Impact of EU risk assessment process and administrative regulations for manufacturers of combined hormonal contraceptive prescribing. An analysis of developments in Germany and the implications

Iva Selke Krulichová[1], Gisbert W. Selke[2], Uwe Eichler[2], Veronika Lappe[3], Brian Godman[4,5,6,7], Ingrid Schubert[3]

[1]Institute for Medical Biophysics, Medical Faculty in Hradec Králové, Charles-University, Šimkova 870, 50038 Hradec Králové, Czech Republic. Email: krulich@lfhk.cuni.cz
[2]AOK Research Institute (WIdO), Rosenthaler Straße 31, 10178 Berlin, Germany. Email: gisbert.selke@wido.bv.aok.de, uwe.eichler@wido.bv.aok.de
[3]PMV research group, Clinic and Policlinic for Psychiatry, Psychosomatics and Psychotherapy of Children and Adolescents, Cologne University, Germany. Email: veronika.lappe@uk-koeln.de, ingrid.schubert@uk-koeln.de
[4]Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow G4 ORE, UK. Email: brian.godman@strath.ac.uk
[5]Health Economics Centre, Liverpool University Management School, Chatham Street, Liverpool, UK. Email: Brian.Godman@liverpool.ac.uk
[6]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se
[7]Department of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Garankuwa, South Africa

*Author for correspondence: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: Brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562 and Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone + 46 8 58581068. Fax + 46 8 59581070

Abstract
Objective: Combined hormonal contraceptives (CHC) exhibit differing risks for cardiovascular and thrombotic events (VTE). A European referral process confirmed higher VTE risks for 3rd generation gestagens and drospirenone. CHC are now grouped in risk classes (RC) I, II and III, with RC III having a higher risk than RC I and X (risk not yet known). Marketing authorisation holders were obliged to implement pharmacovigilance measures and risk minimization measures including changes of prescribing information. The study assessed whether these activities induced changes in prescription patterns. Methods: German prescription data for 1.1 million women below 20 were used to analyse the effects of interventions and potential influence factors using logistic regression. Descriptive statistics were calculated for prescriptions for 3.3 million women from January 2011 to March 2016. Results: Shares of RC I and RC X recipients rose substantially over the observation period, while RC III recipient share showed a steady decrease. The referral induced a slightly faster decrease in RC III and increase in RC X. The implementation of pharmacovigilance measures manifested no additional effect. Conclusion: The decrease in RC III share already observed before the referral process can be explained with pre-existing discussions around CHC. The effect attributable to the referral was statistically significant, though very small. While evidence for a connection between interventions and prescription change is only indirect, the study shows that routine data are suitable for impact analyses, and monitoring prescribing patterns can be recommended as feedback after regulatory or political interventions. This is being followed up.

1. Introduction

The risks of "the pill" for contraception have frequently been reported internationally both in professional and in public media. An example of this was a brochure by a German health care fund[1] in late 2015, which was widely discussed in the media. The focus on the brochure was the choice of contraception taking into account the spectrum of adverse effects, and in particular on

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thromboembolism and myocardial infarctions. Already one year before, the manufacturers of combined hormonal contraceptives (CHC) had been obliged to include warnings regarding the increased risk of thromboembolism for what were, at that time, called 3rd and 4th generation gestagens, into their package inserts. This was a consequence of a European risk evaluation process (so-called referral process), which the European Medicines Agency (EMA) had initiated at the request of the French marketing authority[2]. The review confirmed a higher risk for the gestagens desogestrel and gestodene and also for drospirenone. For chlormadinone, dienogest and nomegestrol, no verdict could be reached based on available evidence[3-6]. It was anticipated that this process, and the implementation in the form of warnings, should lead to decreased prescribing of these CHCs. In the meantime, gestagens have been classified in risk classes instead of (historically motivated) generations. The CHC subject to the referral can be found in risk class (RC) I (norgestimate), III (desogestrel, gestoden, drospirenone), and X (nomegestrol, chlormadinone, dienogest). Risk class III shows a higher risk for venous thromboembolism (VTE) than class I[7,8]. For risk class X, no final assessment of VTE risk has been made. Risk assessment must take into account that these CHCs are typically taken for many years by women. Various epidemiological studies have shown that 60% of young women use oral contraception already at the age of 17, and by aged 19 this rises to 80%[1,9].

CHC prescribing patterns have been the subject of various studies, both nationally and internationally[9-13], including in the context of guidelines for the choice of hormone[14,15]. Developments though differ between countries. To the best of our knowledge, in Germany the impact of the referral process has not yet been studied. This study aims therefore to analyse whether the referral process, and the subsequent obligation for implementation of the pharmacovigilance measures, led to a change in CHC prescribing patterns. This is important not only to update current prescribing practices for CHCs in the most populous European country, but also emphasise whether additional pertinent interventions are needed to improve the prescribing of CHCs in Germany and wider.

2. Material and methods

2.1 Data and study population:
Two data sources were employed. In order to be able to make conclusions for all CHC recipients independent of the specific health care fund women are covered by[16], nation-wide prescription data of the German Statutory Health Insurance Rapid Drugs Information (GAmSi) were analysed. These are routinely collected as stipulated by law (article 84 section 5 of Social Code Book vol. V). These data, which are gathered through the pharmacy computing centres, are completely anonymous, i.e. they contain no reference to individuals. For approximately 3.3 million female insurees aged between 10 and under 20, analyses can be broken down by substance, patients' age, region (of doctors' offices) and physician specialty. Results are presented per 1000 insured women in the age group. As an additional data set, we used nation-wide data (so-called Act*rapid*! data) of the largest German health care fund group, AOK, which includes an anonymous person identifier. CHC prescription data for 1.1 million women (2nd quarter 2015) insured by AOK and aged between 10 and under 20 were used in order to assess the prevalence and incidence of treatment. Data included IDs for prescribing physicians, from which information on, e.g., physician specialty and region can be derived. Since both data sources consist of fully anonymised health claims data without any reference to individuals, no ethics approval was needed.

The age group "10 to under 20 years" was chosen to match previous German publications and information. The specific reason for this is that within the German statutory health insurance system, oral contraceptives are only reimbursed, with few exceptions, up to the 20th birthday. Due to this, there are no reliable health insurance routine data for other age groups. We also know from previous research that by the age of 19, 80%[1,9] of young women use oral contraceptives. Since girls under the age of 15 contribute only very little to overall CHC use, we also include a description concentrating on the more relevant subgroup, i.e. 15 years to under 20 years.

2.2 Hormonal substances in this study and their classification:
The CHC studied are listed in Table 1, which also states their risk class and generation.

Insert Table 1 here

CHC treatment prevalence is calculated as the percentage of female insurees with at least one CHC prescription in the period at issue. A prescription is assumed to be incident if and only if there was no CHC prescription within the 365 days prior to the first prescription within the period at issue. Incidence

is calculated as the number of female insurees with a first prescription of a CHC, divided by 1000 person years of the (sub)group studied.

2.3 Design and reporting period

The issues are analysed both descriptively and using time series analysis for the following four phases:
- 1st Jan 2011 to 31st Dec 2012: pre-intervention phase
- 1st Jan 2013 to 31st Jan 2014: referral phase
- 1st Feb .2014 to 31st Dec 2014: implementation of EMA conditions
- 1st Jan 2015 to 31st Mar 2016: post-intervention phase[†][1]

2.4 Statistics

Statistical analysis was performed using R 3.3.2. Development of the consumption of substance groups is shown descriptively as their respective shares on all CHC prescriptions and also as treatment prevalence. Regarding the time series analysis, for each risk class and each month in the study period, we calculated the number of women in the base population who had received a drug from the risk class at issue within that month. This number was then divided by the total number of women within the base population who had received any CHC within that month. We chose to work with these shares instead of absolute values since the absolute prescription volume varies substantially between months. This variation is partly due to the German system of defining cases of treatment on a quarterly base, which imposes a strong three-month rhythm on all ambulatory treatment volumes, and in particular on prescribing. In addition shifting public holidays, and especially school holidays, can lead to stockpiling of prescriptions. Both these factors are independent of prevalence and must therefore be eliminated from the analysis.

The time series were analysed using an extension of ARIMA (autoregressive integrated moving averages) models[17] such that the effects of interventions at known points in time could be assessed. ARIMA is often used for time series analyses, when the observations for the various time points are not independent of each other (auto-correlation of measurements).

As points of intervention we chose (a) the start of the referral process (January 2013) and (b) the start of the implementation of EMA conditions through prescribing information from the marketing authorisation holders and through Dear Doctor letters (start of February 2014). Fitting the models involved first a visual check of the residuals of the auto-correlation and the partial auto-correlation functions (ACF and PACF, respectively). For checking that the residuals were free of auto-correlation, the Ljung-Box Q-test was used. Existence of a unit root was tested with the Augmented Dickey-Fuller test.

After an appropriate model of the time series process had been developed, the influence of exogeneous interventions could be assessed. For each of the two interventions a binary dummy variable was introduced, which had the value 0 for the months before the respective intervention and 1 for every month starting with the month of intervention. Subsequently, the model was augmented with two interventional components as functions of the dummy variables. If an interventional component increases the explanatory power of the model by a statistically significant amount, this justifies the conclusion that the respective intervention had a statistically significant influence on the time series[17].

Both interventions were modelled as gradual onset and permanent effect. The extended model therefore has one additional pair of parameters (ω and δ, cf. below) per intervention. Further explanations can be found in Table 2.

Insert Table 2

Regarding the logistic regression, for assessing the factors influencing the first observed instance of a prescription of a certain CHC risk class only those insurees are included who received a CHC from risk classes I or III in the post-intervention phase (January 2015 until March 2016) and no drug of the respective risk class in the 365 days prior to that prescription. For insurees who received both a CHC

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† Time series analyses of prevalences was limited up until Oct 2015. Annual prevalences are shown only up to 2015, inclusively.

of risk class I and risk class III drug in the post-intervention phase, only the first such prescription in time is included.

Further factors included were patient ages, previous CHC status (naïve vs. use of drugs from some other risk class) and physician-related factors age (of physician), gender, region (by Doctors' Regional Association – Kassenärztliche Vereinigung, KV) and specialty. The significance of the contribution which the various factors added to the logistic regression model was tested using the Wald test. 95% confidence intervals (CI) were calculated according to the formula:

$$\left(e^{\hat{\beta}_j} - SE(\hat{\beta}_j) \cdot z_{1-\alpha/2}, e^{\hat{\beta}_j} + SE(\hat{\beta}_j) \cdot z_{1-\alpha/2}\right), \text{ where } \hat{\beta}_j \text{ is the estimated parameter, } SE(\hat{\beta}_j) \text{ is the}$$

standard error of the estimate and $z_{1-\alpha/2}$ is the quantile of normal distribution (in our case α = 0.05).

Since the study used only anonymised claims data of health insurance funds (secondary data use), no ethics committee approval was necessary. This is similar to other published studies[19].

3. Results

3.1 Development of CHC prescriptions
GAmSi data (data source A) show a steady increase in defined daily doses (DDD)[18] in all four phases for CHC in RC I and RC X (in total +12% and +37%, respectively) (Table 3). The DDD amount of RC II contraceptive medicines (vaginal preparations) is roughly constant on a low level. A substantial decrease (– 53%) occurs for RC III. This reflects also in the decreasing share of these CHCs as part of total CHC consumption. CHC consumption was almost constant over time at +4%.

Insert Table 3

The decrease of prescriptions of RC III drugs is comparable for both gynaecologists and general practitioners (GPs). However, GPs exhibit a higher increase of RC X drugs compared to gynaecologists (+38% vs. +30%, respectively). The importance of GPs as CHC prescribers decreased between 2010 (17.2% of total CHC DDDs) and 2015 (12.4%). The main prescribers, as expected in Germany, are gynaecologists.

3.2 Development of prevalence and incidence among AOK insurees
Data source B shows a decrease in the number of young women with at least one CHC prescription between 2011 and 2015 (0.356 million and 0.322 million respectively) due to a decrease in the number of women in this age bracket (the share of CHC recipients stayed constant at 30%) (Table 4a). Treatment prevalence of RC I was also slightly decreasing in absolute figures, but the share of RC I recipients on all CHC recipients grew from 35% in 2011 to 38% in 2015. The highest increase is observed for RC X. RC III shows, by contrast, a steady decrease. RC X has the highest incidence (Table 4b) in the various phases, the highest increase though happens for RC I. While RC I incidence share on all CHC was 38% before the referral, in the post-intervention phase it was nearly 44%. The number of new RC III recipients decreased by 21% during this period. Since CHC use below the age of 15 is very rare, the main group of users within the target population (i.e., starting at 15 and below 20) is documented separately in Table 4 b.

Insert Tables 4a and 4b

3.3 Development of the relative importance of the various risk classes
The development over time of the share of recipients of the various risk classes is displayed in Figure 1. The vertical lines mark the points in time of the interventions (start of referral and of implementation, respectively) used in modelling.
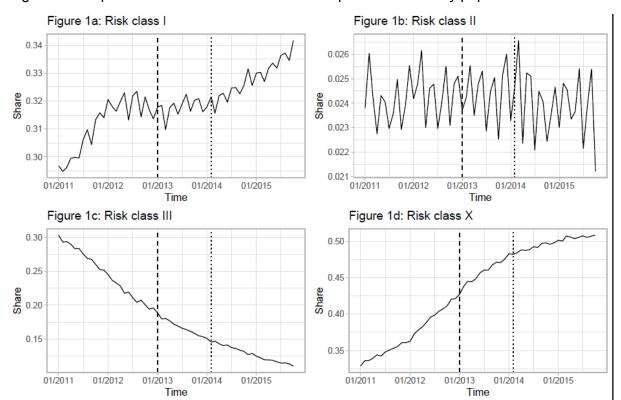
Figure 1: Recipients of CHC: Share of all CHC recipients in the study population

NB: The two vertical lines mark the start of the European risk assessment process (left line) and the point in time of the implementation (right line). Note that the *y* axes are scaled differently in order to show the values more clearly even though levels are different.

The analysis of the temporal trend for RC III shows a statistically significant decrease for the first month of the referral phase (change in the share of prevalent cases by $\omega=-0.0035$, i.e. a decrease by 0.35 percentage points, $p<0.001$). This indicates that the pre-existing decrease of RC III treatment prevalence was slightly enhanced by the referral process (interpreted here as a factor of influence). However, the second intervention (implementation of EMA conditions) showed no statistically significant effect. In other words, the decrease observed during the referral phase was not enhanced any further. For RC X drugs there is also a statistically significant effect of the referral phase on the development of prescription; however, this was in the opposite direction, i.e. after the start of the referral, prescriptions increased more strongly than in the months before (+0.46 percentage points, $p=0,009$). The estimate for the asymptotic total effect of the start of the referral process is roughly 1 percentage point. Like RC III, RC X showed no additional effect of the start of implementation (Table 5).

Insert Table 5

3.4 Factors influencing incidence
For insurees who received a RC I or III CHC for the first time during the post-intervention phase, factors influencing the prescription were investigated (Table 6). The odds of receiving a RC III CHC rather than a RC I CHC is almost three times as high when the insuree had received a CHC of a different class before. It doubles whenever a GP rather than a gynaecologist is the prescriber. There are also marked regional differences. In the federal state of Saarland, the odds compared to Baden-Württemberg are 1.3, while for Bremen it is only 0.77 (Table 6). The odds for receiving a RC III drug is roughly 25% lower whenever the prescribing physician is female.

Insert Table 6

4. Discussion

4.1 Comparison with other studies of CHC prescribing patterns

For the pre-referral period, the results from the present analysis are similar to the study by Ziller et al.[20], which analysed contraceptive prescriptions to women aged 12 to 18 for the years 2007 and 2011 based on prescription data from 167 gynaecological offices. The authors described an increase in treatment prevalence for levonorgestrel (RC I) and chlormadinone (RC X) as well as a decrease for drospirenone (RC III) and desogestrel (RC III). They stated that gynaecologists had changed their prescribing habits according to then available evidence of risk for VTE. At that time, however, 3rd and 4th generation CHC (as they were called at the time) had already been critically assessed with respect to their risk for thromboembolism, and further data on drug safety had been called for. An analysis of claims data by German health care fund Techniker Krankenkasse[1] for the years 2011 to 2013 also supports our finding that many young women received contraceptives of high or unclear risk. Changes from rather low risk drugs to those of higher or unclear risk were described. A similar pattern is reported by Bezemer et al. for the Netherlands, the UK, and Italy, in the period from 2009 to 2010 looking at women aged 16 to 49 years[21]. However, the authors also point out country-specific differences in the choice of CHC. In the Netherlands, predominantly 2nd generation CHCs were used at the time (79%), whereas in the other two countries 3rd generation CHCs were more common (UK: 44%, Italy: 62%). Similarly, according to our data, the share of 3rd and 4th generation on all CHC was around 67% during the period from 2011 to 2012.

We found regional differences in RC III use in line with regional data reported for CHC use in general by Boeschen et al.[1] Regional variations in health care use and prescribing are often reported,[22,23] but valid explanations are still an issue for research. As possible influencing factors we can therefore only assume, amongst others, differences in risk communication and policies.

4.2 Intervention analyses performed in other countries

An impact analysis of administrative measures was also performed by Briggs et al.[24]. The authors studied whether the guidelines from 2006 for prescribing CHCs depended on an individual risk assessment for each woman were actually employed. The share of women who were advised not to use a CHC due to their risk profile had decreased significantly since the publication of the guidelines, but the authors nevertheless describe it as too high given that better alternatives are available for prescribing. Successful intervention of the Danish Institute of Rational Pharmacotherapy in favour of prescribing 2nd generation CHC (levonorgestrel) is reported by Løkkegard and Nielsen[12]. Between 2010 and 2013, the number of recipients of 3rd and 4th generation CHC substantially decreased (–65% and –77%, respectively for the age group 14 to 19 years). Lemaitre et al.[10] report a similar development for France in 2012 und 2013, after a series of measures for influencing prescribing practice had been taken.

4.3 Limitations and strengths

As with all studies based on claims data, only prescription and redemption in the pharmacy can be observed but not actually taking the medicine. While the data sources allow extended periods of time to be observed and analysed, a limitation is that only indirect conclusions can be made since other possible factors of influence cannot be directly accounted for. The influence of any such factors is, however, minimised by the statistical design chosen, viz., comparison against secular trends, which is a standard method used for impact analysis[25].

We are also aware that the study only includes women up to their 20th birthday because, as mentioned, only for this group can complete prescription data from health care fund claims data can be accessed. We cannot prove that the results are transferable to other age groups; however, we believe there are strong hints to this effect. According to IMS data (2014)[1] more than half of the most frequently used contraceptives belong to risk classes III or X.

For modelling the time series, we used the period from January 2011 to October 2015. The period of observation was cut short by several months compared to initial plans because there seemed to be a substantial change of trends starting from the end of 2015, which stands in no plausible connection to the interventions studied here. Including the period at the very end would have had repercussions on the whole model and might have hidden the effect of the interventions studied here. Any causes for further changes were outside the scope of this study.

Among the strengths of the study are its use of two different data sources for controlling health care fund specific bias[16], the size of the data, and the long period of observation. Of particular interest is the linkage of prescriptions to selected characteristics of both receivers and prescribers, which made it possible to study factors influencing the prescribing patterns. The study shows that routine data can be used to obtain evidence on the impact of regulatory measures.

5. Conclusion

To the best of our knowledge, we believe this is the first study to investigate changes of prescribing patterns in connection with the referral process in Germany and wider. It is evident that such changes have already taken place before the start of the referral. This comes as no surprise given that the safety of contraceptives had been widely discussed in professional circles. The risks of oral contraceptives have been assessed as early as 1996 and again in 2001. This sets the context for the development of prescriptions and the effects described here. Proving a separate effect of the implementation of the conditions imposed by EMA is complicated by the fact that the marketing authorisation holders changed the prescribing information only step by step; hence, any effect is more difficult to separate from simultaneously occurring secular changes in prescribing. In addition, the ongoing effect of the start of the referral process on the perception within professional circles may "mask" any effect the second, additive intervention may have had.

It merits separate discussion whether the small, although statistically significant effects of the first intervention, have practical significance. But similarly, to observe no separate statistically significant effect of the second intervention should not lead to the conclusion that the conditions imposed by the marketing authorisation bodies were superfluous. In particular, in our opinion, they may have contributed to persisting the observed decreases. Not allowing to let the evidence slip from the mind of prescribers may prevent later increases. For reasons of principle, however, such effects are not amenable to proof by observing factual developments of prescription.

There are only hypotheses on the causes for the developments observed. Amongst others, it is an open question whether the warnings provided in prescribing information documents and in package inserts were sufficient. E.g., arznei-telegramm, an independent drug information journal, criticised in 2015 the phrasing used for prescribing information and suggested an unequivocal labelling of these CHC as "medicines of subordinate choice"[26]. Control of usage may also be achieved through rules for reimbursement and regulatory policies like in France.

Ongoing medical education in this area addresses mostly gynaecologists in Germany; however, GPs are also implicated in these prescriptions. They are in need of guidance for these medicines and their associated risks. We have been able to show that the risk of receiving a CHC with unfavourable risk profile is substantially increased among GPs compared to gynaecologists. This suggests that the communication of risks to GPs can still be improved upon and not be left to pharmaceutical companies. Substantial regional differences might also be explained by different information and risk communication policies in the various regions. This also needs to be addressed to ensure appropriate contraception for young women in Germany and wider. These are projects for the future

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Tables

Table 1 Combined hormonal contraceptives

Risk class	Gene- ration	ATC code[†]	Drug combination	Fixed combination (F)/sequential preparation (S)	Relative risk compared to levonor- gestrel	Estimate of incidence (per 1000 women per year)
I	1	G03AA05	norethisteron and ethinylestradiol	F		
I	1	G03AB04	norethisteron and ethinylestradiol	S		
I	2	G03AA07	levonorgestrel and ethinylestradiol	F	(reference)	5–7
I	2	G03AB03	levonorgestrel and ethinylestradiol	S	(reference)	5–7
I	3	G03AA11	norgestimat and ethinylestradiol	F	1.0	5–7
I	3	G03AB09	norgestimat and ethinylestradiol	S	1.0	5–7
II	(vagi- nal)	G02BB01	vaginal ring with gestagens and estrogens	n/a		
II	(vagi- nal)	G03AA13	norelgestromin and ethinylestradiol	F	1.0–2.0	6–12
III	3	G03AA09	desogestrel and ethinylestradiol	F	1.5–2.0	9–12
III	3	G03AA10	gestoden and ethinylestradiol	F	1.5–2.0	9–12
III	3	G03AB05	desogestrel and ethinylestradiol	S	1.5–2.0	9–12
III	4	G03AA12	drospirenone and ethinylestradiol	F	1.5–2.0	9–12
X	4	G03AA14	nomegestrol and estradiol	F	Unknown	
X	4	G03AA15	chlormadinone and ethinylestradiol	F	Unknown	
X	4	G03AA16	dienogest and ethinylestradiol	F	Unknown	
X	4	G03AB07	chlormadinone and ethinylestradiol	S	Unknown	
X	4	G03AB08	dienogest and estradiol	S	Unknown	

† ATC: Anatomical therapeutic chemical classification[18]

Table 2: Explanation of the parameters shown in Table 5

Parameter	Explanation
O(AR)	Order of auto-correlation in the ARIMA model
O(I)	Order of differences in the ARIMA model
O(MA)	Order of the moving averages in the ARIMA model
AR_n	Auto-correlation coefficient of order n
MA_n	Moving averages coefficient of order n
ω_n†	Effect on level of the nth intervention
δ_n‡	Effect on slope of the nth intervention
AIC	Akaike Information Criterion of the model (Measure of model quality: the lower the value, the more informative the model)
LBT	Test statistic (χ^2) and p-value of the Ljung-Box Q-test for the model (aim to have $p > 0,05$)
ADF	Test statistic and p-value of the Augmented Dickey-Fuller tests for the model (aim to have $p < 0,05$)

† Parameter ω estimates the difference between the share of prevalent cases in the first month after the respective intervention as it was actually observed on the one hand, and as it would have then been expected to be without the intervention. This is the effect in the first month only.

‡ Parameter δ describes how the monthly differences develop afterwards. For the second month after the intervention the effect of the first month is assumed to persist ("permanent effect"), but an additional effect is assumed ("gradual onset"). This additional effect is described by $\delta \cdot \omega$. The total effect for the second month compared to the expected value without any intervention is therefore $\omega + \delta \cdot \omega$. Analogously, the total effect in the third month will be $\omega + \delta \cdot \omega + \delta^2 \cdot \omega$ etc. If δ is non-negative and less than 1, the asymptotic total effect over time will be $\omega/(1 - \delta)$. This value can thus be interpreted as an estimate for the long-term effect of the intervention. The speed with which this long-term effect is approximated is described by parameter δ: The smaller the value of δ, the faster the monthly effect figures will approach the final value. (In the extreme case of $\delta = 0$ the maximum effect would be reached immediately after the intervention, whose effect would then be shock-like.) It should be noted that these considerations are valid only if parameter ω is significantly different from 0. Otherwise, one cannot assume to have shown an effect of the intervention. (The present study follows the widespread convention of a 5% level for significance.) The estimate for the asymptotic long-term effect is valid only if the value of δ is also significantly different from 0. Otherwise, one could not exclude with sufficient certainty that $\delta = 0$. In this case, as noted above, the effect in the first month would already be the final value.

Table 3: Development of DDD† per year per 1000 insured women in the age between 10 and under 20, broken down by CHC‡ risk classes

Risk class	Pre-Intervention	Referral	Implementation	Post-Intervention	Ratio
	A	B	C	D	D/A
I	26,122.7	27,667.6	28,448.2	29,225.6	1.12
II	1,991.2	2,029.4	2,002.5	1,932.2	0.97
III	21,353.0	14,825.9	12,138.7	9,933.6	0.47
X	32,334.7	40,235.2	43,736.1	44,144.2	1.37
Total	81,801.5	84,758.2	86,325.5	85,235.5	1.04
Share of III on Total (%)	26.1	17.5	14.1	11.7	0.45

All phases are normalised to a length of 12 months.
† DDD: defined daily dose, ‡ CHC: combined hormonal contraceptives

Table 4 a: Annual prevalence (in 1000 units) of risk classes for AOK-insured† women aged 10 to under 20 years

Risk class	2011		2012		2013		2014		2015	
I	126.6	(35.4%)	124.2	(36.0%)	120.4	(35.7%)	119.8	(36.0%)	122.9	(38.1%)
II	11.2	(3.1%)	10.8	(3.1%)	10.6	(3.1%)	10.1	(3.0%)	9.8	(3.0%)
III	109.9	(30.7%)	83.4	(24.2%)	65.1	(19.3%)	52.1	(15.7%)	41.8	(13.0%)
X	142.0	(39.7%)	155.8	(45.2%)	170.2	(50.5%)	176.0	(52.9%)	172.3	(53.4%)
Total	357.7	(100.0%)	345.0	(100.0%)	337.3	(100.0%)	332.4	(100.0%)	322.4	(100.0%)

†AOK: Local health care funds

Table 4 b: Incidence per 1000 insuree years of CHC† recipients aged under 20, broken down by risk class

Risk class	Pre-intervention	Referral	Implementation	Post intervention	Ratio
	(A)	(B)	(C)	(D)	(D/A)
All age groups (10 to under 20)					
I	58.2	67.8	84.7	118.3	2.03
II	2.9	3.6	4.1	5.1	1.76
III	27.3	24.4	24.1	21.7	0.80
X	66.4	94.6	112.2	125.6	1.89
Total	154.7	190.4	225.1	270.7	1.75
Subgroup 15 to under 20					
I	83.5	83.2	93.1	120.6	1.45
II	4.4	4.6	4.8	5.5	1.24
III	41.1	30.8	27.7	23.4	0.57
X	96.2	117.0	127.0	132.7	1.38
Total	225.2	235.6	252.6	282.3	1.25

† CHC: combined hormonal contraceptives

Table 5: Model parameters for the various risk classes

Parameter	Risk class I			Risk class III			Risk class X		
	Value	Std Err	*p*-Value	Value	Std Err	*p*-Value	Value	Std Err	*p*-Value
O(AR)	4			2			2		
O(I)	1			2			2		
O(MA)	0			2			1		
AR_1	-0.6398	0.114	<0.001	-0.8791	0.113	<0.001	-0.5868	0.187	<0.001
AR_2	-0.0738	0.098	0.453	-0.7928	0.094	<0.001	-0.6313	0.112	<0.001
AR_3	0.7465	0.100	<0.001						
AR_4	0.4909	0.114	<0.001						
MA_1				-0.6980	0.192	<0.001	-0.5897	0.128	<0.001
MA_2				0.2854	0.195	0.143			
δ_1	**-0.0000**	**n/a**	**n/a**	**0.3421**	**0.246**	**0.165**	**0.5201**	**0.255**	**<u>0.041</u>**
ω_1	**0.0002**	**n/a**	**n/a**	**-0.0035**	**0.001**	**<u>0.001</u>**	**0.0046**	**0.002**	**<u>0.009</u>**
δ_2	0.0000	n/a	n/a	0.4900	0.350	0.161	0.0055	n/a	n/a
ω_2	-0.0006	n/a	n/a	-0.0018	0.001	0.179	0.0000	n/a	n/a
AIC	-504.0069			-526.3275			-496.2445		
LBT	25.0452		0.200	15.1708		0.767	13.0957		0.905
ADF	-3.4982		0.050	-3.5291		0.047	-3.5694		0.044

Legend: cf table 2

Table 6: Odds Ratio for incident recipients of risk class III compared to risk class I during the post-intervention phase

Factor	Value	Odds Ratio (95% CI)	p-value†
Intercept		0.108 (0.088, 0.134)	< 0.001
Age		1.049 (1.037, 1.062)	< 0.001
Region	Baden-Württemberg	Reference	-
	Bavaria	1.037 (0.973, 1.105)	0.266
	Berlin	1.116 (0.965, 1.288)	0.135
	Brandenburg	0.956 (0.808, 1.126)	0.593
	Bremen	0.766 (0.617, 0.943)	0.014
	Hamburg	0.859 (0.710, 1.034)	0.114
	Hesse	0.925 (0.841, 1.017)	0.108
	Mecklenburg-Vorpommern	1.090 (0.913, 1.295)	0.333
	Lower Saxony	0.878 (0.816, 0.945)	< 0.001
	North-Rhine	1.007 (0.934, 1.085)	0.855
	Rhineland-Palatinate	0.964 (0.868, 1.069)	0.487
	Saarland	1.293 (1.030, 1.614)	0.024
	Saxony	0.784 (0.710, 0.864)	< 0.001
	Saxony-Anhalt	0.801 (0.686, 0.933)	0.005
	Schleswig-Holstein	0.965 (0.856, 1.086)	0.555
	Thuringia	1.017 (0.902, 1.146)	0.780
	Westphalia-Lippe	1.170 (1.084, 1.263)	< 0.001
	Unknown	0.788 (0.319, 1.756)	0.579
Specialty	Gynecologists	Reference	-
	General practitioners	1.973 (1.830, 2.126)	< 0.001
	Other	1.189 (0.899, 1.565)	0.220
Physicians' Gender	Male	Reference	-
	Female	0.752 (0.720, 0.785)	< 0.001
	Unknown	1.020 (0.795, 1.302)	0.876
Age of physician	Under 45	Reference	-
	45 to below 60	1.004 (0.949, 1.063)	0.881
	60 and older	1.032 (0.965, 1.103)	0.363
Patient's CHC status	Naïve	Reference	-
	Previously exposed	2.780 (2.663, 2.901)	< 0.001

†p-values obtained from Wald test.