoanaleptics) possibly including, in addition to occasional users, those with poor compliance to psychopharmacological treatment.

In summary, fertile-aged women with psychiatric disorders, as identified by prescriptions of psychiatric medications, have higher odds of using HC in Finland, with a specific pattern in the type of contraceptives used. Whether our observation of adequate use of effective contraception among women with psychiatric disorders translates into an actual reduction in the number of unwanted pregnancies, and thus of induced abortions, in this population, it remains to be examined.

CONTRIBUTORSHIP STATEMENT

ET, AB, OH, AL, TP and JH contributed to the study planning and design, interpretation of the data, and critical revision of the manuscript. ET and JH verified the data. ET and JH had full access to all the data and performed statistical analyses. ET wrote the first draft of the manuscript. ET, AB, OH,

AL, TP and JH approved the submitted version of the manuscript and accepted responsibility to submit for publication. ET and JH are the guarantors.

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COMPETING INTERESTS

OH reports a research grant from the Jane and Aatos Erkko Foundation during the conduct of the study; personal fees from Bayer Health Care AG, personal fees from Gedeon-Richter outside the submitted work; OH serves as president for the Finnish Gynecological Society and for the Nordic Federation of the Societies of Obstetrics and Gynecology, and is the chairperson for the Finnish national guideline committee on induced abortion care. The other authors report no conflicts of interest.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Helsinki (3/2018).

DATA SHARING

The data that support the findings of this study are available from Statistics Finland, the Finnish Institute for Health and Welfare, and the Social Insurance Institution, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of FinData (https://www.findata.fi/en/).

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Figure 1. Associations between occasional use of psychotropic medications (one prescription) between 2013 and 2016, and type of hormonal contraceptives used in 2017. Panel A: antipsychotics; Panel B: anxiolytics; Panel C: hypnotics/sedatives; Panel D: antidepressants. Results are from multinomial logistic regression models among HC users. Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017. Reference category: G03AA, progestogens and estrogens, fixed combinations for systemic use –including monophasic combined oral contraceptives and transdermal patch. G02BA: intrauterine device with progestogen; G02BB: vaginal ring with progestogen and estrogen; G03AB: progestogens and estrogens, sequential preparations for systemic use; G03AC: progestogens for systemic use; G03HB01: cyproterone and estrogen.

Figure 2. Associations between regular use of psychotropic medications (two or more prescriptions) between 2013 and 2016, and type of hormonal contraceptives used in 2017. Panel A: antipsychotics; Panel B: anxiolytics; Panel C: hypnotics/sedatives; Panel D: antidepressants. Results are from multinomial logistic regression models among HC users. Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017. Reference category: G03AA, progestogens and estrogens, fixed combinations for systemic use –including monophasic combined oral contraceptives and transdermal patch. G02BA: intrauterine device with progestogen; G02BB: vaginal ring with progestogen and estrogen; G03AB: progestogens and estrogens, sequential preparations for systemic use; G03AC: progestogens for systemic use; G03HB01: cyproterone and estrogen.

Supplementary Figure 1. Proportions of different types of HC used in Finland in 2017.

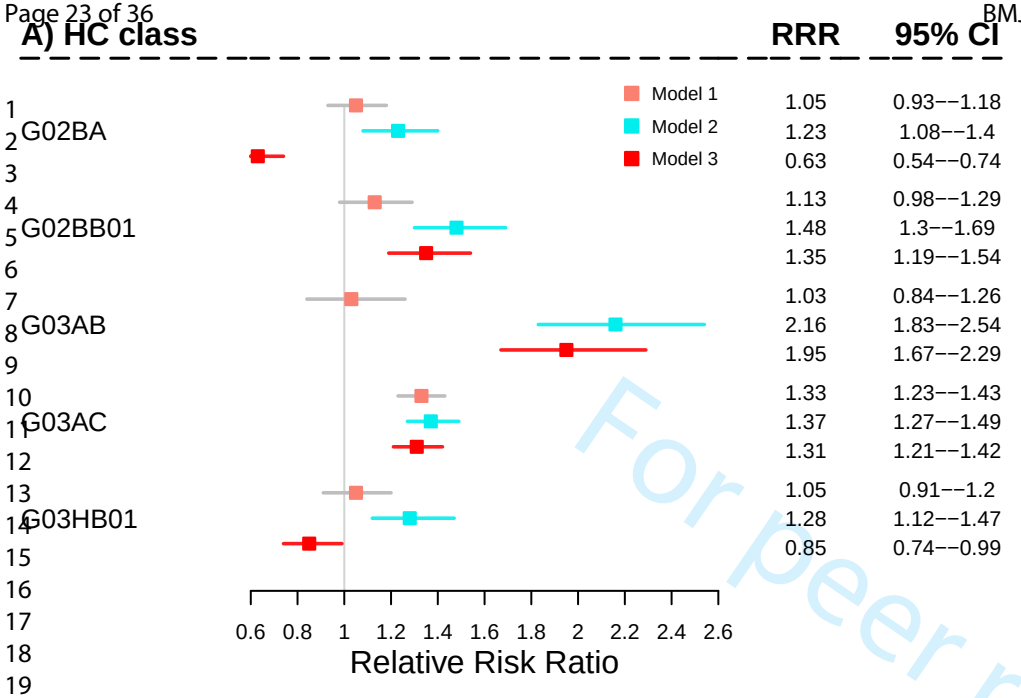
Supplementary Figure 2. Associations between one or more prescriptions of psychotropic medications and use of hormonal contraception in 2017, stratified by age group.

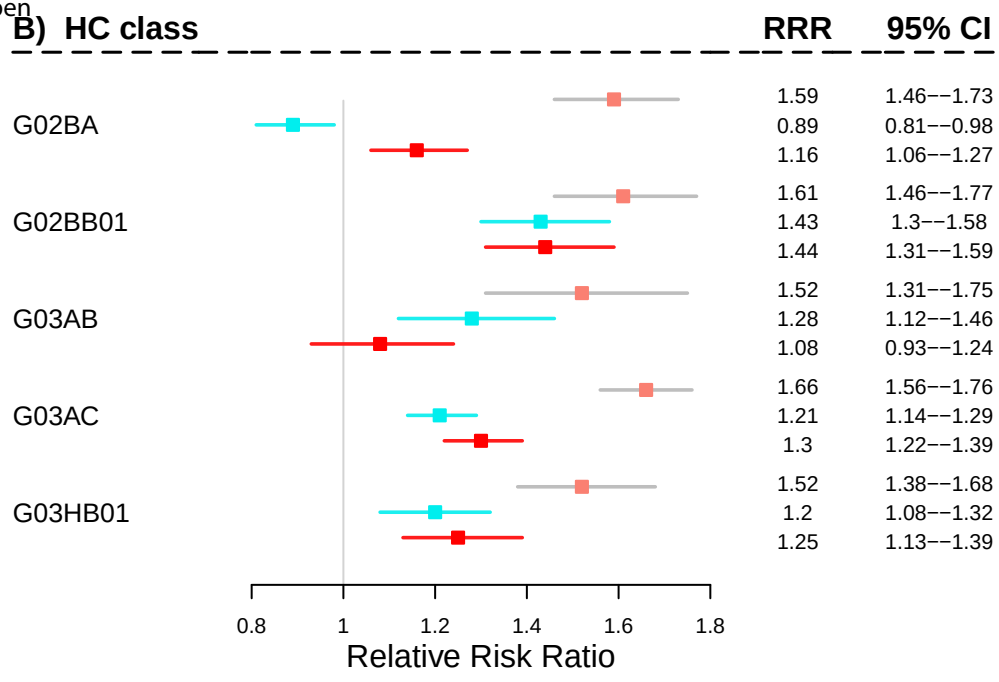
Supplementary Figure 3. Proportions of HC use among women using and not using different classes of psychotropic medications in 2017, by age group.

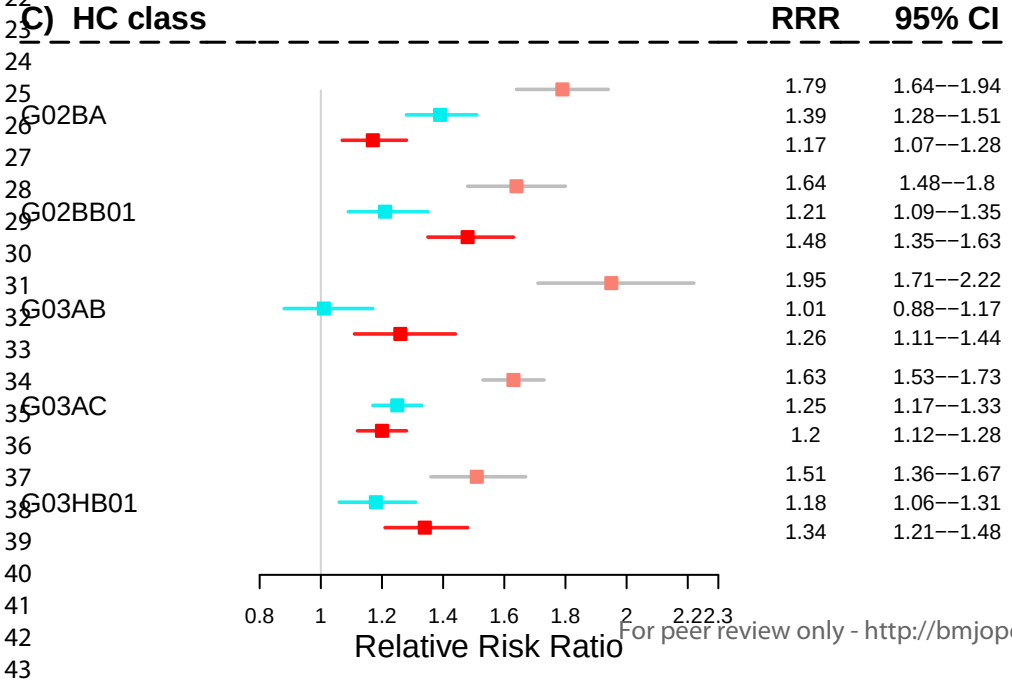
Supplementary Figure 4. Associations between occasional (one prescription) or regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016, and hormonal contraception use in 2017, stratified by age group.

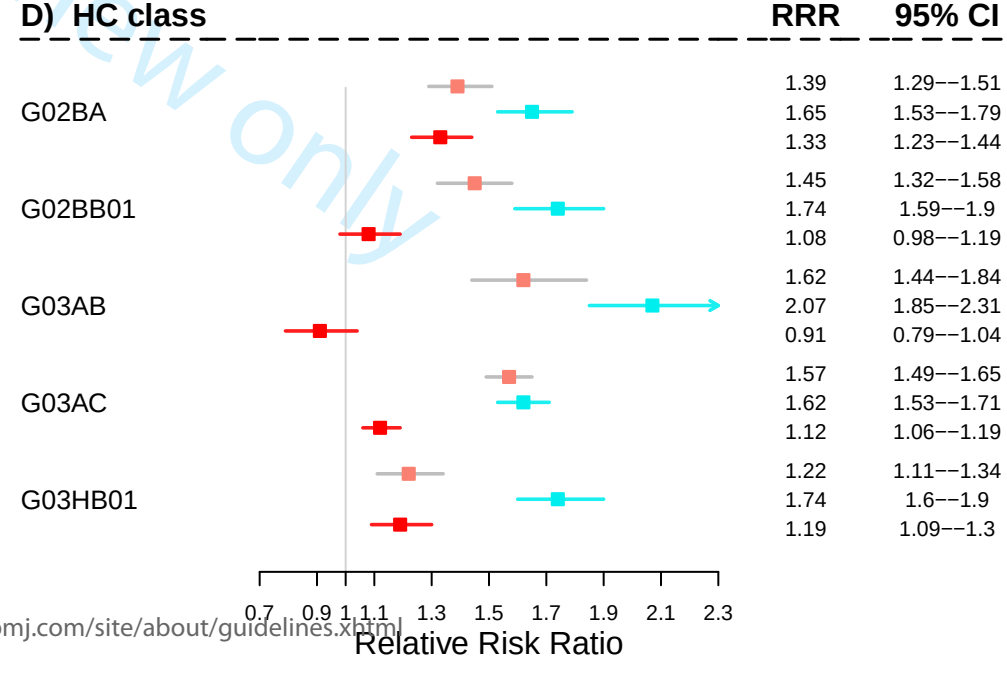
Supplementary Figure 5. Proportions of HC use in 2017 among women with no, occasional (one prescription) and regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016.

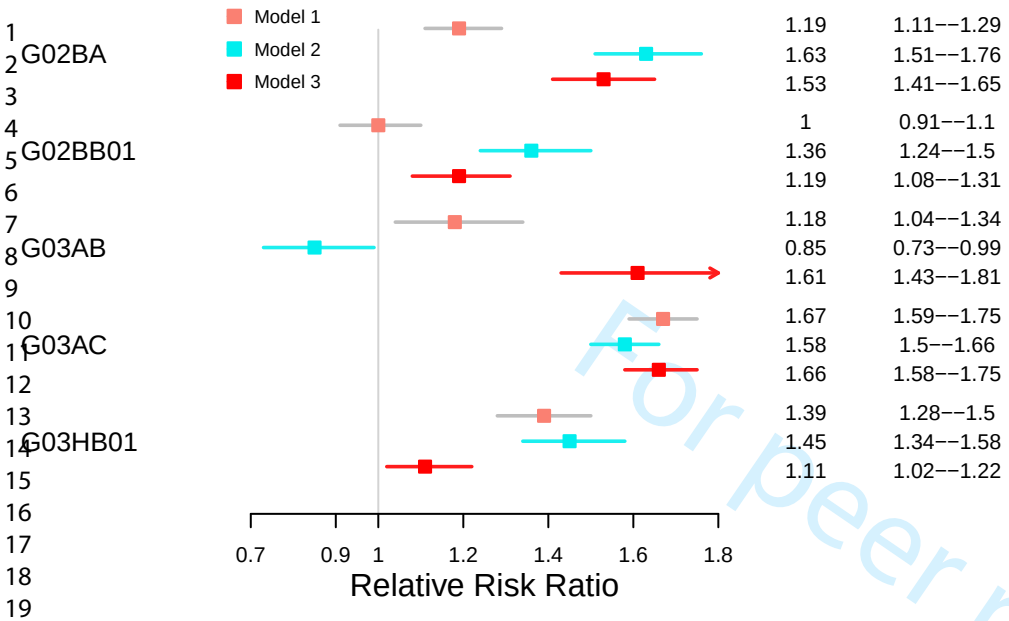
Supplementary Figure 6. Proportions of types of hormonal contraceptives used in 2017 by women with occasional (one prescription) and regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016.

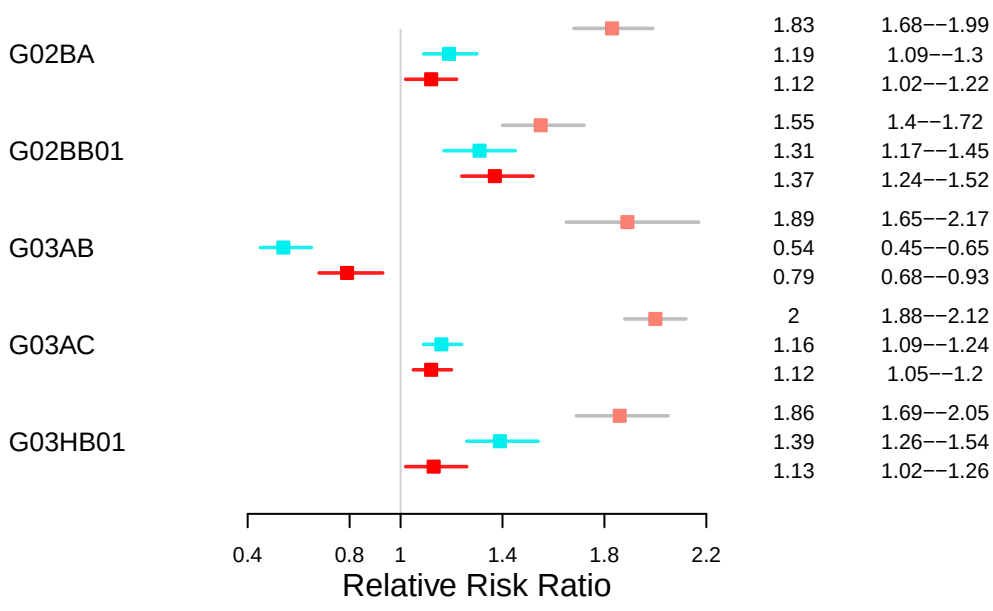


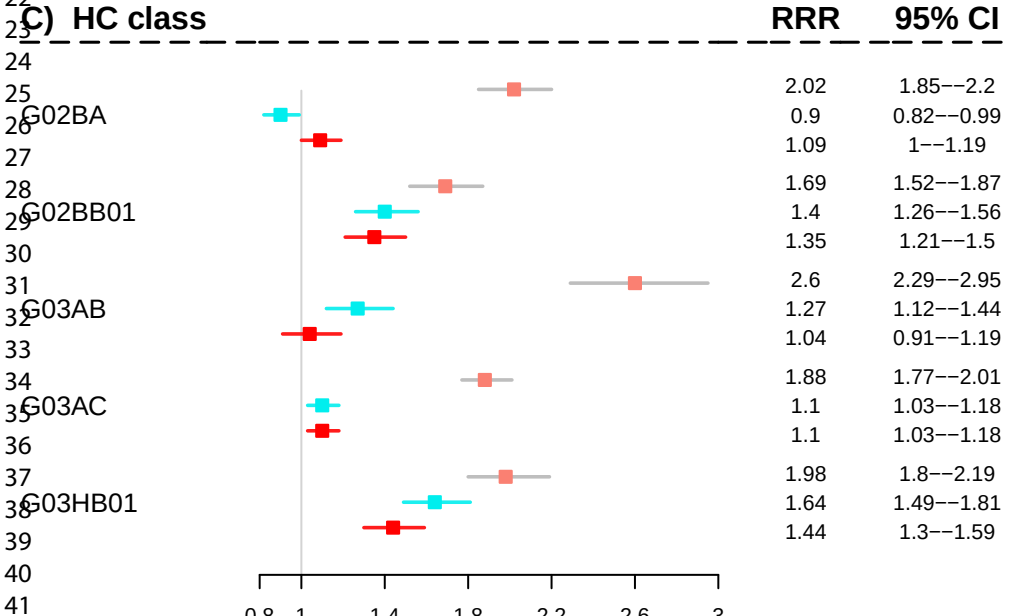


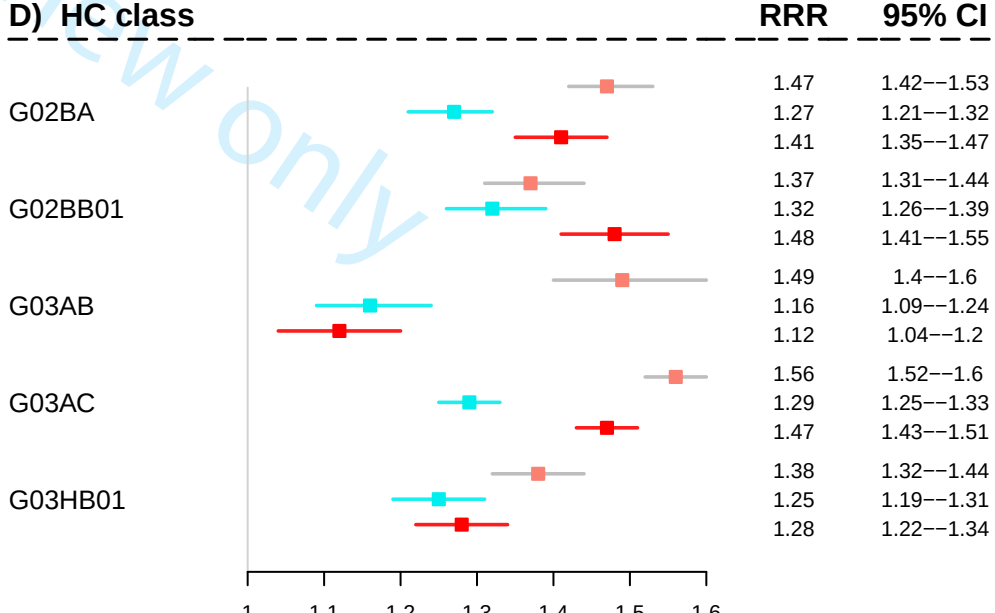


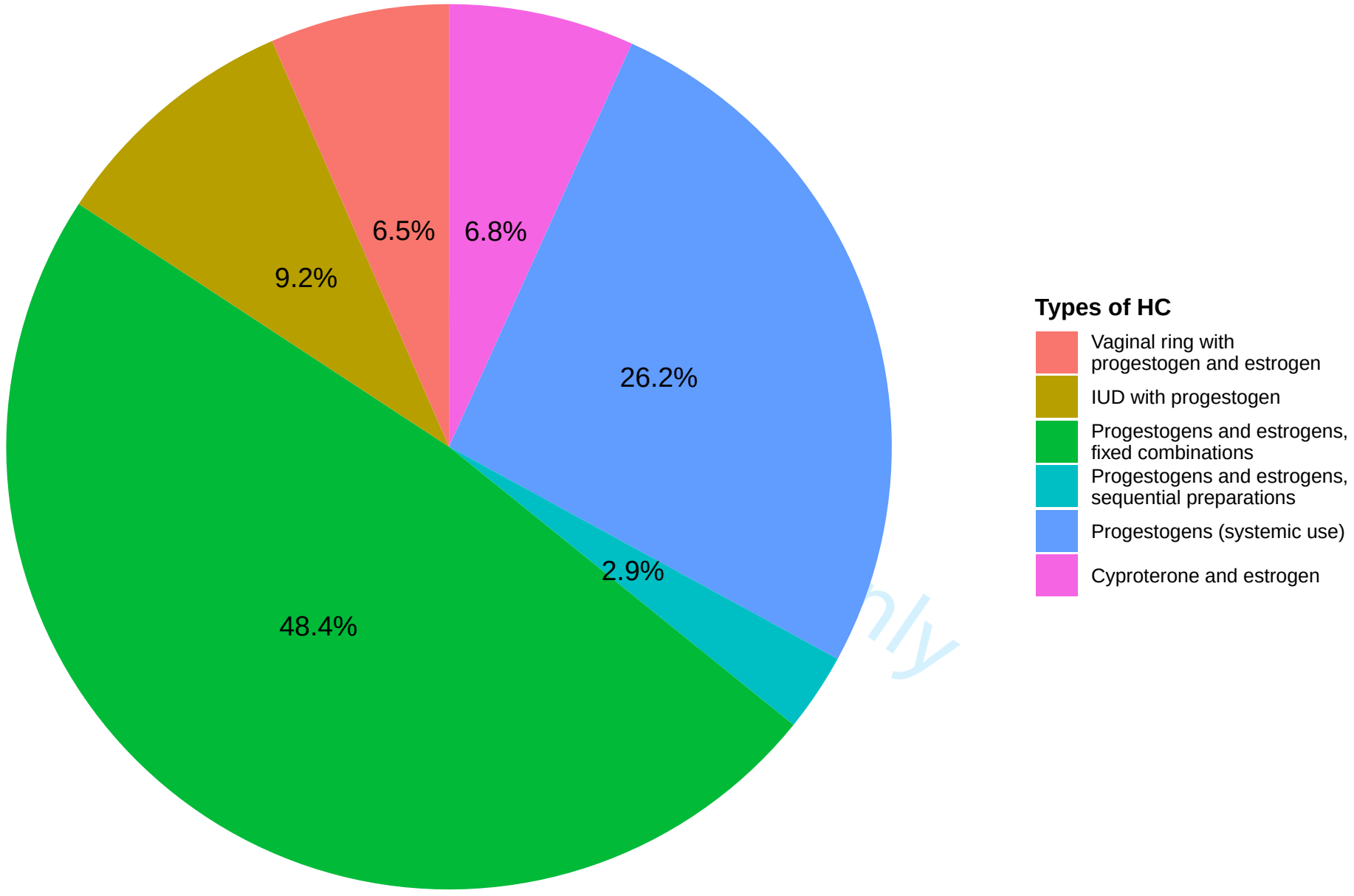


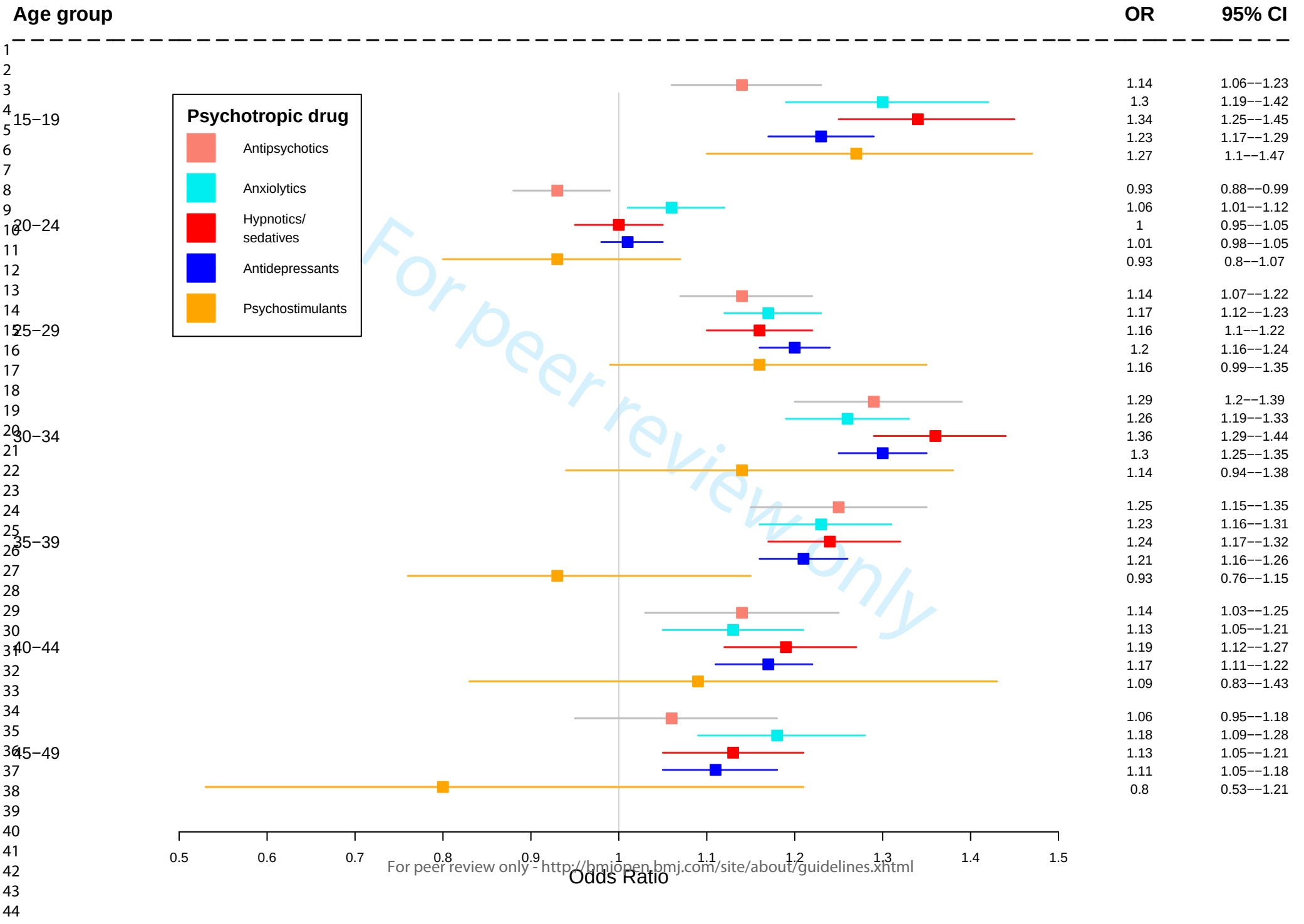


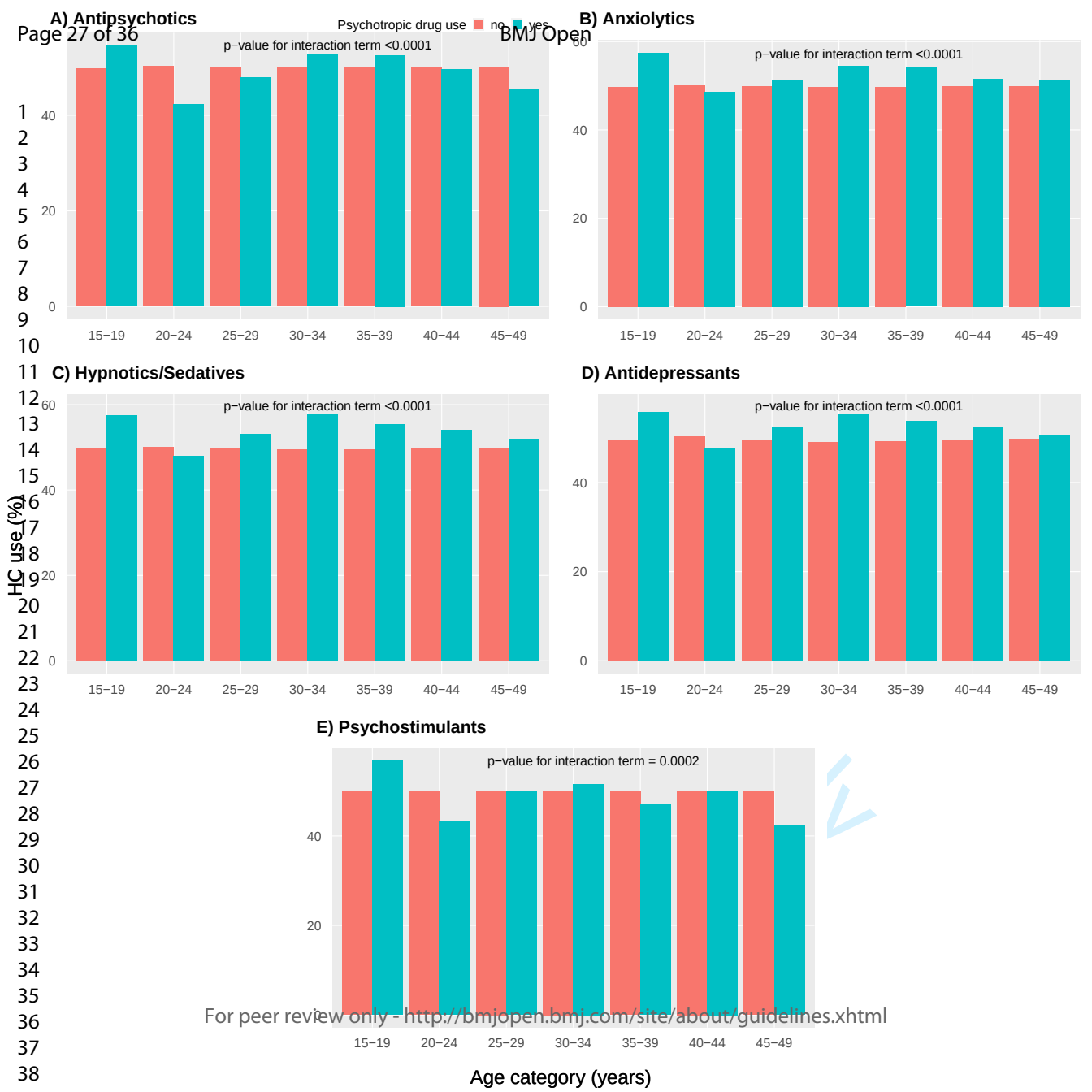


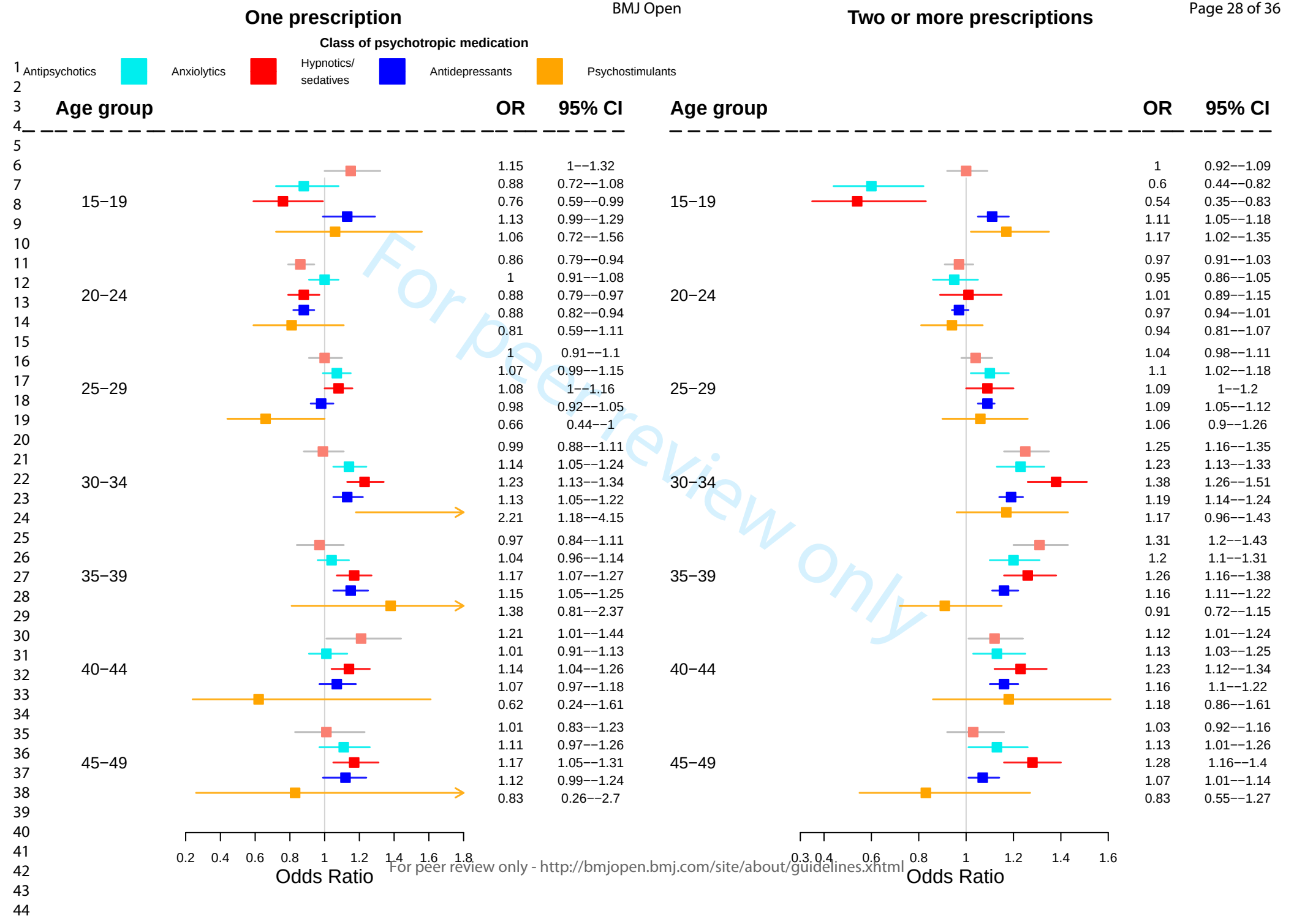


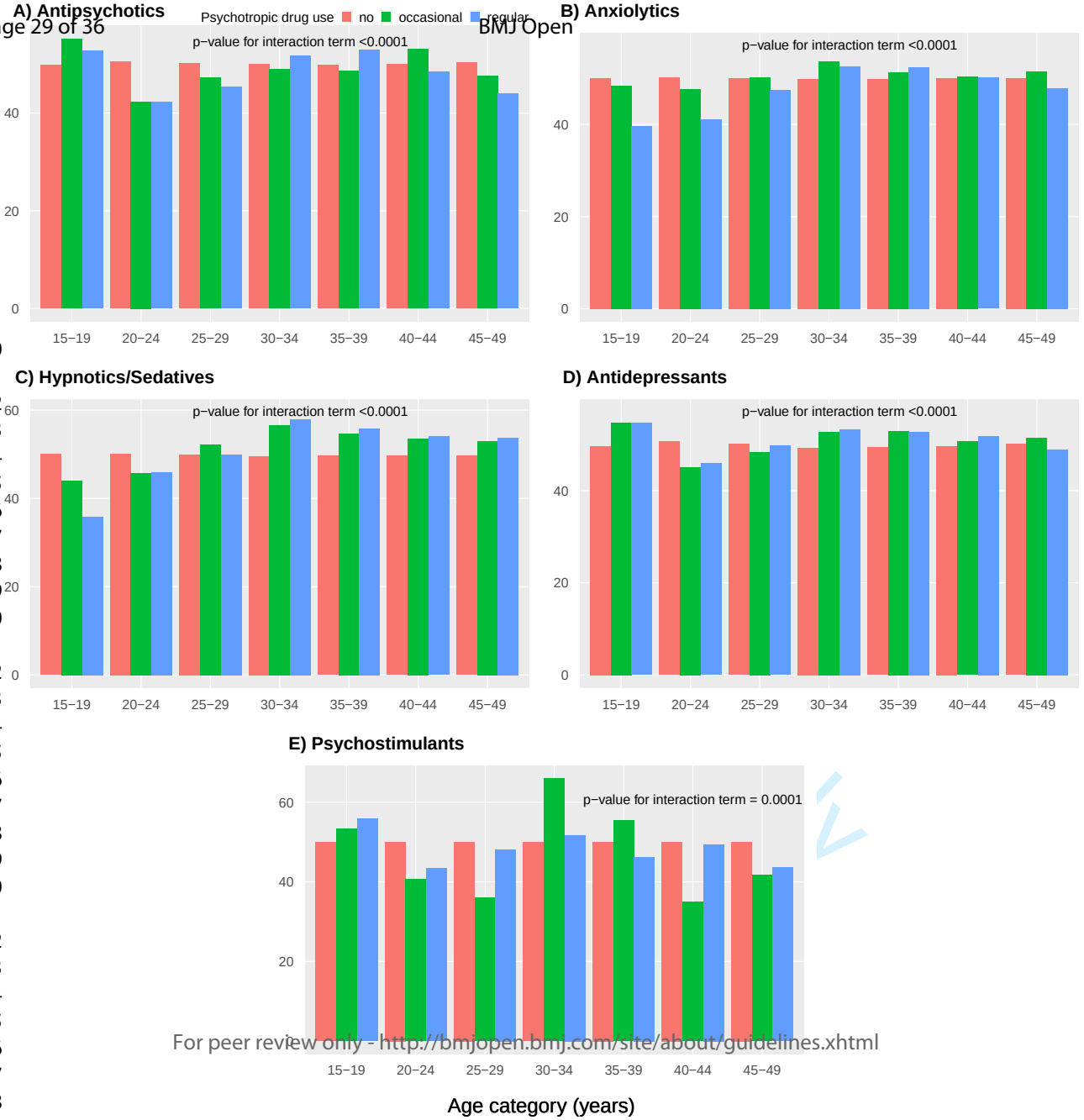


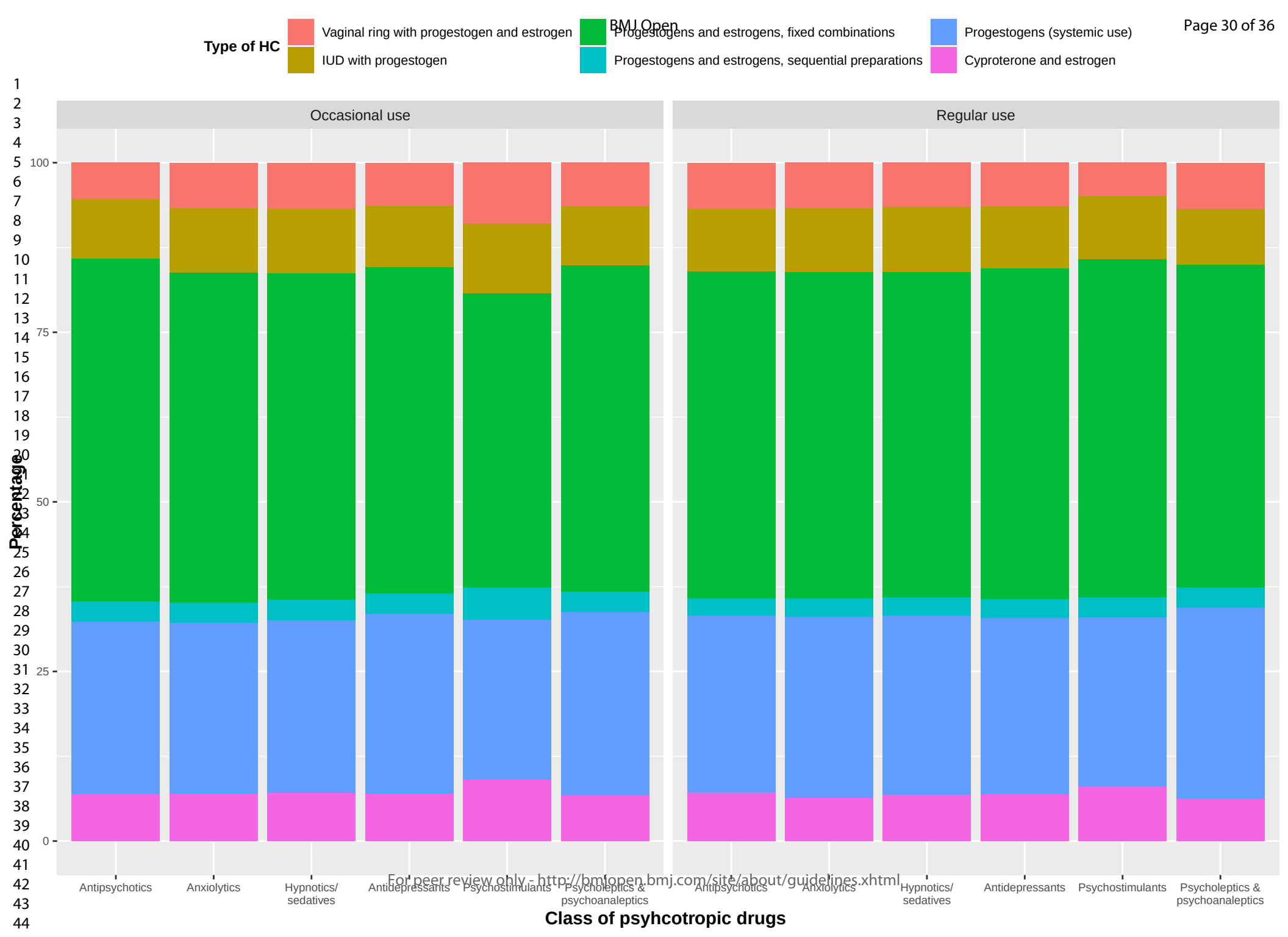












Supplementary Table 1. Associations between levels of use of psychotropic medications (based on quantiles of redeemed DDD) between 2013 and 2016, and HC use in 2017.

Class of psychotropic medication	Level of use*	Model 1			Model 2			Model 3			Model 4		
		OR	95% CI	*p*-value	OR	95% CI	p-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Antipsychotics	Low	0.95	0.91 to 0.99	0.0056	1.00	0.96 to 1.04	0.975	1.01	0.97 to 1.05	0.740	1.00	0.96 to 1.04	0.916
	Intermediate	0.92	0.88 to 0.96	0.0001	0.99	0.95 to 1.04	0.714	1.03	0.99 to 1.08	0.158	1.03	0.99 to 1.08	0.176
	High	0.83	0.79 to 0.86	<0.0001	0.90	0.87 to 0.94	<0.0001	1.06	1.02 to 1.10	0.0050	1.06	1.01 to 1.11	0.0090
Anxiolytics	Low	1.04	1.00 to 1.09	0.0418	1.05	1.01 to 1.09	0.0267	1.04	1.00 to 1.09	0.0557	1.03	0.99 to 1.08	0.117
	Intermediate	1.00	0.96 to 1.04	0.959	1.02	0.98 to 1.07	0.292	1.04	1.00 to 1.09	0.0507	1.04	1.00 to 1.09	0.074
	High	0.93	0.89 to 0.97	0.0008	1.01	0.97 to 1.06	0.545	1.14	1.09 to 1.19	<0.0001	1.14	1.09 to 1.19	<0.0001
Hypnotics/ sedatives	Low	1.13	1.09 to 1.17	<0.0001	1.11	1.08 to 1.15	<0.0001	1.08	1.05 to 1.12	<0.0001	1.08	1.04 to 1.12	<0.0001
	High	1.16	1.12 to 1.20	<0.0001	1.16	1.12 to 1.21	<0.0001	1.20	1.15 to 1.24	<0.0001	1.21	1.16 to 1.25	<0.0001
Antidepressants	Low	1.00	0.98 to 1.02	0.9113	1.03	1.01 to 1.05	0.0168	1.02	1.00 to 1.05	0.084	1.02	1.00 to 1.05	0.098
	Intermediate	1.02	1.00 to 1.05	0.0543	1.05	1.03 to 1.08	0.0001	1.06	1.04 to 1.09	<0.0001	1.06	1.04 to 1.09	<0.0001
	High	1.02	1.00 to 1.05	0.0772	1.04	1.02 to 1.07	0.0014	1.10	1.08 to 1.13	<0.0001	1.10	1.08 to 1.13	<0.0001
Psychostimulants	Low	0.88	0.79 to 0.98	0.019	0.94	0.84 to 1.05	0.261	0.96	0.86 to 1.07	0.415	0.95	0.85 to 1.06	0.394
	Intermediate	0.92	0.82 to 1.03	0.151	0.98	0.88 to 1.11	0.790	1.00	0.89 to 1.13	0.972	1.00	0.89 to 1.12	0.956
	High	1.03	0.92 to 1.15	0.674	1.11	0.99 to 1.24	0.071	1.13	1.00 to 1.26	0.043	1.12	1.00 to 1.26	0.046
Psycholeptics and psychoanaleptics	Low	1.22	1.10 to 1.36	0.0001	1.21	1.09 to 1.34	0.0004	1.19	1.07 to 1.32	0.0011	1.20	1.08 to 1.33	0.0010
	High	1.27	1.14-1.42	<0.0003	1.29	1.15 to 1.44	<0.0001	1.33	1.19 to 1.49	<0.0001	1.34	1.19 to 1.50	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017). DDD, defined daily dose; HC, hormonal contraception.

* Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination.

Supplementary Table 2. Multinomial logistic regression models among HC users, showing the associations between levels of use of psychotropic medications (based on quantiles of redeemed DDD) between 2013 and 2016, and type of HC used in 2017.

Class of HC*	Level of use†	Model 1			Model 2			Model 3		
		RRR	95% CI	p-value	RRR	95% CI	p-value	RRR	95% CI	p-value
	Antipsychotics									
G02BA IUD with progestogen	Low	0.94	0.85 to 1.04	0.238	0.94	0.84 to 1.04	0.204	1.03	0.94 to 0.13	0.543
	Intermediate	1.18	1.05 to 1.31	0.0045	1.01	1.91 to 1.13	0.847	1.25	1.12 to 1.40	0.0001
	High	1.45	1.30 to 1.61	<0.0001	1.14	1.02 to 1.27	0.021	1.92	1.73 to 2.12	<0.0001
G02BB01 vaginal ring with progestogen and estrogen	Low	1.04	0.92 to 1.16	0.557	0.92	0.82 to 1.04	0.185	0.92	0.82 to 1.03	0.155
	Intermediate	1.08	0.95 to 1.24	0.247	1.27	1.13 to 1.42	0.0001	1.02	0.89 to 1.17	0.790
	High	0.99	0.85 to 1.14	0.838	0.90	0.78 to 1.03	0.112	1.92	1.71 to 2.15	<0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	0.92	0.77 to 1.10	0.364	1.14	0.98 to 1.32	0.086	1.03	0.88 to 1.19	0.730
	Intermediate	1.24	1.03 to 1.49	0.023	0.88	0.73 to 1.06	0.187	0.27	0.19 to 0.38	<0.0001
	High	1.35	1.12 to 1.62	0.0016	1.03	0.87 to 1.22	0.762	0.93	0.75 to 1.15	0.487
G03AC Progestogens (systemic use)	Low	1.30	1.22 to 1.38	<0.0001	1.00	0.94 to 1.07	0.960	0.70	0.65 to 0.76	<0.0001
	Intermediate	1.46	1.36 to 1.57	<0.0001	0.96	0.89 to 1.04	0.341	1.58	1.48 to 1.70	<0.0001
	High	2.10	1.96 to 2.25	<0.0001	0.78	0.72 to 0.85	<0.0001	1.19	1.10 to 1.29	<0.0001
G03HB01 cyproterone and estrogen	Low	1.07	0.96 to 1.20	0.239	1.12	1.00 to 1.25	0.048	1.10	0.99 to 1.22	0.067
	Intermediate	1.37	1.22 to 1.54	<0.0001	0.86	0.75 to 0.98	0.028	1.43	1.28 to 1.61	<0.0001
	High	1.52	1.35 to 1.72	<0.0001	1.02	0.90 to 1.16	0.785	1.80	1.60 to 2.01	<0.0001
	Anxiolytics									
G02BA IUD with progestogen	Low	1.55	1.40 to 1.71	<0.0001	1.34	1.21 to 1.47	<0.001	1.13	1.02 to 1.25	0.018
	Intermediate	1.84	1.66 to 2.04	<0.0001	1.01	0.91 to 1.13	0.855	0.98	0.88 to 1.10	0.739
	High	1.75	1.56 to 1.96	<0.0001	0.74	0.65 to 0.84	<0.0001	1.13	1.02 to 1.26	0.026
	Low	1.67	1.49 to 1.87	<0.0001	1.41	1.27 to 1.58	<0.0001	0.88	0.78 to 1.01	0.061

G02BB01 vaginal ring with progestogen and estrogen	Intermediate	1.58	1.40 to 1.78	<0.0001	1.00	0.88 to 1.14	0.985	0.82	0.71 to 0.94	0.0042
	High	1.47	1.28 to 1.68	<0.0001	0.97	0.85 to 1.11	0.658	0.75	0.65 to 0.86	0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.34	1.12 to 1.60	0.0014	0.60	0.48 to 0.75	<0.0001	0.86	0.71 to 1.03	0.099
	Intermediate	1.92	1.63 to 2.26	<0.0001	0.86	0.71 to 1.04	0.119	0.99	0.83 to 1.18	0.930
	High	1.93	1.62 to 2.30	<0.0001	0.97	0.80 to 1.17	0.750	0.29	0.21 to 0.40	<0.0001
G03AC Progestogens (systemic use)	Low	1.62	1.51 to 1.74	<0.0001	0.93	0.86 to 1.00	0.065	1.10	1.02 to 1.18	0.0125
	Intermediate	1.75	1.62 to 1.88	<0.0001	1.01	0.94 to 1.09	0.764	1.10	1.02 to 1.18	0.0138
	High	2.16	2.01 to 2.34	<0.0001	0.85	0.78 to 0.92	0.0001	0.86	0.79 to 0.93	0.0001
G03HB01 cyproterone and estrogen	Low	1.42	1.26 to 1.60	<0.0001	1.46	1.32 to 1.63	<0.0001	0.91	0.81 to 1.04	0.156
	Intermediate	1.68	1.49 to 1.89	<0.0001	1.14	1.01 to 1.28	0.0038	0.88	0.78 to 1.01	0.062
	High	2.04	1.81 to 2.30	<0.0001	1.63	1.46 to 1.82	<0.0001	0.62	0.53 to 0.72	<0.0001
	Hypnotics/Sedatives									
G02BA IUD with progestogen	Low	1.70	1.56 to 1.85	<0.0001	0.88	0.80 to 0.97	0.010	0.70	0.64 to 0.78	<0.0001
	High	2.14	1.96 to 2.33	<0.0001	1.54	1.41 to 1.67	<0.0001	0.88	0.79 to 0.97	0.012
G02BB01 vaginal ring with progestogen and estrogen	Low	1.63	1.48 to 1.79	<0.0001	1.11	1.00 to 1.22	0.0514	1.16	1.06 to 1.28	0.0020
	High	1.70	1.52 to 1.89	<0.0001	1.00	0.89 to 1.12	0.948	1.55	1.41 to 1.71	<0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.89	1.66 to 2.16	<0.0001	0.76	0.65 to 0.89	0.0008	1.27	1.12 to 1.45	0.0004
	High	2.69	2.37 to 3.06	<0.0001	1.27	1.10 to 1.46	0.0011	0.95	0.80 to 1.12	0.523
G03AC Progestogens (systemic use)	Low	1.60	1.51 to 1.70	<0.0001	1.07	1.01 to 1.14	0.0329	0.79	0.74 to 0.84	<0.0001
	High	1.93	1.81 to 2.06	<0.0001	1.06	0.99 to 1.13	0.093	1.35	1.27 to 1.44	0.007
G03HB01 cyproterone and estrogen	Low	1.48	1.34 to 1.64	<0.0001	1.10	1.00 to 1.22	0.060	0.93	0.84 to 1.03	0.138
	High	2.03	1.84 to 2.24	<0.0001	1.41	1.28 to 1.56	<0.0001	1.06	0.95 to 1.19	0.282
	Antidepressants									
G02BA IUD with progestogen	Low	1.30	1.23 to 1.39	<0.0001	0.95	0.89 to 1.01	0.085	0.88	0.82 to 0.94	0.0001
	Intermediate	1.37	1.29 to 1.46	<0.0001	1.29	1.22 to 1.36	<0.0001	0.95	0.89 to 1.01	0.089

	High	1.73	1.63 to 1.83	<0.0001	0.76	0.71 to 0.81	<0.0001	0.89	0.84 to 0.95	0.0005
G02BB01 vaginal ring with progestogen and estrogen	Low	1.40	1.31 to 1.50	<0.0001	0.89	0.83 to 0.96	0.0223	1.06	0.99 to 1.13	0.121
	Intermediate	1.31	1.22 to 1.40	<0.0001	1.00	0.93 to 1.07	0.919	1.06	0.99 to 1.14	0.102
	High	1.45	1.36 to 1.56	<0.0001	1.16	1.09 to 1.24	<0.0001	0.95	0.88 to 1.02	0.132
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.46	1.33 to 1.61	<0.0001	1.00	0.91 to 1.11	0.933	1.02	0.93 to 1.13	0.664
	Intermediate	1.38	1.25 to 1.52	<0.0001	0.79	0.71 to 0.88	<0.0001	0.90	0.81 to 0.99	0.0381
	High	1.74	1.58 to 1.91	<0.0001	0.98	0.89 to 1.09	0.738	0.95	0.85 to 1.05	0.268
G03AC Progestogens (systemic use)	Low	1.49	1.44 to 1.56	<0.0001	1.00	0.96 to 1.04	0.887	0.98	0.94 to 1.02	0.387
	Intermediate	1.42	1.37 to 1.48	<0.0001	1.02	0.98 to 1.07	0.362	1.01	0.97 to 1.06	0.544
	High	1.79	1.72 to 1.87	<0.0001	0.89	0.85 to 0.93	<0.0001	0.90	0.87 to 0.94	<0.0001
G03HB01 cyproterone and estrogen	Low	1.19	1.11 to 1.28	<0.0001	0.98	0.92 to 1.05	0.609	1.00	0.93 to 1.07	0.972
	Intermediate	1.29	1.21 to 1.39	<0.0001	1.24	1.16 to 1.32	<0.0001	0.89	0.82 to 0.95	0.0011
	High	1.59	1.48 to 1.70	<0.0001	0.99	0.92 to 1.06	0.786	1.01	0.94 to 1.08	0.836

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017.

*Reference: G03AA, Progestogens and estrogens, fixed combinations (systemic use).

† Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination.

DDD, defined daily dose; HC, hormonal contraception; RRR, relative risk ratio.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5,6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6,7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7,12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6-14
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-14
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	14,15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16
Other information			
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	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Associations between use of psychotropic medications and use of hormonal contraception among girls and women aged 15–49 years in Finland - a nationwide, register-based, matched case-control study

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Abstract

Objectives. The relationship between use of contraception and of psychiatric medications is understudied. We examined whether the current and past use of psychotropic medications is associated with the use and type of hormonal contraception (HC).

Design. Nationwide register-based matched case-control study.

Settings. All fertile-aged (15-49 years) girls and women living in Finland in 2017; data from several national registers.

Participants. 294,356 girls and women with a redeemed prescription of HC in 2017, and their same-sized control group of non-users (n=294,356) identified through the Prescription Centre.

Main outcome measures. Associations between the use of psychotropic medications and the use of HC, and the type of HC tested in logistic regression models.

Results. Altogether 19.5% of the HC users, and 18% of the HC non-users received at least one prescription for a psychotropic medication in 2017. Among HC users, the proportions of occasional and regular users of psychotropic medications in 2013–2016 were 4.5% and 14.8%, while among HC non-users the respective figures were 4.3% and 14.6%. In multivariable logistic regression models both use of psychotropic medications in 2017, and their occasional or regular use between 2013–2016 were associated with higher odds of HC use, although with small to very small effect sizes (ORs between 1.37 and 1.06, 95% confidence intervals 1.22 to 1.53, and 1.03 to 1.09, respectively). After adjustment for covariates, when fixed combinations of progestogens and estrogens for systemic use was the reference category, women using almost any class of psychotropic medications had higher odds of using other types of HC.

Conclusions. Fertile-aged girls and women with current and past use of psychotropic medications have higher odds of using HC, with a specific pattern in the type of contraceptives used. Further research is warranted to examine whether our observations indicate a reduction of unwanted pregnancies in women with psychiatric disorders.

Keywords: women, fertile-age, hormonal contraception, psychotropic medication.

ARTICLE SUMMARY

Strengths and limitations of this study

- The studied population is highly representative of all fertile-aged women in Finland.
- The combination of a cross-sectional and longitudinal retrospective design provides stability to psychiatric prescriptions as predictor of interest.
- Levels of use of psychotropic medications were determined through different approaches.
- Women suffering from and seeking help for their psychiatric disorders, and thus receiving a pharmacological treatment, represent a more conscious and healthy subgroup of this population.
- Misclassification of both psychiatric disorders and HC use as based on drug prescription cannot be ruled out; additionally, because of the observational nature of the data, causality cannot be determined in the associations identified.

INTRODUCTION

The relationship between the use of hormonal contraception (HC) and women's mental health continues to be debated.[1] While ample evidence has been provided showing no associations between the use of contraception and the increased risk of depressive or anxiety disorders,[1-3] findings from recent studies are challenging this view. Recent observations report that women using HC (especially oral contraceptives, OC) have higher odds of depression,[4] and of suicidal behavior,[5,6] with a long-term risk of depression later in adulthood for those who started their OC use during adolescence.[7]

However, while these findings indicate a link between contraceptive use and mental health status, the reverse association is likewise plausible and of public health and clinical relevance. Women suffering from psychiatric disorders seem to have higher risk of unplanned pregnancy and induced abortion, as well as risky sexual behavior including non-use or inconsistent use of contraception,[8-10] or use of less effective contraceptive methods.[11,12] For instance, among teenagers and young women, those with baseline depressive and stress symptoms had higher odds of reporting mood changes, of OC discontinuation, and of inconsistent use of contraception.[13,14] It has been hypothesized that a subgroup of women may be more sensitive to hormonal fluctuations, and thus more prone to develop mood symptoms or disorders in relation to reproductive events (e.g., the premenstrual phase, the postpartum, or the perimenopause),[15] as well as while on contraception.[16] Consequently, women with mental health problems, either because they are more likely to experience mood side effects of HC or to consider their perceived mood changes as caused by HC, are also more likely to discontinue contraception use. In line with these observations, we previously found that a recent care episode for a psychiatric disorder was associated with lower odds of HC use among almost 600,000 women aged 15-49 years in Finland.[17] The study used register records with a psychiatric discharge diagnosis in 2016, thus including only the most severe cases of psychiatric disorders. However, because mild and moderate mental disorders not requiring hospitalization are highly prevalent in the population, the overall relationship between mental health and HC use remains largely unknown. Thus, the aim of this study was to explore the associations between the current and previous prescriptions of psychotropic medications, and HC use in 2017, in a population inclusive of all fertile-aged women using HC in Finland, and their reference group of non-users. A further aim was to test whether the use of psychotropic medications was associated with the type of HC used.

METHODS

This work is part of a larger register-based study on HC in Finland, described in detail elsewhere.[17] Briefly, the population was selected on the basis of the unique personal identification number given

at birth or at immigration to each person permanently residing in Finland. The group of HC users, selected from the Prescription Centre in the Kanta Services,[18] included all fertile-aged girls and women (15–49 years) with at least one redeemed prescription for HC in 2017 (n=294,445). The same-sized control group of HC non-users included women, matched by age and municipality of residence, with no redeemed HC prescriptions in 2017. Altogether 89 women who received a prescription with Anatomical Therapeutic Chemical (ATC) code "G03AD" (i.e., emergency contraception, which is usually available without prescription in Finland), and their matched controls, were excluded, leaving a final population of 588,712 women. As such, the study population included 52% of all fertile-aged girls and women living in Finland in 2017. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Helsinki (3/2018). Because this is a register-based study, no individual consent is needed.

The registers

Information on redeemed medications for each person living in Finland is stored in the Prescription Centre, a centralized database in the Kanta Services. The recorded data include, among others, the product ATC code, date of prescription and of purchase, and the redeemed amount in defined daily dose (DDD). In addition to selection of the study population, the Prescription Centre was used to gather information on redeemed prescriptions for psychotropic medications between 2013 and 2017 for all the study members. Use of psychotropic medications in 2017 was defined as one or more redeemed prescriptions in the same year. Users of psychotropic medications between 2013 and 2016 were divided into occasional and regular users, defined as women with only one vs. two or more redeemed prescriptions of the same class drug.

The examined HC types included intrauterine device (IUD) with progestogen (i.e., the levonorgestrel-releasing intrauterine system, LNG-IUS, ATC code G02BA); vaginal ring with progestogen and estrogen (G02BB); progestogens and estrogens, fixed combinations – including monophasic combined OCs and transdermal patch (G03AA); progestogens and estrogens, sequential preparations for systemic use (G03AB); progestogens for systemic use (G03AC); and cyproterone and estrogen (G03HB01). Psychotropic medications included antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A), psychostimulants (N06B), psycholeptics and psychoanaleptics in combination (N06C).

The Population Register Centre contains basic information of all Finnish citizens and foreign citizens residing permanently in Finland. From this register we obtained information on age, municipality of residence, civil status, socioeconomic group, highest level of education, and annual income of all the study members on 31 December 2017.

The Medical Birth Register includes data on all live births and stillbirths in Finland since 1987; the Register of Induced Abortions contains data on induced abortions since 1983, and the Register of Sterilizations on all sterilizations since 1987. Based on these registers, we gathered information on pregnancies with birth dates in 2016 and 2017, induced abortions performed in 2016 and 2017, and sterilizations between 1987 and 2016.

The Care Register of Health Care, which includes data on inpatient care in hospitals, health centers, day surgeries and specialized outpatient care, was used to identify women who had received a psychiatric diagnosis (International Classification of Diseases, 10th Revision codes F10–F19 -substance abuse-, F30–F39 -mood disorders-, F40–F48 -anxiety disorders-, F50 -eating disorders- and F60 -personality disorders-) between 2013 and 2016.

Statistical analyses

The frequency of use of each class of psychotropic medications among HC users and non-users was compared via chi-squared test. We assessed the percentages of women using each type of HC within users of categories of psychotropic medications. Women with redeemed prescriptions of two or more different types of HC in 2017 were classified on the basis of their first redeemed prescription.

Associations between use of each class of psychotropic medications and HC use were tested via univariable (BL-Model 1) and multivariable binary logistic regression models using the "gnm" R-package,[19] which, through the argument "eliminate", allows for handling parameters of stratification factors with a large number of levels (in our case, "municipality of residence"). Separate models were conducted to test the associations with the use of psychotropic medications in 2017, and with occasional or regular use from 2013 to 2016. Multivariable models were progressively adjusted for age group, marital status and education level (BL-Model 2), socioeconomic status and income level (BL-Model 3), and reproductive characteristics (pregnancies in 2017, induced abortions in 2016–2017, and sterilization before 2017) (BL-Model 4). A separate fully adjusted model further tested the interaction between age and use of psychotropic medications; if there was a significant interaction, age-stratified multivariable analyses were performed.

To further confirm the results and take into account a potential "healthcare user bias", sensitivity analyses were conducted utilizing the purchased amount in DDD as indicator of use of psychiatric medications between 2013 and 2016. To this end, the total purchased DDD for each class was divided into tertiles, and groups of low, intermediate and high-level users were created accordingly. Because of the data distribution with duplicate values, only two groups were created for high and low level

users of hypnotics/sedatives (cut off at the 50th percentile), and of psycholeptics and psychoanaleptics in combination (cut off at the 60th percentile).

We further examined whether the odds of using distinct types of HC in 2017 differed by occasional or regular use of psychotropic medications between 2013 and 2016. To this end, we conducted univariable (ML-Model 1) and multivariable multinomial logistic regression models among HC users, controlling for age, marital and socioeconomic status, education and income levels (ML-Model 2), and reproductive characteristics (pregnancies or induced abortions in 2016–2017) (ML-Model 3). Because of the relatively small number of women using psychostimulants or psycholeptics and psychoanaleptics in combination, these classes were excluded from these analyses. Sensitivity analyses were additionally performed utilizing groups of users based on the purchased DDD, as described above.

For all the analyses, the two-tailed *p*-values of <0.05 were considered statistically significant. All the analyses were performed with R software version 3.5.1.[20]

Patient and public involvement

Patients and the public were not directly involved in the research process.

RESULTS

A quarter (25.6%, n=294,356) of all fertile-aged girls and women in Finland were using HC in 2017. Their characteristics as well as those of the control women (n=294,356) are described in detail elsewhere.[17] The proportions of different utilized HC types are illustrated in Supplementary Figure 1.

Use of psychotropic medications in 2017

Altogether 110,112 (18.7%) women had redeemed at least one prescription of a psychotropic medication in 2017; of them, 52% (n=57,478) used also HC. The proportions of women using and not using HC who also had one or more prescriptions of psychotropic medications by ATC codes are reported in Table 1.

In univariable logistic regression models the use of psychotropic medications in 2017 was associated with higher odds of HC use (ORs: any medication=1.12; anxiolytics=1.10; hypnotics/sedatives=1.17; antidepressants=1.11; psycholeptics and psychoanaleptics in combination=1.30, $p<0.0001$). The associations remained after controlling for age group, education and income levels, marital and socioeconomic status, and reproductive characteristics. Additionally, in partially and fully adjusted

models, the use of antipsychotics was also associated with higher odds of being a HC user (ORs=1.10 to 1.09, $p<0.0001$) (Table 2).

There was a significant interaction between age and a recent prescription of psychotropic medications, except for psycholeptics and psychoanaleptics in combination. Regardless of the type of medication, the proportions of HC users among those with a recent psychotropic prescription were consistently higher especially in teenagers but lower in the young age group (20–24 years) as compared to non-users. Among those with a recent psychiatric prescription, the highest rates of using HC were seen for teenagers (varying from 54.6% for antipsychotics to 55.8% for antidepressants, and 57.5% for anxiolytics and sedatives/hypnotics) (Supplementary Figures 2 and 3).

Table 1. Proportions of HC users and non-users receiving one or more prescriptions for psychotropic medications in 2017.

Class of psychotropic medication ATC code, class	**HC users**	**HC non-users**	***p*-value**
Any psychotropic medication	57,478 (19.5%)	52,634 (17.9%)	<0.0001
N05A, antipsychotics	11,136 (3.8%)	11,688 (4.0%)	0.0002
N05B, anxiolytics	17,181 (5.8%)	15,744 (5.4%)	<0.0001
N05C, hypnotics/sedatives	17,829 (6.1%)	15,397 (5.2%)	<0.0001
N06A, antidepressants	40,488 (13.8%)	37,028 (12.6%)	<0.0001
N06B, psychostimulants	1,681 (0.57%)	1,715 (0.58%)	0.570
N06C, psycholeptics and psychoanaleptics (amitriptyline) in combination	1,237 (0.4%)	952 (0.3%)	<0.0001

ATC, Anatomical Therapeutic Chemical; HC, hormonal contraception

Table 2. Associations between prescriptions of psychotropic medications in 2017 and HC use in 2017.

Psychotropic medication.	Model 1			Model 2			Model 3			Model 4		
ATC code, class	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Any psychotropic medication	1.12	1.10 to 1.13	<0.0001	1.15	1.13 to 1.16	<0.0001	1.16	1.14 to 1.17	<0.0001	1.15	1.13 to 1.17	<0.0001
N05A, antipsychotics	0.95	0.93 to 0.98	0.00019	1.02	0.99 to 1.05	0.212	1.10	1.07 to 1.13	<0.0001	1.09	1.06 to 1.12	<0.0001
N05B, anxiolytics	1.10	1.07 to 1.12	<0.0001	1.14	1.12 to 1.17	<0.0001	1.16	1.14 to 1.19	<0.0001	1.16	1.14 to 1.19	<0.0001
N05C, hypnotics/ sedatives	1.17	1.14 to 1.20	<0.0001	1.19	1.16 to 1.21	<0.0001	1.18	1.15 to 1.20	<0.0001	1.17	1.14 to 1.20	<0.0001
N06A, antidepressants	1.11	1.09 to 1.13	<0.0001	1.14	1.12 to 1.15	<0.0001	1.16	1.14 to 1.17	<0.0001	1.15	1.13 to 1.16	<0.0001
N06B, psychostimulants	0.98	0.92 to 1.05	0.56	1.05	0.98 to 1.13	0.142	1.08	1.00 to 1.15	0.039	1.07	1.00 to 1.15	0.057
N06C, psycholeptics and psychoanaleptics	1.30	1.20 to 1.42	<0.0001	1.31	1.20 to 1.42	<0.0001	1.27	1.17 to 1.39	<0.0001	1.26	1.16 to 1.38	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017).

Use of psychotropic medications between 2013 and 2016

A total of 112,609 women of our study population redeemed at least one prescription of a psychotropic medication between 2013 and 2016; of them, 20.8% (n=23,379) received a psychiatric diagnosis in the same period according to the records in the Care Register of Health Care; conversely, 18.5% (n=5,302) of the 28,681 women with a psychiatric diagnosis between 2013 and 2016 had not redeemed any psychiatric prescriptions.

Approximately 15% of the women (n=86,644) were regular users of psychotropic medications in the period 2013–2016, while 4.4% (n=25,965) received only one psychiatric prescription (Table 3, left side).

Higher odds for using HC were predicted by (occasional and regular) use of hypnotics/sedatives and psycholeptics and psychoanaleptics, and by regular use of antidepressants during 2013–2016 in unadjusted logistic regression models. On the contrary, occasional and regular use of antipsychotics and regular use of anxiolytics were associated with lower odds of HC use (Table 4). After adjustment for covariates occasional use of hypnotics/sedatives and psycholeptics and psychoanaleptics, and regular use of almost all the classes of psychiatric medications predicted belonging to the HC user group, although with small to very small effect sizes (ORs ranging between 1.06 and 1.37).

Sensitivity analyses using quantiles of redeemed DDD as indicator of psychotropic drug use (Table 3, right side) substantially confirmed these findings. Specifically, women with higher use (i.e., belonging to the highest levels of redeemed DDD) of all psychotropic medications had higher odds of using HC compared to women with no redeemed medications (i.e., with a DDD of zero for the respective drug class). Lower use of psychotropic medications was generally not associated with HC use (Supplementary Table 1).

There was a significant age*psychotropic medication interaction in predicting HC use for all the medication classes ($p \leq 0.0001$), with the exception of psycholeptics and psychoanaleptics. In detail, among occasional and regular users of psychotropic medications, the odds of HC use tended to be lower (than in non-users of psychotropic medications) in teenagers and young women (20–29 years), but higher in middle-age women (Supplementary Figures 4 and 5).

Table 3. Proportions of HC users and non-users receiving one or more prescriptions of psychotropic medications between 2013 and 2016, as number of prescriptions (left side) or levels of use (based on quantiles of redeemed DDD) (right side).

Class of psychotropic medication	Number of prescriptions	HC users	HC non-users	*p*-value*	Level of use**	HC users	HC non-users	*p*-value*
Any psychotropic medication				0.0001				
	one prescription	13,269 (4.5%)	12,696 (4.3%)	0.0008	---	---	---	---
	≥ 2 prescriptions	43,572 (14.8%)	43,072 (14.6%)	0.179	---	---	---	---
Antipsychotics				<0.0001				<0.0001
	one prescription	3,867 (1.5%)	4,273 (1.3%)	<0.0001	Low	5,445 (1.85%)	5,709 (1.94%)	0.037
					Intermediate	4,385 (1.49%)	4,734 (1.61%)	0.0008
	≥ 2 prescriptions	10,548 (3.6%)	11,694 (4.0%)	<0.0001	High	4,582 (1.56%)	5,519 (1.88%)	<0.0001
Anxiolytics				0.011				0.0013
	one prescription	6,748 (2.3%)	6,564 (2.2%)	0.222	Low	4,852 (1.65%)	4,650 (1.58%)	0.115
					Intermediate	4,503 (1.53%)	4,506 (1.53%)	2.924
	≥ 2 prescriptions	6,705 (2.3%)	7,001 (2.4%)	0.023	High	4.098 (1.39%)	4,409 (1.50%)	0.0022
Hypnotics/sedatives				<0.0001				<0.0001
	one prescription	6,786 (2.3%)	6,072 (2.1%)	<0.0001	Low	6,865 (2.33%)	6,134 (2.08%)	<0.0001
	≥ 2 prescriptions	6,321 (2.2%)	5,493 (1.9%)	<0.0001	High	6,232 (2.12%)	5,407 (1.84%)	<0.0001
Antidepressants				0.053				0.088
	one prescription	8,395 (2.9%)	8,460 (2.9%)	1.233	Low	14,815 (2.52%)	14,867 (2.53%)	2.288
					Intermediate	14,998 (2.55%)	14,689 (2.50%)	0.219
	≥ 2 prescriptions	36,396 (12.4%)	35,793 (12.2%)	0.050	High	14,978 (2.54%)	14,697 (2.50%)	0.308
Psychostimulants				0.11				0.052
	one prescription	236 (0.08%)	276 (0.09%)	0.154	Low	617 (0.21%)	702 (0.24%)	0.058

	≥ 2 prescriptions	1,604 (0.6%)	1,669 (0.6%)	0.512	Intermediate High	563 (0.19%) 617 (0.21%)	612 (0.21%) 602 (0.21%)	0.459 2.003
Psycholeptics-psychoanaleptics in combination				<0.0001				<0.0001
	one prescription	809 (0.28%)	673 (0.23%)	0.0008	Low	804 (0.27%)	658 (0.22%)	0.0003
	≥ 2 prescriptions	697 (0.24%)	538 (0.18%)	<0.0001	High	702 (0.24%)	553 (0.19%)	<0.0001

ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose; HC, hormonal contraception.

* *p*-values are from overall chi-square tests, and from post hoc pairwise comparisons adjusted for multiple testing

** Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination).

Table 4. Associations between number of prescriptions of psychotropic medications between 2013 and 2016, and HC use in 2017

Class of psychotropic medication	Number of prescriptions	Model 1			Model 2			Model 3			Model 4		
		OR	95% CI	*p*-value	OR	95% CI	p-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Any psychotropic medication	one prescription	1.05	1.02 to 1.08	0.0001	1.06	1.04 to 1.09	<0.0001	1.04	1.01 to 1.06	0.0072	1.03	1.01 to 1.06	0.014
	≥ 2 prescriptions	1.02	1.00 to 1.03	0.0295	1.04	1.03 to 1.06	<0.0001	1.08	1.06 to 1.09	<0.0001	1.07	1.06 to 1.09	<0.0001
Antipsychotics	one prescription	0.90	0.86 to 0.94	<0.0001	0.95	0.91-1.00	0.0335	0.96	0.92 to 1.01	0.104	0.96	0.92 to 1.00	0.069
	≥ 2 prescriptions	0.90	0.88 to 0.92	<0.0001	0.97	0.94 to 1.00	0.0198	1.06	1.03 to 1.09	0.0001	1.06	1.03 to 1.09	0.0002
Anxiolytics	one prescription	1.03	0.99 to 1.06	0.121	1.04	1.00 to 1.08	0.0295	1.04	1.01 to 1.08	0.0214	1.04	1.00 to 1.07	0.055
	≥ 2 prescriptions	0.96	0.93 to 0.99	0.0117	1.02	0.98 to 1.05	0.309	1.10	1.06 to 1.14	<0.0001	1.10	1.06 to 1.14	<0.0001
Hypnotics/ sedatives	one prescription	1.12	1.09 to 1.16	<0.0001	1.12	1.08 to 1.16	<0.0001	1.09	1.05 to 1.13	<0.0001	1.09	1.05 to 1.13	<0.0001
	≥ 2 prescriptions	1.16	1.12 to 1.20	<0.0001	1.16	1.11 to 1.20	<0.0001	1.18	1.14 to 1.23	<0.0001	1.19	1.15 to 1.24	<0.0001
Antidepressants	one prescription	1.00	0.96 to 1.03	0.724	1.02	0.99 to 1.06	0.165	1.01	0.98 to 1.04	0.479	1.01	0.98 to 1.04	0.575
	≥ 2 prescriptions	1.02	1.00 to 1.04	0.0178	1.04	1.03 to 1.06	<0.0001	1.07	1.06 to 1.09	<0.0001	1.07	1.06 to 1.09	<0.0001
Psychostimulants	one prescription	0.86	0.72 to 1.02	0.077	0.92	0.77 to 1.09	0.323	0.95	0.79 to 1.13	0.535	0.94	0.79 to 1.13	0.510

	≥ 2 prescriptions	0.96	0.90 to 1.03	0.252	1.03	0.96 to 1.10	0.405	1.05	0.98 to 1.12	0.213	1.04	0.97 to 1.12	0.247
Psycholeptics and	one prescription	1.20	1.09 to 1.33	0.0004	1.19	1.07 to 1.32	0.0012	1.17	1.06 to 1.30	0.0025	1.18	1.06 to 1.31	0.0024
psychoanaleptics	≥ 2 prescriptions	1.30	1.16 to 1.45	<0.0001	1.31	1.17 to 1.47	<0.0001	1.35	1.21 to 1.52	<0.0001	1.37	1.22 to 1.53	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017). HC, hormonal contraception.

Psychotropic medications and HC types

Supplementary Figure 6 illustrates the types of HC used in 2017 by occasional and regular users of psychotropic medications between 2013 and 2016.

In univariable and multivariable (adjusted for age group, marital and socioeconomic status, education and income level, recent pregnancy or induced abortion) multinomial logistic regression models, when fixed combinations of progestogens and estrogens for systemic use (ATC: G03AA) was the reference category, women either occasionally (Figure 1) or regularly (Figure 2) using almost any class of psychotropic medications had higher odds of using any other types of HC (such as the LNG-IUS and, to a lesser extent, vaginal ring and progestogens for systemic use). The main exception was a reduced (or a tendency to reduced) relative risk ratio of use of sequential preparations for systemic use (G03AB) in regular users of anxiolytics and hypnotics/sedatives in a fully adjusted model. The results were substantially confirmed in unadjusted and, to a lesser extent, adjusted models using quantiles of redeemed DDD (Supplementary Table 2).

DISCUSSION

According to our results, the current as well as past uses of psychotropic medications are associated with higher odds of using HC among Finnish girls and women of fertile age. This association holds also in relation to regular and, although to a lesser extent, occasional use of psychiatric medications during the four previous years. This study additionally indicates that the use of psychotropic medications is associated with the type of contraceptive chosen.

Our study has a number of limitations. First, misclassification of HC use cannot be ruled out. Because we had no information on contraception use before 2017, it is possible that a number of women in the control group were in fact using HC, especially LARC methods, which may have been prescribed or inserted before 2017. The lack of information on HC use before 2017 further limits the interpretability of the detected prospective associations, which can in fact reflect a more complex path between (unidentified) HC use between 2013–2016, psychiatric problems in the same period, and HC use in 2017. It is also possible that the detected associations in fact result from a selection bias, where unobserved confounding may underlie the choice of using HC, especially in young women. Additionally, we lacked information on the use of contraceptives that do not require a prescription, such as copper IUD or condoms, or on young women who obtained free contraception as part of municipal programs. We may expect that a proportion of women with psychiatric disorders, being usually high utilizers of healthcare services, may have received free-of-charge (and thus without a prescription) contraception, and thus being erroneously classified as non-users. However, if this were

the case, it would even further support our results. Likewise, because more than 20% of women who receive free contraception opt for a LARC method such as the LNG-IUS or contraceptive implants,[21] the same bias may concern the analyses on the HC types.

Additionally our results cannot be generalized to women with psychiatric disorders. Because our predictor of interest was a prescription of psychotropic medications, women with mild conditions, who do not need a pharmacological treatment, as well as women with more severe disorders but not yet receiving (or with poor adherence to) a pharmacological treatment, may have been included in the reference group. However, by distinguishing regular vs. occasional past psychiatric prescriptions, and by conducting sensitivity analyses utilizing the amount of purchased drug, we partly took into account these factors. Similarly, it cannot be excluded that users of hormonal contraceptives prefer pharmacological treatment strategies for psychiatric disorders, whereas non-user of hormonal contraceptives with psychiatric diagnoses prefer non-pharmacological treatments such as psychotherapy.

P-values in the study are reported with descriptive purpose only, without intent to do formal statistical testing based on them; hence, no adjustments for multiple testing have been performed; however, results have been interpreted using estimates and their confidence intervals.

Moreover, given the observational nature of the data, causality cannot be determined in the associations identified.

Among the strengths of the study, our population was highly representative, including more than half of fertile-aged women in Finland. Additional strengths are the use of register data with proven good validity and reliability, and the combination of a cross-sectional and longitudinal retrospective design, which provides stability to our predictor of interest. Our findings are further supported by the use of different approaches to determine levels of use of psychotropic medications.

To the best of our knowledge, this is the first study to examine, on a nationwide scale, the associations between the concurrent and past class-specific use of psychotropic medications and class-specific HC use. The observation of higher odds for HC use among girls and women using psychotropic medications contrasts with large part of the available evidence on psychiatric disorders.[1] In fact, previous studies reported associations between psychiatric disorders and risky sexual behavior, lower contraceptive compliance, contraceptive non-use, unintended pregnancy, and use of less effective methods.[9,11,12,22-29] However, other works showed either no relationships between depressive/anxiety symptoms or psychological distress and inconsistent use of contraception or use of less effective methods, or even higher odds of choosing a more effective method.[30-33]

On the other hand, our results are substantially in line with those of the few studies that have specifically looked at associations between HC and use of psychotropic medications, although from a different perspective. Two Swedish register-based studies have shown positive associations between some types of combined HCs and progestin-only HCs, and antidepressant use among women aged 16-31 years, with the highest odds in the youngest age group (16-19 years). In particular, the authors reported more pronounced associations with antidepressant use among young women using LARC methods (IUS, implants, injections and transdermal patch). However, because the studies did not take into account the sequence of drugs used, no assumption on the directionality of the associations could be made.[34,35] Another recent Swedish register-based study confirmed higher subsequent use of antidepressants in HC users, especially in contexts composed by immigrant, low-income women with previous mental issues.[36] The same authors had previously found an OR of 1.34 for subsequent psychotropic drug use in young women (12-30 years) using HC compared to non-users, with the strongest association in adolescents (but no association after adolescence).[37] Again, because all these, including ours, are epidemiological studies based on observational data, assumptions on causality and directionality of the associations cannot be made.

Although not totally comparable, our findings, supported by the use of both a cross-sectional and a longitudinal design, suggest that girls and women with repeated prescriptions of psychotropic medications (and as such at least partly representative of those with a psychiatric disorder) have good access to, and are well aware of contraceptive options in Finland. The use of contraception was especially higher among teenagers who used psychiatric medications than in their peers who were not using the same drugs. However, it tended to invert the figure for the young age group (20–24 years), possibly suggesting that the adequate psychiatric and reproductive counselling and education likely offered through the school system may not be completely continued after high school.

The observation of a relationship between the use of psychotropic drugs and the type of contraceptive chosen provides additional information on the reproductive health status of these women. Specifically, the use of psychiatric medications was associated with higher odds of using types of contraception other than the monophasic OCs, and especially long-acting reversible contraception (LARC) methods such as the LNG-IUS, as well as vaginal ring and progestogens for systemic use including implants. Because the oral preparations in particular require daily motivation, the use of less user-dependent LARC methods may be advisable especially in women who, because of their psychological challenges, may have difficulty with a method necessitating daily remembering. This is in line with the observation of lower odds of using sequential preparations (highly user-dependent) in regular users of anxiolytics and hypnotics/sedatives.

It could be argued that our findings may be affected by a healthcare user bias. In other words, it is likely that women suffering from and seeking help for their psychiatric disorders, and thus receiving a pharmacological treatment, represent a more conscious and healthy subgroup of this population. As such, they may obtain a better control of their symptoms (as compared to their peers not using psychiatric medications), and thus also of other areas of their lives, including contraception. Moreover, because more likely to visit healthcare services, they may also be more likely to receive and adhere to any medical prescription. Reciprocally, women who use HC are likely to see healthcare providers, and thus to have their psychiatric symptoms diagnosed and pharmacologically treated. This assumption is supported by the observation that the detected associations were substantially consistent for women with either repeated prescriptions or belonging to the highest DDD group, but almost completely non-existent for occasional users or those with the lowest purchased DDD. However, in our sensitivity analyses part of the associations hold also in the group of women with intermediate/low use (e.g., in the case of hypnotic/sedatives, antidepressants, psycholeptics and psychoanaleptics) possibly including, in addition to occasional users, those with poor compliance to psychopharmacological treatment.

Taken together, our results indicate that girls and women of fertile age who use psychiatric medications have access to and use adequate contraceptive options, suggesting effectiveness of the reproductive and public health strategies and policies implemented to date in Finland. However, because users of psychiatric medications plausibly represent only a subgroup of those with psychiatric disorders, the need for still reaching the entire psychiatric population and satisfy their needs for birth control should be addressed in further studies.

In summary, fertile-aged girls and women using psychiatric medications have higher odds of using HC in Finland, with a specific pattern in the type of contraceptives used. Whether our observation of adequate use of effective contraception among girls and women using psychotropic medications translates into an actual reduction in the number of unwanted pregnancies, and thus of induced abortions, in women with psychiatric disorders, it remains to be examined.

CONTRIBUTORSHIP STATEMENT

ET, AB, OH, AL, TP and JH contributed to the study planning and design, interpretation of the data, and critical revision of the manuscript. ET and JH verified the data. ET and JH had full access to all

the data and performed statistical analyses. ET wrote the first draft of the manuscript. ET, AB, OH, AL, TP and JH approved the submitted version of the manuscript and accepted responsibility to submit for publication. ET and JH are the guarantors.

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COMPETING INTERESTS

OH reports a research grant from the Jane and Aatos Erkko Foundation during the conduct of the study; personal fees from Bayer Health Care AG, personal fees from Gedeon-Richter outside the submitted work; OH serves as president for the Finnish Gynecological Society and for the Nordic Federation of the Societies of Obstetrics and Gynecology, and is the chairperson for the Finnish national guideline committee on induced abortion care. The other authors report no conflicts of interest.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Helsinki (3/2018).

DATA SHARING

The data that support the findings of this study are available from Statistics Finland, the Finnish Institute for Health and Welfare, and the Social Insurance Institution, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of FinData (https://www.findata.fi/en/).

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Figure 1. Associations between occasional use of psychotropic medications (one prescription) between 2013 and 2016, and type of hormonal contraceptives used in 2017. Panel A: antipsychotics; Panel B: anxiolytics; Panel C: hypnotics/sedatives; Panel D: antidepressants. Results are from multinomial logistic regression models among HC users. Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017. Reference category: G03AA, progestogens and estrogens, fixed combinations for systemic use –including monophasic combined oral contraceptives and transdermal patch. G02BA: intrauterine device with progestogen; G02BB: vaginal ring with progestogen and estrogen; G03AB: progestogens and estrogens, sequential preparations for systemic use; G03AC: progestogens for systemic use; G03HB01: cyproterone and estrogen.

Figure 2. Associations between regular use of psychotropic medications (two or more prescriptions) between 2013 and 2016, and type of hormonal contraceptives used in 2017. Panel A: antipsychotics; Panel B: anxiolytics; Panel C: hypnotics/sedatives; Panel D: antidepressants. Results are from multinomial logistic regression models among HC users. Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017. Reference category: G03AA, progestogens and estrogens, fixed combinations for systemic use –including monophasic combined oral contraceptives and transdermal patch. G02BA: intrauterine device with progestogen; G02BB: vaginal ring with progestogen and estrogen; G03AB: progestogens and estrogens, sequential preparations for systemic use; G03AC: progestogens for systemic use; G03HB01: cyproterone and estrogen.

Supplementary Figure 1. Proportions of different types of HC used in Finland in 2017.

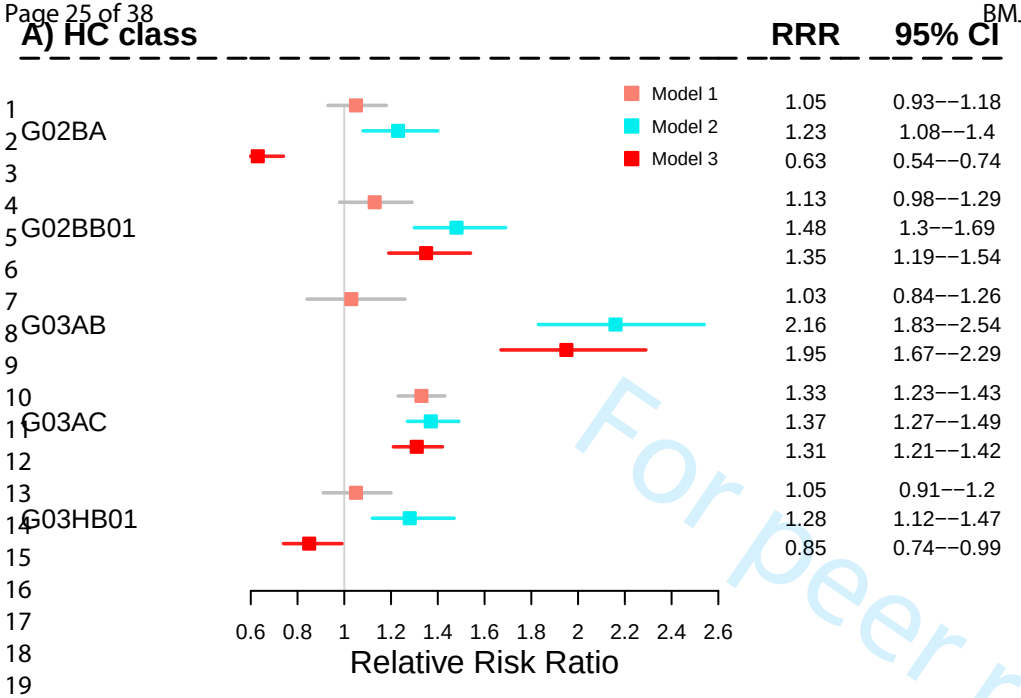
Supplementary Figure 2. Associations between one or more prescriptions of psychotropic medications and use of hormonal contraception in 2017, stratified by age group.

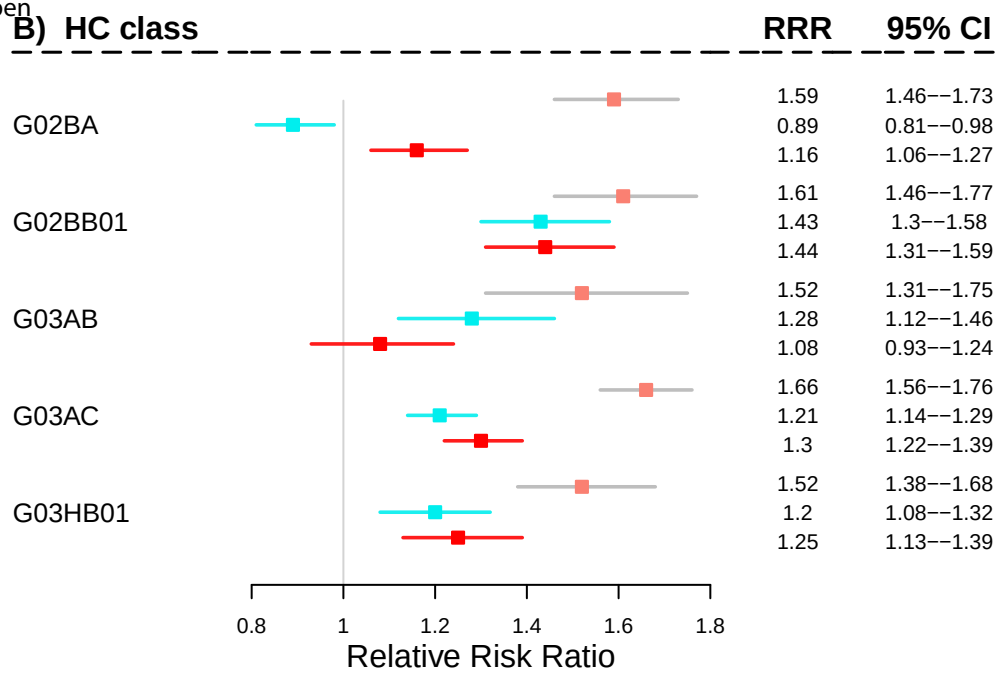
Supplementary Figure 3. Proportions of HC use among women using and not using different classes of psychotropic medications in 2017, by age group.

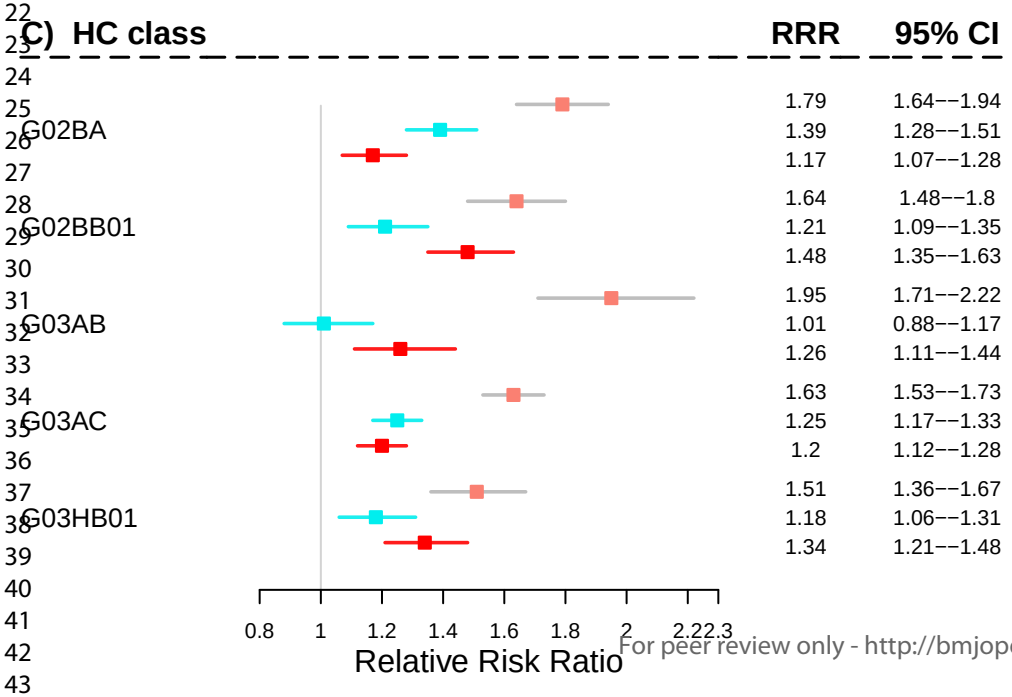
Supplementary Figure 4. Associations between occasional (one prescription) or regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016, and hormonal contraception use in 2017, stratified by age group.

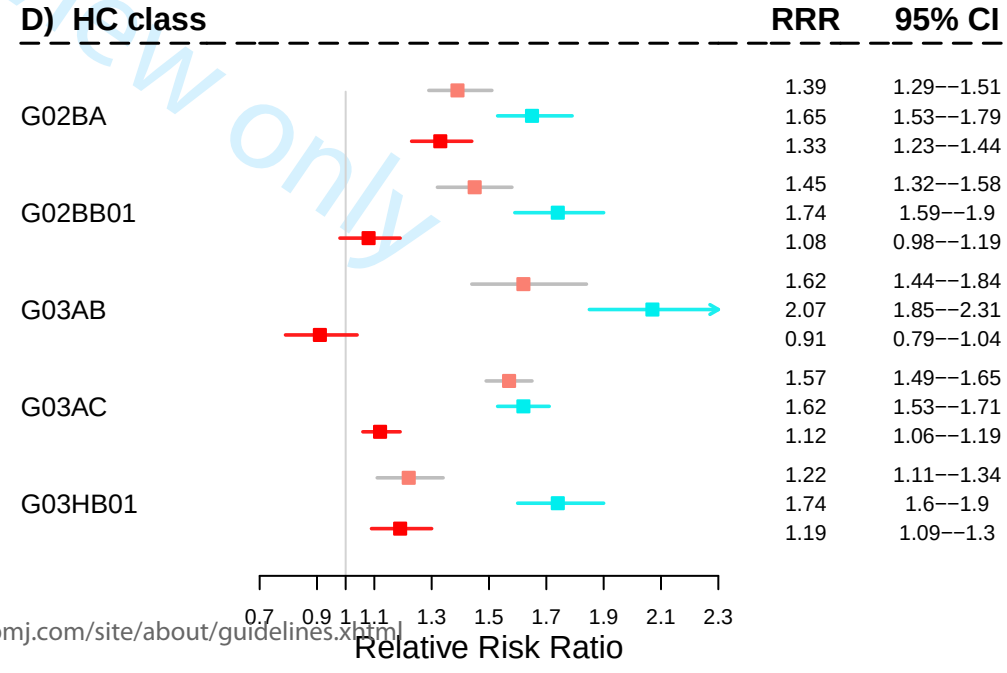
Supplementary Figure 5. Proportions of HC use in 2017 among women with no, occasional (one prescription) and regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016.

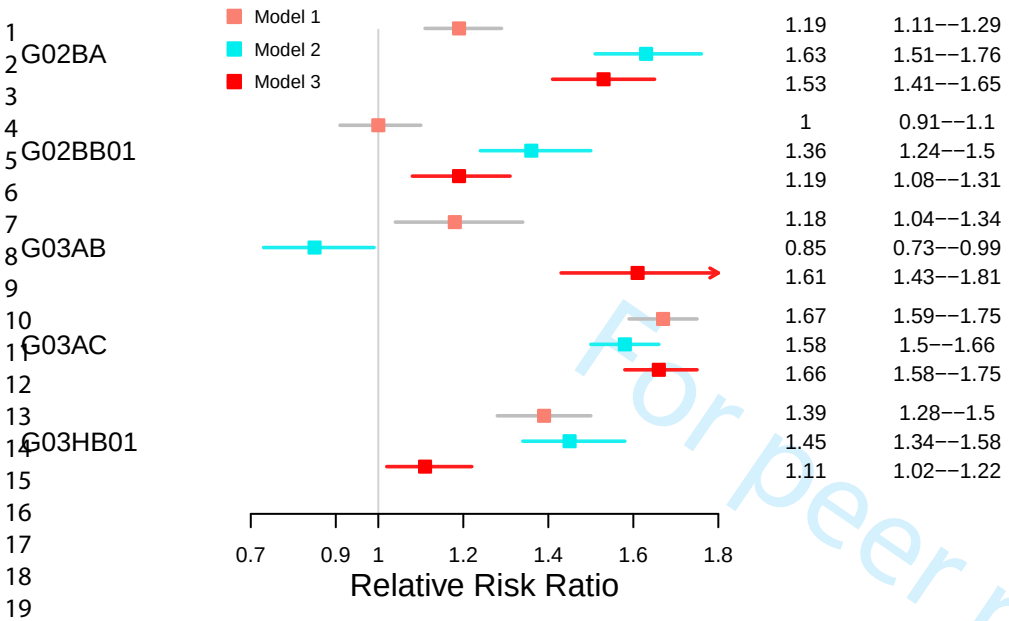
Supplementary Figure 6. Proportions of types of hormonal contraceptives used in 2017 by women with occasional (one prescription) and regular (two or more prescriptions) use of psychotropic medications between 2013 and 2016.

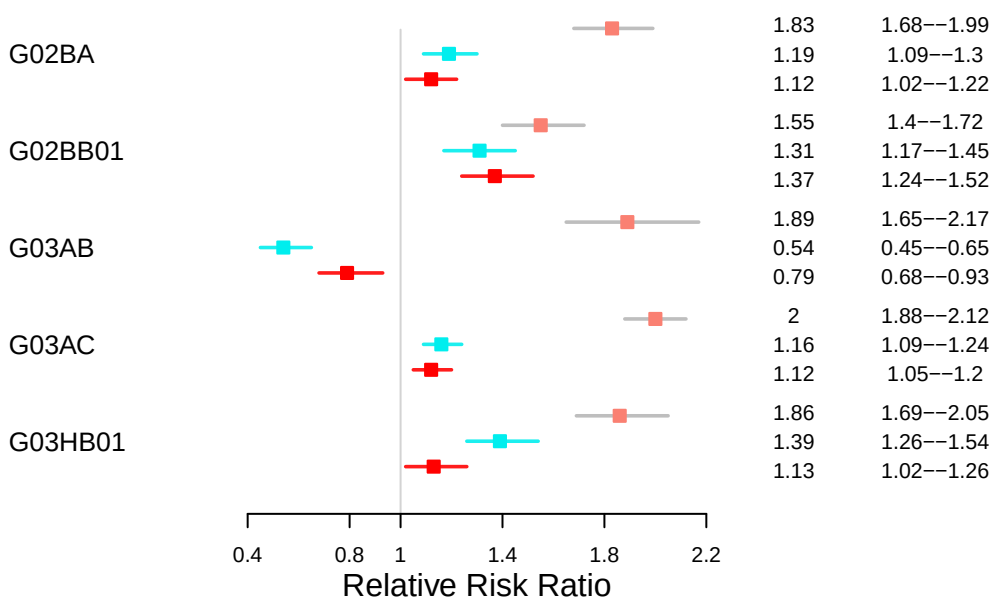


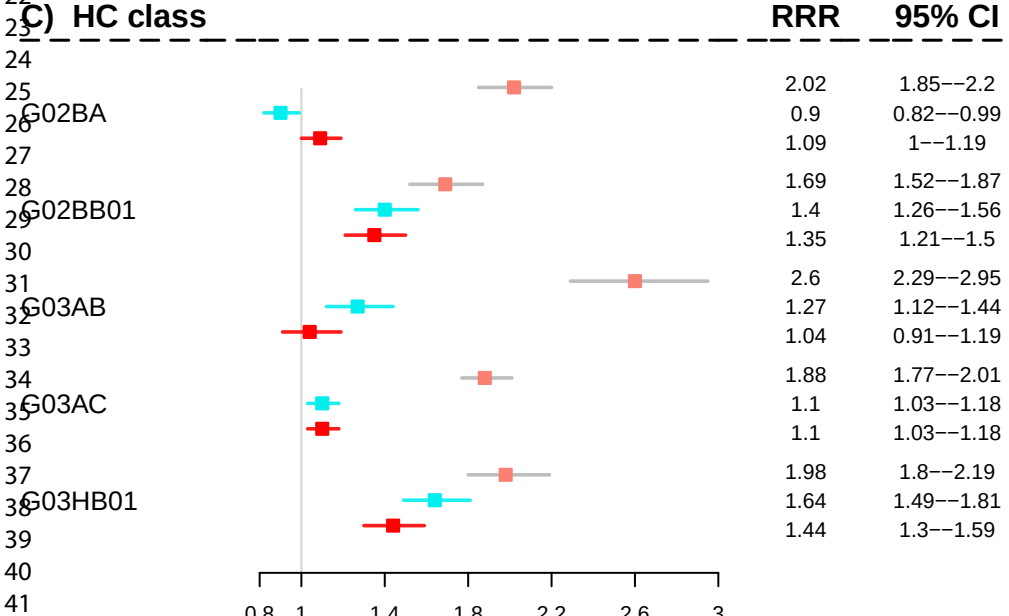


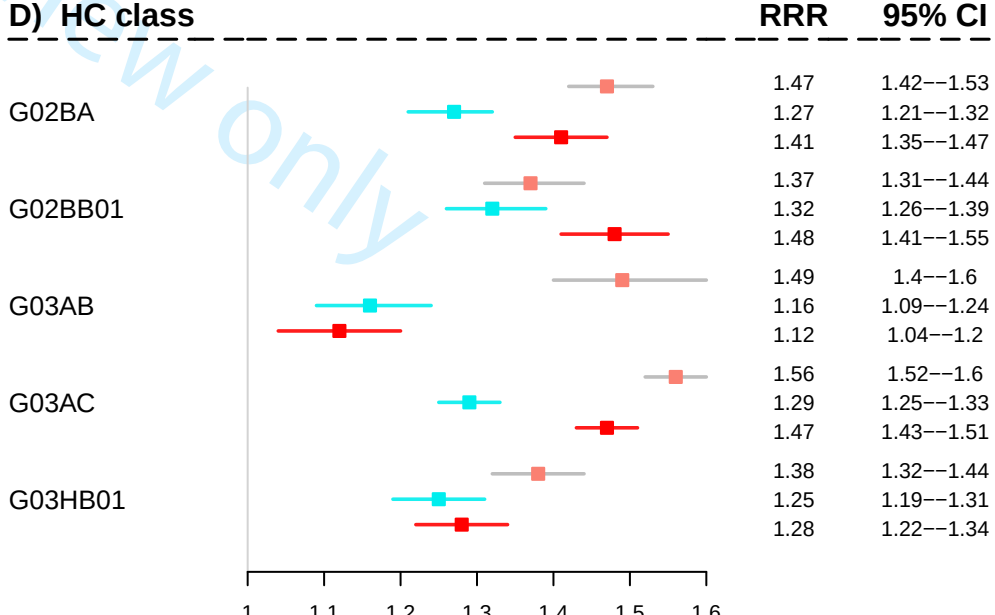


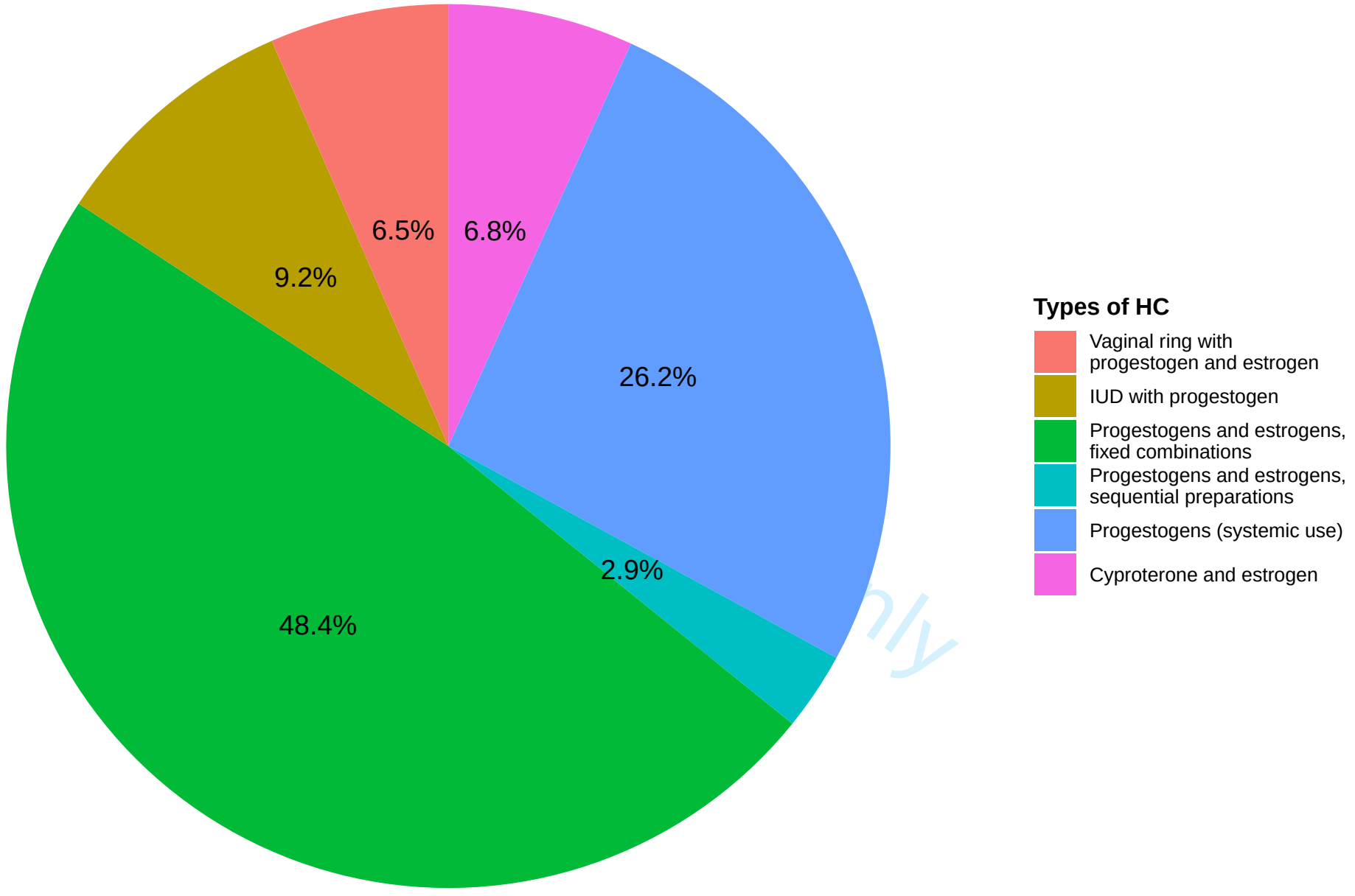


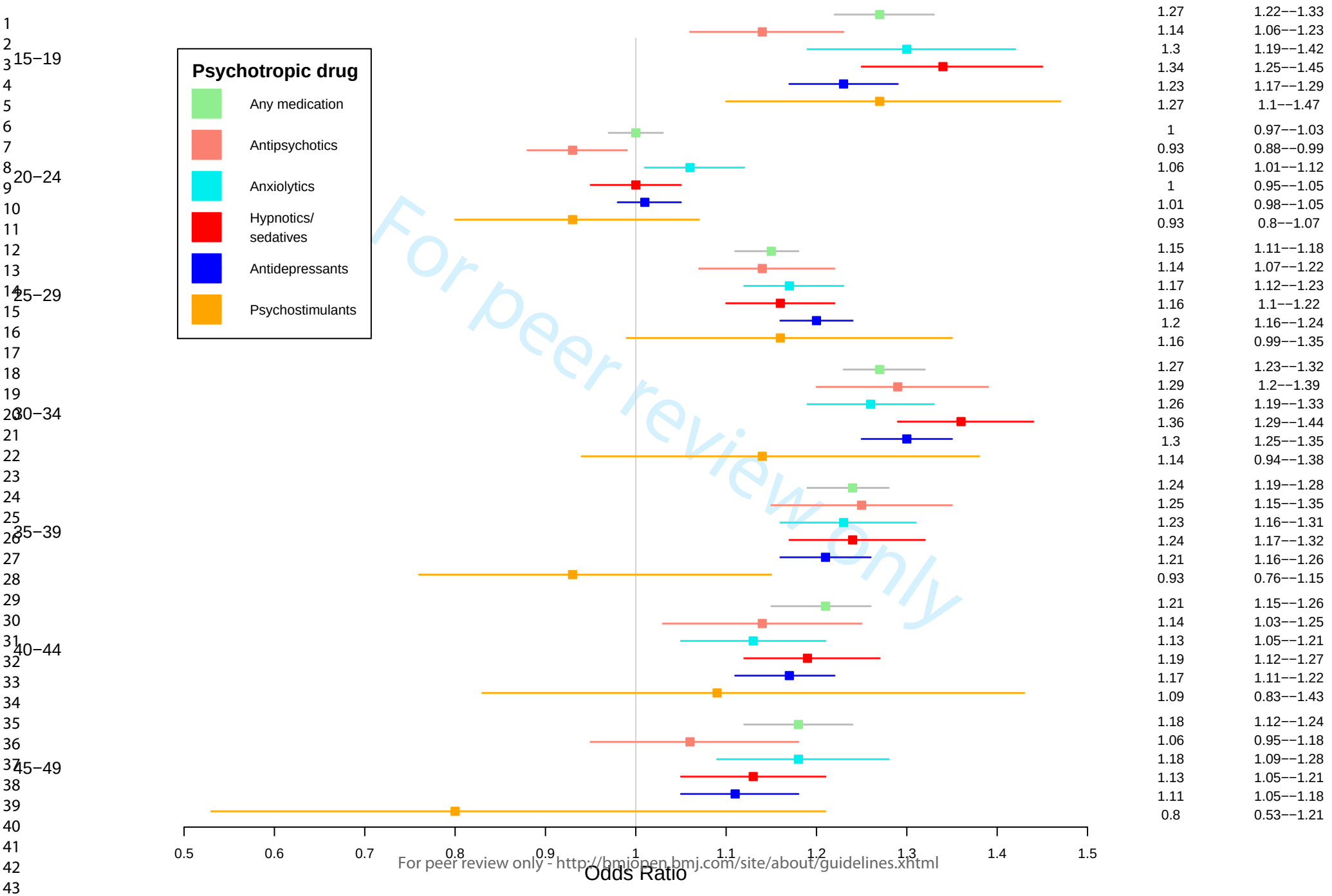


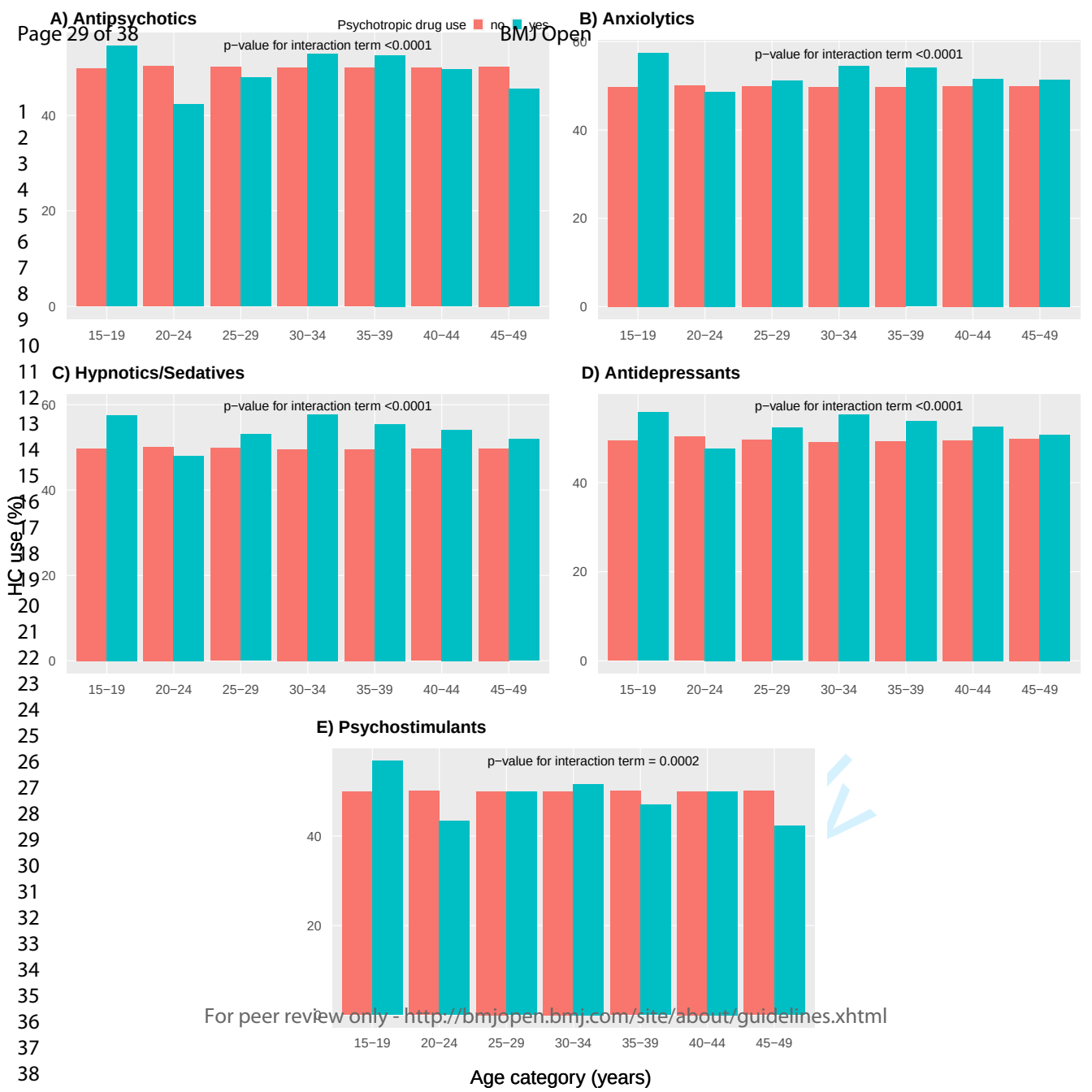


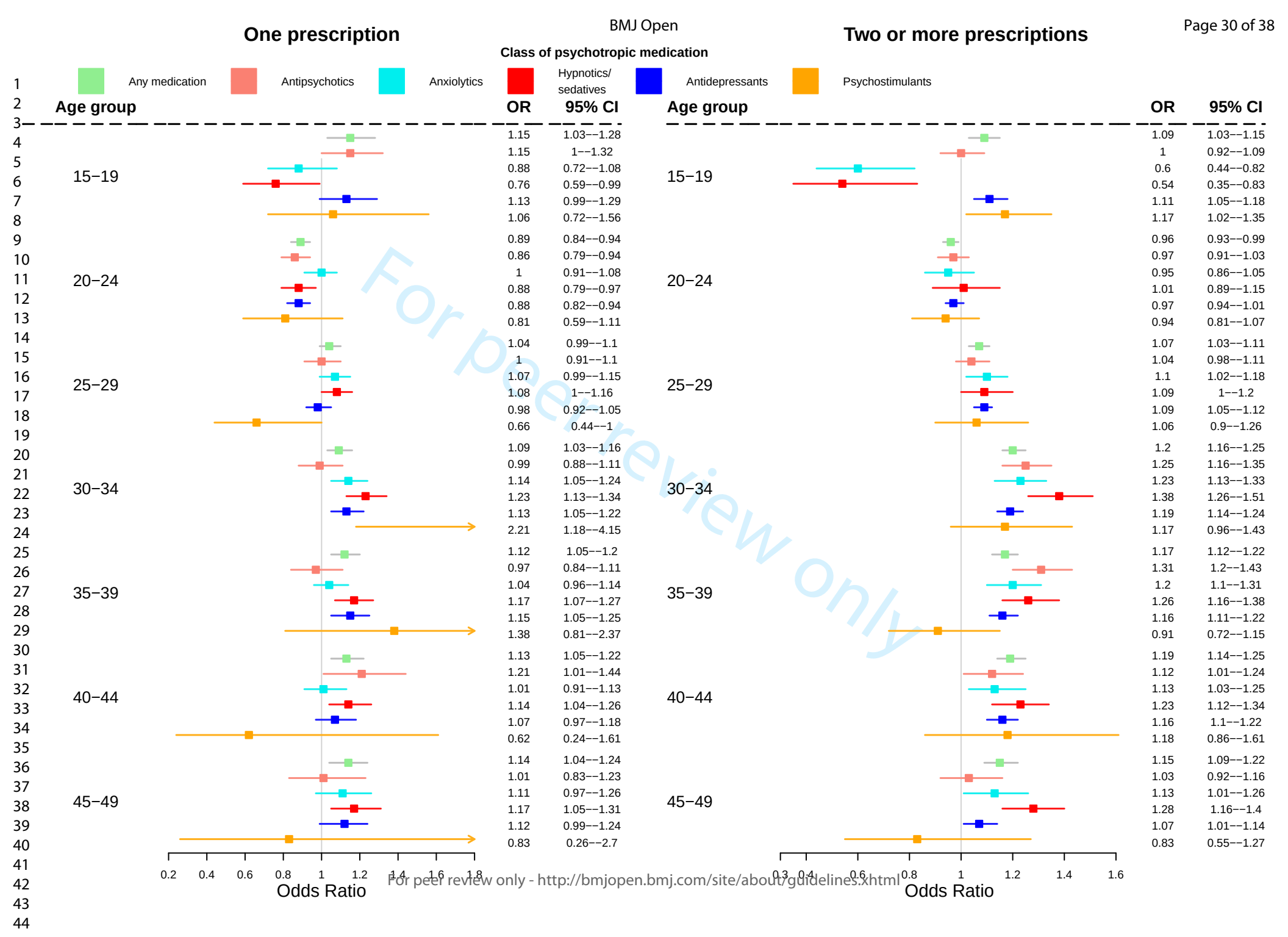


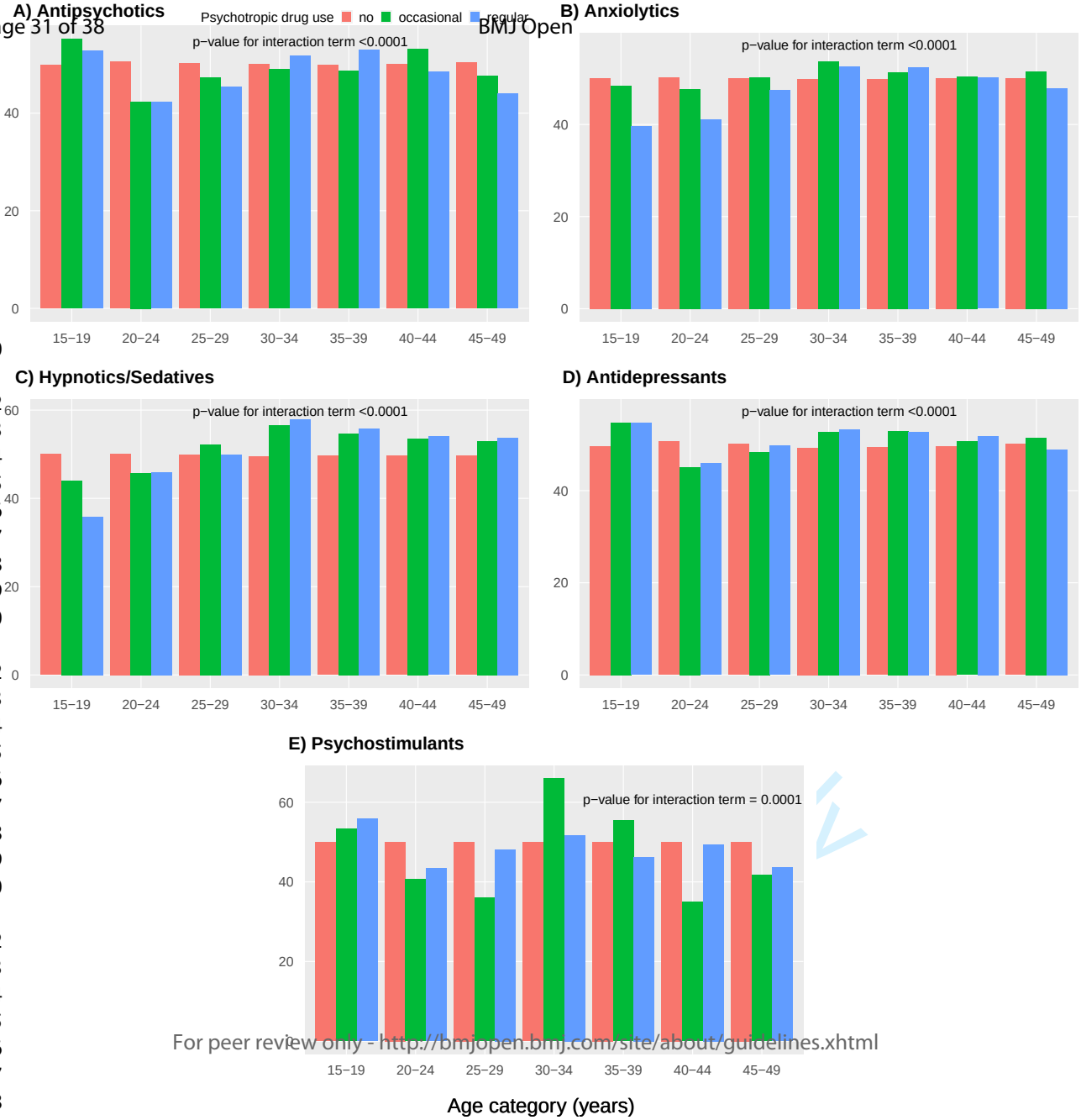


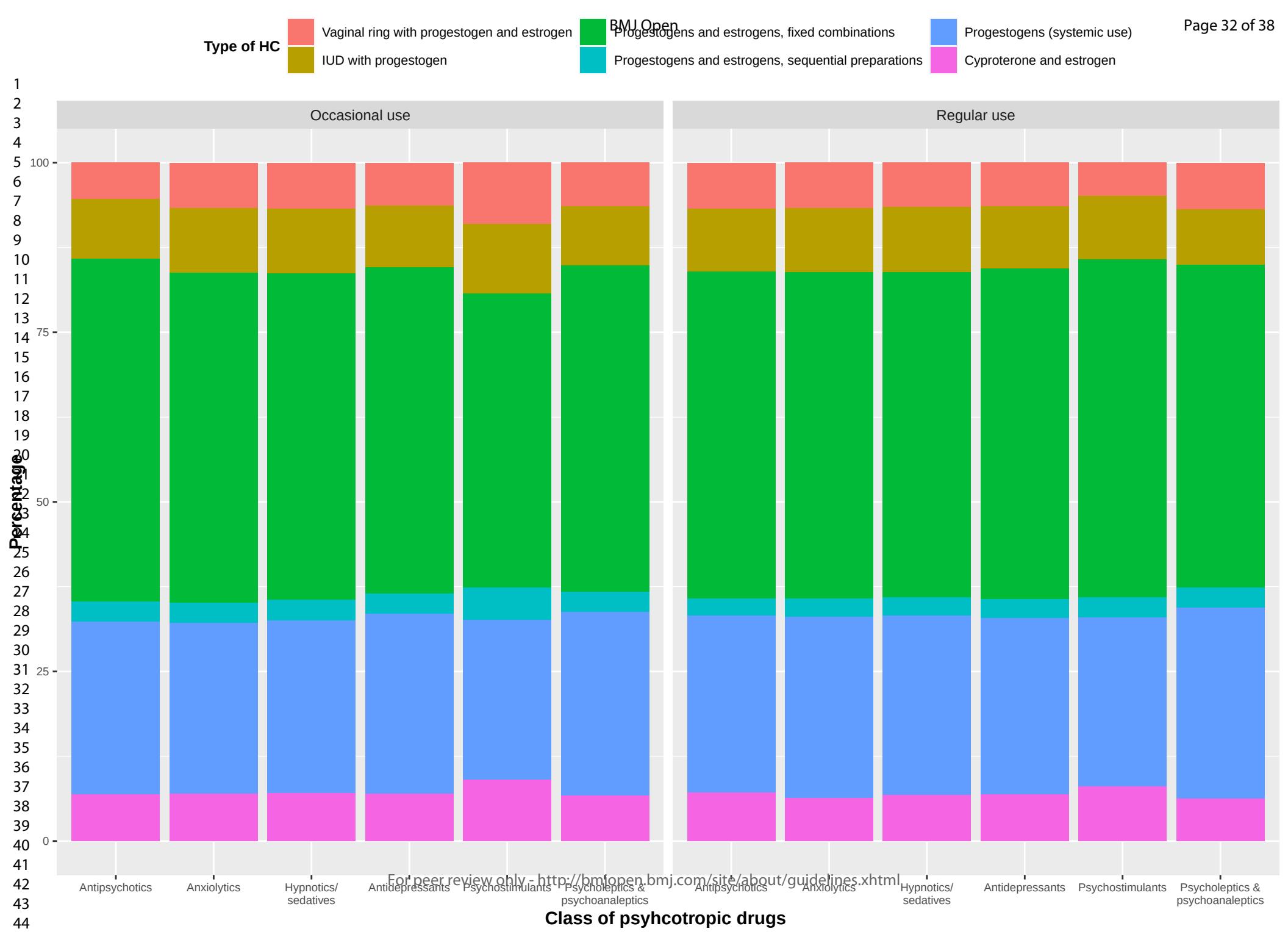












Supplementary Table 1. Associations between levels of use of psychotropic medications (based on quantiles of redeemed DDD) between 2013 and 2016, and HC use in 2017.

Class of psychotropic medication	Level of use*	Model 1			Model 2			Model 3			Model 4		
		OR	95% CI	*p*-value	OR	95% CI	p-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Antipsychotics	Low	0.95	0.91 to 0.99	0.0056	1.00	0.96 to 1.04	0.975	1.01	0.97 to 1.05	0.740	1.00	0.96 to 1.04	0.916
	Intermediate	0.92	0.88 to 0.96	0.0001	0.99	0.95 to 1.04	0.714	1.03	0.99 to 1.08	0.158	1.03	0.99 to 1.08	0.176
	High	0.83	0.79 to 0.86	<0.0001	0.90	0.87 to 0.94	<0.0001	1.06	1.02 to 1.10	0.0050	1.06	1.01 to 1.11	0.0090
Anxiolytics	Low	1.04	1.00 to 1.09	0.0418	1.05	1.01 to 1.09	0.0267	1.04	1.00 to 1.09	0.0557	1.03	0.99 to 1.08	0.117
	Intermediate	1.00	0.96 to 1.04	0.959	1.02	0.98 to 1.07	0.292	1.04	1.00 to 1.09	0.0507	1.04	1.00 to 1.09	0.074
	High	0.93	0.89 to 0.97	0.0008	1.01	0.97 to 1.06	0.545	1.14	1.09 to 1.19	<0.0001	1.14	1.09 to 1.19	<0.0001
Hypnotics/ sedatives	Low	1.13	1.09 to 1.17	<0.0001	1.11	1.08 to 1.15	<0.0001	1.08	1.05 to 1.12	<0.0001	1.08	1.04 to 1.12	<0.0001
	High	1.16	1.12 to 1.20	<0.0001	1.16	1.12 to 1.21	<0.0001	1.20	1.15 to 1.24	<0.0001	1.21	1.16 to 1.25	<0.0001
Antidepressants	Low	1.00	0.98 to 1.02	0.9113	1.03	1.01 to 1.05	0.0168	1.02	1.00 to 1.05	0.084	1.02	1.00 to 1.05	0.098
	Intermediate	1.02	1.00 to 1.05	0.0543	1.05	1.03 to 1.08	0.0001	1.06	1.04 to 1.09	<0.0001	1.06	1.04 to 1.09	<0.0001
	High	1.02	1.00 to 1.05	0.0772	1.04	1.02 to 1.07	0.0014	1.10	1.08 to 1.13	<0.0001	1.10	1.08 to 1.13	<0.0001
Psychostimulants	Low	0.88	0.79 to 0.98	0.019	0.94	0.84 to 1.05	0.261	0.96	0.86 to 1.07	0.415	0.95	0.85 to 1.06	0.394
	Intermediate	0.92	0.82 to 1.03	0.151	0.98	0.88 to 1.11	0.790	1.00	0.89 to 1.13	0.972	1.00	0.89 to 1.12	0.956
	High	1.03	0.92 to 1.15	0.674	1.11	0.99 to 1.24	0.071	1.13	1.00 to 1.26	0.043	1.12	1.00 to 1.26	0.046
Psycholeptics and psychoanaleptics	Low	1.22	1.10 to 1.36	0.0001	1.21	1.09 to 1.34	0.0004	1.19	1.07 to 1.32	0.0011	1.20	1.08 to 1.33	0.0010
	High	1.27	1.14-1.42	<0.0003	1.29	1.15 to 1.44	<0.0001	1.33	1.19 to 1.49	<0.0001	1.34	1.19 to 1.50	<0.0001

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age group, education and marital status; Model 3 is Model 2 adjusted for socioeconomic status and income level; Model 4 is Model 3 adjusted for recent pregnancy (in 2017), abortion (in 2016-2017) and sterilization (before 2017). DDD, defined daily dose; HC, hormonal contraception.

* Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination.

Supplementary Table 2. Multinomial logistic regression models among HC users, showing the associations between levels of use of psychotropic medications (based on quantiles of redeemed DDD) between 2013 and 2016, and type of HC used in 2017.

Class of HC*	Level of use†	Model 1			Model 2			Model 3		
		RRR	95% CI	p-value	RRR	95% CI	p-value	RRR	95% CI	p-value
	Antipsychotics									
G02BA IUD with progestogen	Low	0.94	0.85 to 1.04	0.238	0.94	0.84 to 1.04	0.204	1.03	0.94 to 0.13	0.543
	Intermediate	1.18	1.05 to 1.31	0.0045	1.01	1.91 to 1.13	0.847	1.25	1.12 to 1.40	0.0001
	High	1.45	1.30 to 1.61	<0.0001	1.14	1.02 to 1.27	0.021	1.92	1.73 to 2.12	<0.0001
G02BB01 vaginal ring with progestogen and estrogen	Low	1.04	0.92 to 1.16	0.557	0.92	0.82 to 1.04	0.185	0.92	0.82 to 1.03	0.155
	Intermediate	1.08	0.95 to 1.24	0.247	1.27	1.13 to 1.42	0.0001	1.02	0.89 to 1.17	0.790
	High	0.99	0.85 to 1.14	0.838	0.90	0.78 to 1.03	0.112	1.92	1.71 to 2.15	<0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	0.92	0.77 to 1.10	0.364	1.14	0.98 to 1.32	0.086	1.03	0.88 to 1.19	0.730
	Intermediate	1.24	1.03 to 1.49	0.023	0.88	0.73 to 1.06	0.187	0.27	0.19 to 0.38	<0.0001
	High	1.35	1.12 to 1.62	0.0016	1.03	0.87 to 1.22	0.762	0.93	0.75 to 1.15	0.487
G03AC Progestogens (systemic use)	Low	1.30	1.22 to 1.38	<0.0001	1.00	0.94 to 1.07	0.960	0.70	0.65 to 0.76	<0.0001
	Intermediate	1.46	1.36 to 1.57	<0.0001	0.96	0.89 to 1.04	0.341	1.58	1.48 to 1.70	<0.0001
	High	2.10	1.96 to 2.25	<0.0001	0.78	0.72 to 0.85	<0.0001	1.19	1.10 to 1.29	<0.0001
G03HB01 cyproterone and estrogen	Low	1.07	0.96 to 1.20	0.239	1.12	1.00 to 1.25	0.048	1.10	0.99 to 1.22	0.067
	Intermediate	1.37	1.22 to 1.54	<0.0001	0.86	0.75 to 0.98	0.028	1.43	1.28 to 1.61	<0.0001
	High	1.52	1.35 to 1.72	<0.0001	1.02	0.90 to 1.16	0.785	1.80	1.60 to 2.01	<0.0001
	Anxiolytics									
G02BA IUD with progestogen	Low	1.55	1.40 to 1.71	<0.0001	1.34	1.21 to 1.47	<0.001	1.13	1.02 to 1.25	0.018
	Intermediate	1.84	1.66 to 2.04	<0.0001	1.01	0.91 to 1.13	0.855	0.98	0.88 to 1.10	0.739
	High	1.75	1.56 to 1.96	<0.0001	0.74	0.65 to 0.84	<0.0001	1.13	1.02 to 1.26	0.026
	Low	1.67	1.49 to 1.87	<0.0001	1.41	1.27 to 1.58	<0.0001	0.88	0.78 to 1.01	0.061

G02BB01 vaginal ring with progestogen and estrogen	Intermediate	1.58	1.40 to 1.78	<0.0001	1.00	0.88 to 1.14	0.985	0.82	0.71 to 0.94	0.0042
	High	1.47	1.28 to 1.68	<0.0001	0.97	0.85 to 1.11	0.658	0.75	0.65 to 0.86	0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.34	1.12 to 1.60	0.0014	0.60	0.48 to 0.75	<0.0001	0.86	0.71 to 1.03	0.099
	Intermediate	1.92	1.63 to 2.26	<0.0001	0.86	0.71 to 1.04	0.119	0.99	0.83 to 1.18	0.930
	High	1.93	1.62 to 2.30	<0.0001	0.97	0.80 to 1.17	0.750	0.29	0.21 to 0.40	<0.0001
G03AC Progestogens (systemic use)	Low	1.62	1.51 to 1.74	<0.0001	0.93	0.86 to 1.00	0.065	1.10	1.02 to 1.18	0.0125
	Intermediate	1.75	1.62 to 1.88	<0.0001	1.01	0.94 to 1.09	0.764	1.10	1.02 to 1.18	0.0138
	High	2.16	2.01 to 2.34	<0.0001	0.85	0.78 to 0.92	0.0001	0.86	0.79 to 0.93	0.0001
G03HB01 cyproterone and estrogen	Low	1.42	1.26 to 1.60	<0.0001	1.46	1.32 to 1.63	<0.0001	0.91	0.81 to 1.04	0.156
	Intermediate	1.68	1.49 to 1.89	<0.0001	1.14	1.01 to 1.28	0.0038	0.88	0.78 to 1.01	0.062
	High	2.04	1.81 to 2.30	<0.0001	1.63	1.46 to 1.82	<0.0001	0.62	0.53 to 0.72	<0.0001
	Hypnotics/Sedatives									
G02BA IUD with progestogen	Low	1.70	1.56 to 1.85	<0.0001	0.88	0.80 to 0.97	0.010	0.70	0.64 to 0.78	<0.0001
	High	2.14	1.96 to 2.33	<0.0001	1.54	1.41 to 1.67	<0.0001	0.88	0.79 to 0.97	0.012
G02BB01 vaginal ring with progestogen and estrogen	Low	1.63	1.48 to 1.79	<0.0001	1.11	1.00 to 1.22	0.0514	1.16	1.06 to 1.28	0.0020
	High	1.70	1.52 to 1.89	<0.0001	1.00	0.89 to 1.12	0.948	1.55	1.41 to 1.71	<0.0001
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.89	1.66 to 2.16	<0.0001	0.76	0.65 to 0.89	0.0008	1.27	1.12 to 1.45	0.0004
	High	2.69	2.37 to 3.06	<0.0001	1.27	1.10 to 1.46	0.0011	0.95	0.80 to 1.12	0.523
G03AC Progestogens (systemic use)	Low	1.60	1.51 to 1.70	<0.0001	1.07	1.01 to 1.14	0.0329	0.79	0.74 to 0.84	<0.0001
	High	1.93	1.81 to 2.06	<0.0001	1.06	0.99 to 1.13	0.093	1.35	1.27 to 1.44	0.007
G03HB01 cyproterone and estrogen	Low	1.48	1.34 to 1.64	<0.0001	1.10	1.00 to 1.22	0.060	0.93	0.84 to 1.03	0.138
	High	2.03	1.84 to 2.24	<0.0001	1.41	1.28 to 1.56	<0.0001	1.06	0.95 to 1.19	0.282
	Antidepressants									
G02BA IUD with progestogen	Low	1.30	1.23 to 1.39	<0.0001	0.95	0.89 to 1.01	0.085	0.88	0.82 to 0.94	0.0001
	Intermediate	1.37	1.29 to 1.46	<0.0001	1.29	1.22 to 1.36	<0.0001	0.95	0.89 to 1.01	0.089

	High	1.73	1.63 to 1.83	<0.0001	0.76	0.71 to 0.81	<0.0001	0.89	0.84 to 0.95	0.0005
G02BB01 vaginal ring with progestogen and estrogen	Low	1.40	1.31 to 1.50	<0.0001	0.89	0.83 to 0.96	0.0223	1.06	0.99 to 1.13	0.121
	Intermediate	1.31	1.22 to 1.40	<0.0001	1.00	0.93 to 1.07	0.919	1.06	0.99 to 1.14	0.102
	High	1.45	1.36 to 1.56	<0.0001	1.16	1.09 to 1.24	<0.0001	0.95	0.88 to 1.02	0.132
G03AB Progestogens and estrogens, sequential preparations (systemic use)	Low	1.46	1.33 to 1.61	<0.0001	1.00	0.91 to 1.11	0.933	1.02	0.93 to 1.13	0.664
	Intermediate	1.38	1.25 to 1.52	<0.0001	0.79	0.71 to 0.88	<0.0001	0.90	0.81 to 0.99	0.0381
	High	1.74	1.58 to 1.91	<0.0001	0.98	0.89 to 1.09	0.738	0.95	0.85 to 1.05	0.268
G03AC Progestogens (systemic use)	Low	1.49	1.44 to 1.56	<0.0001	1.00	0.96 to 1.04	0.887	0.98	0.94 to 1.02	0.387
	Intermediate	1.42	1.37 to 1.48	<0.0001	1.02	0.98 to 1.07	0.362	1.01	0.97 to 1.06	0.544
	High	1.79	1.72 to 1.87	<0.0001	0.89	0.85 to 0.93	<0.0001	0.90	0.87 to 0.94	<0.0001
G03HB01 cyproterone and estrogen	Low	1.19	1.11 to 1.28	<0.0001	0.98	0.92 to 1.05	0.609	1.00	0.93 to 1.07	0.972
	Intermediate	1.29	1.21 to 1.39	<0.0001	1.24	1.16 to 1.32	<0.0001	0.89	0.82 to 0.95	0.0011
	High	1.59	1.48 to 1.70	<0.0001	0.99	0.92 to 1.06	0.786	1.01	0.94 to 1.08	0.836

Model 1 is the unadjusted model; Model 2 is Model 1 adjusted for age, marital and socioeconomic status, education and income level; Model 3 is Model 2 adjusted for abortion and pregnancy in 2016-2017.

*Reference: G03AA, Progestogens and estrogens, fixed combinations (systemic use).

† Level of use of psychotropic medications was based on quantiles of purchased DDD (tertiles for antipsychotics, anxiolytics, antidepressants and psychostimulants; 50th percentile for hypnotics/sedatives, and 60th percentile for psycholeptics and psychoanaleptics in combination.

DDD, defined daily dose; HC, hormonal contraception; RRR, relative risk ratio.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5,6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6,7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7,12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6-14
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-14
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	14,15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16
Other information			
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	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.