Impact of a physician-targeted letter on opioid prescribing

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IMPACT OF A PHYSICIAN-TARGETED LETTER ON OPIOID PRESCRIBING

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ABSTRACT

We study the effect of a physician-targeted nudge letter on opioid prescribing. In May 2017, the Social Insurance Institution of Finland sent a personal information letter to all physicians who had issued a prescription containing at least 100 tablets of paracetamol-codeine combination to a new patient. The aim of the letter was to draw the physicians' attention to their prescribing practices and to decrease the size of the first codeine prescription. Using individual level register data and a difference-in-differences strategy, we estimate that the letter decreased the average number of tablets purchased by new patients by 12.5 percent and the probability of a first purchase being at least 100 tablets by six percentage points. We also find that these effects were larger among consistent high prescribers. However, we do not find similar effects on other mild or strong opioids.

JEL classification: I10, I12

Keywords: Opioid prescribing, Information letter, Prescription drugs, Difference-in-differences

1 INTRODUCTION

Opioid addiction and opioid related deaths are vast and growing public health problems especially in the United States. In 2016, 1.5% of all deaths in the U.S. were attributable to opioids, and 20% of deaths among adults aged 24 to 35 involved opioids (Gomes et al. 2018). A recent study by Powell et al. (2020) suggests that an increase in the supply of medical opioids has been a significant driver of opioid overdose deaths.

The use of prescription opioids and opioid-related mortality is also growing in Western Europe, but the levels are considerably lower than in the U.S. (van Amsterdam and van den Brink 2015; Fischer et al. 2014). In Europe, the growth in opioid consumption has been even more rapid than in the U.S. in recent years. However, on average, the levels are still considerably lower in the EU countries. There are also significant differences in opioid consumption and associated problems between European countries. In some Eastern and Southern European countries, the problem lies more in the insufficient treatment of pain. In Western and Northern European countries, the levels of use and the risks arising from the overuse of opioids are higher (for a more detailed discussion of the situation in Europe see e.g. Bosetti et al. 2019 or Statistical Bulletin 2019).

In Finland, 395,251 persons purchased reimbursable prescription opioids in 2017. Most of the prescription opioid purchases are mild opioids, paracetamol-codeine combination being the most popular (Nevantaus et al. 2013). Paracetamol-codeine combinations are commonly used in the treatment of both acute and chronic pain. 256,737 persons, which represents around 4.7% of the Finnish population, purchased paracetamol-codeine combinations in 2017. There has been an increasing trend in opioid abuse also in Finland (Häkkinen 2015). It is estimated that in 2017 there were 23,500–29,500 opioid problem users in Finland. That is 0.68–0.86% of the population. The problem users were defined as people who had an official record of opioid use that had caused some social or health

related problem (Rönkä et al. 2020; Selin et al. 2015). Fatal poisonings by prescription opioids accounted for a third of all drug poisonings in 2008 (Häkkinen et al. 2012).

An appealing course of action to reduce the harms is to influence the dose, duration and formulation of the prescriptions (Samet and Kertesz 2018). The size and duration of the first prescription has been shown to be a significant predictor of continuing opioid use (Barnett et al. 2017; Shah et al. 2017). Therefore, reducing the size of the first purchase can be one effective way to mitigate the adverse effects related to opioid prescribing. One means to influence prescribing is to provide education about proper clinical guidelines.

The aim of our study is to analyze the effects of a personal information letter on physicians' opioid prescribing patterns. The letter was sent by the Social Insurance Institution of Finland (Kela) in May 2017 to 4,549 physicians who had prescribed a package containing at least 100 tablets of paracetamol-codeine to a new patient in 2016. The aim of the letter was to draw physicians' attention to their prescribing practices and decrease the package size of the first paracetamol-codeine prescription. The letter gave general information about pain relief with paracetamol-codeine and suggested that treatment be started with a package containing only 10—30 tablets, because of the high risks associated with long-term use of the drug. Two key questions we seek to answer are: First, what effect did the information letter have on paracetamol-codeine purchases among new patients? Second, what was the impact on the probability of a new patient purchasing at least 100 tablets?

We add to recent literature by Doctor et al. (2018) and Sacarny et al. (2016), which studies the effects of large-scale information campaigns on opioid prescribing. A strength of our setting is the universal coverage of health care in Finland. This enables us to identify effects that are not confounded by the availability of health insurance. Additionally, to our knowledge, we are the first to study

a nationwide prescribing information campaign in Europe[1]. The letter was only sent to physicians who had issued a large prescription to a new patient. This yields a quasi-experimental setting, which enables a reliable analysis of the impact of the letter on the physicians' prescribing behavior. We use a difference-in-differences research design, in which the treatment group consists of new patients whose physician received the letter, while the control group consists of new patients whose physician did not receive the letter. The number of physicians who received the letter represents roughly 17 percent of all physicians who prescribed any reimbursed drugs in Finland in 2018. We use comprehensive register data on all reimbursed paracetamol-codeine, tramadol (mild opioid) and oxycodone (strong opioid) purchases with a 12-month follow-up period to analyze the effects of the letter on new patients' paracetamol-codeine purchases as well as on tramadol and oxycodone purchases. Furthermore, we conduct subsample analyses based on physicians' previous prescribing frequency, specialty and place of residence to study the heterogeneous effects of the letter.

There is growing empirical evidence suggesting that influencing physicians' prescribing patterns can have a key role in tackling the opioid epidemic. Schnell and Curie (2018) show that opioid prescribing depends on physicians' initial education in pain management, and training aimed at the most liberal prescribers could be a successful policy tool. Studies have also shown that mandatory prescription drug monitoring programs, which record the patient's prescribing history, have decreased opioid and other prescription drug abuse (Buchmueller and Carey 2017; Dave et al. 2017).

Our study relates to the literature studying the effects of information letters on physician prescribing behavior (e.g. Ho and Venci 2012; Sacarny et al. 2016; Sacarny et al. 2018). In this literature, evidence is somewhat mixed. Ho and

[1] For example, in Søndergaard et al. (2002), Søndergaard et al. (2003), Naughton et al. (2007) and Rokstad et al. (1995) the interventions studied were local and smaller-scale.

Venci (2012) reviewed 39 interventions of which 26 found an impact on at least some of the studied outcomes. Their review also stated that letters targeting one specific drug were more successful than those with a wider range of targets. The letter under evaluation in this paper also targeted one specific drug and had an expert article as an attachment. More recently, informational letter campaigns have been used to tackle the current opioid crisis. Doctor et al. (2018) analyzed the effect of a personal letter from the medical examiner to physicians whose patient had died from an overdose of a controlled substance. Their findings show that the letter decreased opioid prescribing and its recipients were less likely to start a new patient on opioids. However, Sacarny et al. (2016) found no effects when a peer comparison letter was sent to physicians who were identified as potential over-prescribers of controlled substances, which include opioid pain relievers. The letter under evaluation in this study also, although implicitly, informed physicians that they were prescribing more than their peers. Sacarny et al. (2018) found that physicians, who were informed by letter that their prescribing of antipsychotics were under review and their prescribing was compared to their peers', decreased their prescribing of quetiapine 11 percent relative to the comparison group. This is in line with our estimate that the information letter decreased the number of tablets prescribed to new patients by roughly 12.5 percent compared to the pre-letter mean. Doctor et al. (2018) found effects of the same magnitude in their study.

Furthermore, effects of informational letters have been studied, for example, in the context of tax collection (Hallsworth et al. 2017) and energy conservation (Allcott and Rogers 2014), in which social norms have been shown to have a significant impact on behavior.

In more general terms, there is evidence of overuse in several categories of medical services. These include, for example, overprescribing addictive substances and the overuse of screening and diagnostic tests and end-of-life care. These practices can lead to adverse health effects and unnecessary health care

costs. It has been suggested that one of the drivers of overuse, in addition to economic incentives, is inaccurate information about treatment practices. Thus, providing physicians feedback and information on clinical guidelines can be an effective policy tool to reduce the overuse of medical services. (Sacarny et al. 2016; Brownlee et al. 2017; Saini et al. 2017).

A personal information letter may influence physicians' prescribing behavior through several potential mechanisms. First, the letter and its guidelines may have educated physicians about the use of paracetamol-codeine combination in pain treatment especially on new patients. As Sacarny et al. (2016) describe, informative letters could present a form of continuing medical education. Information letters can provide information on proper prescribing practices to physicians relatively cheaply compared to, for example, reading scientific literature or attending seminars. The costs of acquiring information can be associated with the use of certain information in physicians' decision making (Phelps 2000; Phelps and Mooney 1993). Second, the information acquired from the letter is probably more "available" to the physicians right after they receive it than older information, on which their previous prescribing was based. Availability is a well-known concept in psychology and behavioral economics (see e.g. Tversky and Kahneman 1973). Third, the letter may serve as a signal that prescribing patterns are monitored. The possibility of monitoring can lead to a decrease in overall prescribing (Sacarny et al. 2018; Buchmueller and Carey 2017; Dave et al. 2017). Fourth, the information letter implicitly reminds the physicians that they have been prescribing more paracetamol-codeine than most of their peers. This may signal that the physicians are violating a social or a professional norm[2]. Adhering to the professional norm enables that, in the case of an adverse treatment outcome, physicians can refer to the norms they are following. Therefore, complying

[2] Professional norms in medical care are discussed already in Arrow (1963).

with professional norms can lower the "responsibility costs" of the physician (Frank 2004).

2 THE INFORMATION LETTER

On 29 May 2017, Kela sent a letter to 4,549 physicians, informing that they had prescribed a package containing at least 100 tablets of paracetamol-codeine to a new patient. The objective of the letter was to draw the physicians' attention to their prescribing practices regarding paracetamol-codeine combinations and decrease the size of the first prescription for a new patient. The letter included a recommendation that treatment be started with a package containing only 10—30 tablets, because of the high risks associated with long-term use of the drug. Treatment of acute pain with paracetamol-codeine was chosen as the letter's topic, because long-term use of the drug is common and prescribing patterns are known to be independent of patient characteristics or morbidity (Barnett et al. 2017). This scientific reference was also mentioned in the letter.

In addition, the letter included a two-page expert article about the use of paracetamol-codeine combinations in pain treatment. The first page of the article had information about the pharmacology of paracetamol and codeine, the use of their combination in acute pain and the problems associated with their use. For example, the article mentioned that the use of codeine involves the risk of developing into an opioid addiction, after which ending the medication becomes hard for both the physician and the patient.

The second page of the expert article included five suggestions for preventing codeine addiction. The first suggestion encouraged physicians to consider whether the drug was the best alternative for this patient and this acute pain. The second suggestion advised to start the treatment with a package of 10—30 tablets for acute pain. This was also mentioned in the cover letter and on the

first page of the article. The third suggestion was to not renew a prescription for an unknown patient. The fourth suggestion advised to examine reasons, consider alternative treatments, and, if necessary, to start drug rehabilitation if a patient's drug use had become prolonged. Finally, the fifth suggestion was to consult a pain specialist in problematic cases. The translations of the information letter and the expert article are presented in the Online Appendix.

Kela chose the recipients of the information letter based on physicians' past prescribing of paracetamol-codeine to new patients. The recipients were selected in the following manner: Patients who had not purchased a paracetamol-codeine drug between 1 January 2013 and 31 December 2015 but purchased a package that contained at least 100 tablets in 2016 were identified from the national prescription register. Physicians issuing these prescriptions received the letter. In total, the letter was sent to 4,549 physicians, including 14 dentists.

The information content of the letter was also published in a medical journal article (see Saastamoinen et al. 2018) on 16 June 2017, two and a half weeks after the letter was sent out. The article was published simultaneously in the Finnish Medical Journal, which is the leading journal aimed at medical doctors in Finland, and in the Finnish Dental Journal. The journal article had the same information as the expert article in the letter, including the five suggestions to prevent codeine addiction. The letter also received some coverage in Finnish media in 2017.

The contents of the letter reaching physicians who did not receive it personally relied upon these other information channels. Because of the media coverage and the popularity of the Finnish Medical Journal among physicians, it is likely that most physicians became aware that Kela had sent a letter to some of their colleagues. However, receiving a personal letter at one's home address is likely a much stronger "nudge" to influence physicians' prescribing behavior. For example, Wathen and Dean (2004) found that NICE's general guidelines had very little impact on general practitioners prescribing patterns in England.

This was not the first time Kela contacted physicians related to their prescribing. In 1997—2014, Kela sent feedback to all physicians on their general prescribing practices. Since then, physicians have been able to find information on their prescriptions for the last five years through Kela's website. However, this letter was the first incidence of a selected group of physicians receiving a personal letter regarding specific products, including guidelines for prescribing the drugs. Kela also sends letters frequently to its other clients and stakeholders, for example regarding different benefit applications and decisions, and has standardized procedures for mass letter mailings[3]. Thus, the letter campaign was relatively inexpensive and easy to carry out.

3 DATA

We use register data from the National Prescription Register, which is maintained by Kela. The register contains records of all purchases of reimbursed prescription drugs dispensed in outpatient care in Finland. The data of the Prescription Register originates from pharmacies. In total, our data contains a repeated daily cross-section of 146,178 new patients' paracetamol-codeine purchases.

For this study, we retrieved data on all paracetamol-codeine combinations (ATC codes: N02AA59 and N02AJ06), tramadol (ATC code: N02AX02) and oxycodone (ATC code: N02AA05) purchases between 1 January 2013 and 30 June 2018. For each purchase, we use information on the number of tablets or capsules purchased, date of the purchase, strength and route of administration of the drug, whether the package was distributed as a dose dispensing, whether the patient was entitled to special refund and unique identifiers for patients and physicians.

[3] Matikka and Paukkeri (2016) studied the effects of an informational letter that Kela sent to pensioners who were eligible for a new pension program.

We exclude observations in which the purchase was distributed as a dose dispensing, because the purchase frequency of these purchases can differ from other prescriptions. Although we do not observe physicians' prescription decisions directly, patients cannot purchase paracetamol-codeine or other opioids without prescription.

We augment the Prescription Register data with additional information about drugs purchased based on the Nordic Product Number, which is a unique identification number for distinct drug packages. Finally, we merge these data with patient and physician characteristics from the Population Register of Finland and the Kela register of physicians' specialties. These characteristics include age, sex, native language, place of residence, controls for comorbidity, and physicians' possible specialty.

In our main analysis, we use data on new patients who purchased their first paracetamol-codeine prescription between January 2017 and June 2018. Our definition of a new patient is that the patient had not purchased paracetamol-codeine in the previous three years. We identify these new patients for each month between January 2017 and June 2018. We focus on new patients because the information letter was sent based on physicians prescribing paracetamol-codeine to new patients and the aim of the letter was to influence prescribing to new patients.

For filled paracetamol-codeine prescriptions, we use five different outcomes. The first outcome variable is the number of tablets per purchase, which is calculated for each purchase by multiplying package size with the number of packages purchased. We do not use Defined Daily Doses (DDDs)[4] when studying filled paracetamol-codeine prescriptions, because in all paracetamol-codeine purchases in our data the strength of the drug is 500/30 mg and the DDD is three

[4] DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (i.e. a technical unit of measurement for drug consumption) (WHO 2020).

tablets. In addition, for filled paracetamol-codeine prescriptions, we define four indicator variables based on the most common package sizes (100, 50, 40, and 20 tablets) in the data, and use these variables as outcomes in our analysis. For tramadol and oxycodone, we use outcomes based on DDDs as well.

Because we do not possess a list of physicians who received the letter directly linking to the unique physician identifiers in our data, we identified physicians who received the letter using the same information that Kela used in mailing the letters. In the first stage, we identified patients who purchased a large package, at least 100 tablets, of paracetamol-codeine in 2016 and had no purchases in the previous three years. In the second stage, we identified the physicians who prescribed these purchases. This approach enables us to indirectly identify 4,357 out of 4,549 physicians who received the letter from our purchase data. This is 96 percent of the actual recipients of the letter.

Table 1 Descriptive statistics of new patients' first paracetamol-codeine purchases in May 2017

Panel A	Patients					
	No Letter			Letter		
Variable	N	Mean	SD	N	Mean	SD
Tablets per purchase	5,380	32.6	20.0	3,793	48.0	30.0
Purchase of at least 100 tablets, proportion	5,380	0.039	0.19	3,793	0.17	0.37
Age, years	5,380	49.8	18.8	3,793	52.4	19.0
Non-Finnish speaker, proportion	5,380	0.11	0.31	3,793	0.088	0.28
Male, proportion	5,380	0.49	0.50	3,793	0.51	0.50
Comorbidities	5,380	0.74	1.30	3,793	0.84	1.40
Panel B	Physicians					
	No Letter			Letter		
	N	Mean	SD	N	Mean	SD
Tablets per patient (mean)	2,942	33.6	20.6	1,570	49.0	30.4
At least 100 tablets per patient, proportion	2,942	0.053	0.21	1,570	0.18	0.34
Age, years	2,790	42.6	12.0	1,570	45.1	12.2
Non-Finnish speaker, proportion	2,942	0.15	0.36	1,570	0.13	0.34
Male, proportion	2,790	0.47	0.50	1,570	0.61	0.49
Specialist, proportion	2,942	0.38	0.48	1,570	0.47	0.50

Notes: in Panel B, variables Tablets per patient and At least 100 tablets per patient are calculated from data in which all first purchases in May 2017 are aggregated to physician-level.

In Table 1, we present descriptive statistics for May 2017. The letter was mailed on 29 May. Panel A shows the characteristics of patients who were first-time paracetamol-codeine purchasers, based on whether their physician received the information letter. The mean size of the purchase was about 15 tablets higher in the group of patients whose purchase was prescribed by a physician who received the letter. These patients were also on average 2.6 years older than those whose physician did not receive the letter. Otherwise, patient characteristics are quite similar between the two groups. Panel B shows that physicians who received the letter prescribed, on average, over 15 tablets more per purchase, than physicians

who did not receive the letter. The group of physicians who received the letter included 14 percentage points more men and 9 percentage points more specialists than the group of physicians who did not receive the letter.

4 METHODS

Our empirical analysis is based on a patient level difference-in-differences (DD) analysis. As a treatment group, we use patients whose prescription was issued by a physician who received the letter. The control group consists of patients whose prescription was issued by a physician who did not receive the letter. Kela sent the letter on May 29 2017. We use 1 June as our first treatment date, because there was probably some delay in delivering the letters. We do not know the exact time that Finnish mail used delivering the letters, but according to their website, a normal letter was delivered in one or two weekdays in 2017. In our analysis, the difference in purchase sizes between the treatment and control group is the first difference. The second difference is the comparison of before and after the letter.

We use individual-level purchase data on new patients' paracetamol-codeine purchases from January 2017 to June 2018 to estimate models that have the following form:

$$y_{ipt} = \alpha + \gamma_0 After_t + \gamma_1 Letter_p + \delta After_t * Letter_p + X'_{ipt}\beta + u_{ipt}\,, \qquad (1)$$

in which i refers to patients, p to physicians and t to time of the purchase. y is the outcome of interest. $After$ takes value 1 if the purchase was made on June 1 2017 or after, and 0 otherwise. $Letter$ is an indicator taking value 1 if the prescription was issued by a physician who received the letter. $After_t * Letter_p$ is an interaction term taking value 1 if the purchase takes place on June 1 2017 or after and

was prescribed by a physician who received the letter. X is a vector of patient- and physician-level control variables. For patients, we include age, age squared, sex, a control for comorbidities[5] and a dummy indicating if patients' native language is something else than Finnish. For physicians, we include age, sex and dummies for native language and specialists. We also control for common time trends affecting all individuals in our data, by including month dummies in the covariate vector. u is the error term.

Our parameter of main interest is the DD coefficient, δ. This parameter measures the change in purchase size, or in the probability of purchasing at least 100 tablets, in the treatment group relative to the control group.

The letter was sent to all physicians prescribing a large amount of paracetamol-codeine to a new patient. In order to achieve a more reliable research design, the recipients of the letter should have been randomized to intervention and control groups. A potential source of endogeneity in our research design would be a variable that is related to the assignment to receive the information letter and to the outcome trend. Hence, identification in the DD model is based on the assumption of parallel trends between the treatment and control groups in the absence of the information letter. This assumption is not directly testable because the treatment group counterfactual is unobservable. However, we present evidence on parallel pre-treatment trends from January 2017 onwards (Figure 2 and event study figures).

We estimate event study models to support the assumption that unobserved factors are not driving the outcome trends. This also enables us to study

[5] In Finland, patients can apply for entitlement to special reimbursement of certain medicine expenses with a physician's certificate if the condition entitles to this reimbursement. We can observe these entitlements and calculate the number of entitlements for each patient. This is not a perfect measure of comorbidity, but patients have a significant financial incentive to apply for the entitlement to special reimbursement because the reimbursement rate varies from 40% to 100% after the initial deductible of 50 euros. (Kela 2020.)

whether the physicians' reaction to the information letter was instantaneous and whether the effect was lasting or just temporary. The estimated event study equation takes the following form:

$$y_{ipt} = \alpha + \gamma_1 Letter_i + \sum_{t=2017m1}^{2018m6} \delta_t Month_t * Letter_p + X'_{ipt}\beta + u_{ipt}. \quad (2)$$

The parameters of interest in equation (2) are the coefficients on the interaction terms ($Month_t * Letter_p$) between the month dummies and the treatment group indicator. We omit May 2017, the first leading period to the treatment, so that estimated coefficients are measured relative to this first pre-treatment period. The covariate vector X_{ipt} is defined as in the equation (1).

We do not observe if the physicians to whom the letter was sent actually received or read it, so our DD model measures the intention to treat (ITT) effect of the letter. The estimated effect is uncovered within a context where physicians in the control group were not addressed personally but may be aware of the recommendations and guidelines of the letter.

We estimate all our model specifications using ordinary least squares. When using binary outcome indicating whether the quantity of tablets purchased was at least 100 this estimation technique corresponds to a linear probability model. Throughout, we use standard errors clustered at the physician level to account for correlation in error terms across physicians over time. The physician-level is also the level to which the treatment was directed (Bertrand et al. 2004; Abadie et al. 2017).

We use data from 2016 to identify the physicians who received the letter, and data from January 2017 to June 2018 to estimate the DD and event study models. We have three reasons for this: first, because the letter was sent to all physicians who prescribed at least 100 tablets to new patients in 2016, there is no meaningful comparison of the outcome trends between the treatment and control

groups before January 2017 in the case of large purchases. Second, there is a considerable chance of reversion to the mean between treatment and control groups after the selection period ends in December 2016. This is because, in addition to prescribing a large quantity for new patient, the physicians who received the letter prescribed more paracetamol-codeine for new patients in 2016 on average as well. Third, in the beginning of 2017, the monitoring of patients' purchase interval of a given drug was extended to cover drugs in the basic reimbursement category (Government proposal 184/2016). This means that the patient should have used the previous batch of drugs before the next purchase in order to get the reimbursement. Paracetamol-codeine is generally reimbursed at the basic rate and therefore the aforementioned reform in the Finnish reimbursement system could have had an impact on the size of purchases of paracetamol-codeine between 2016 and 2017. We provide results estimated using data from the beginning of 2016 in the Appendix A, Table A1. These results indicate that we would be overestimating the effect of the information letter if we were to use the 2016 data as well.

The disadvantage of using data on drug purchases is that we do not observe actual prescribing by physicians. It is possible that a patient purchases only a fraction of the prescribed drugs. However, the prescription sets an upper limit to the size of the purchase. As a robustness check, Table A2 presents results based on data aggregated to the prescription-level. The prescription is identified based on patient identifier, prescription date, prescriber identifier, ATC code, strength of the drug and drug administration route. Similar aggregation has been used in Böckerman et al. (2019). Our results are robust to this aggregation, which suggests that not necessarily filling out the whole prescription is only a small disadvantage to our study. The advantage of using purchase data is that the number of tablets purchased measures the drugs available to patients better than number of tablets prescribed.

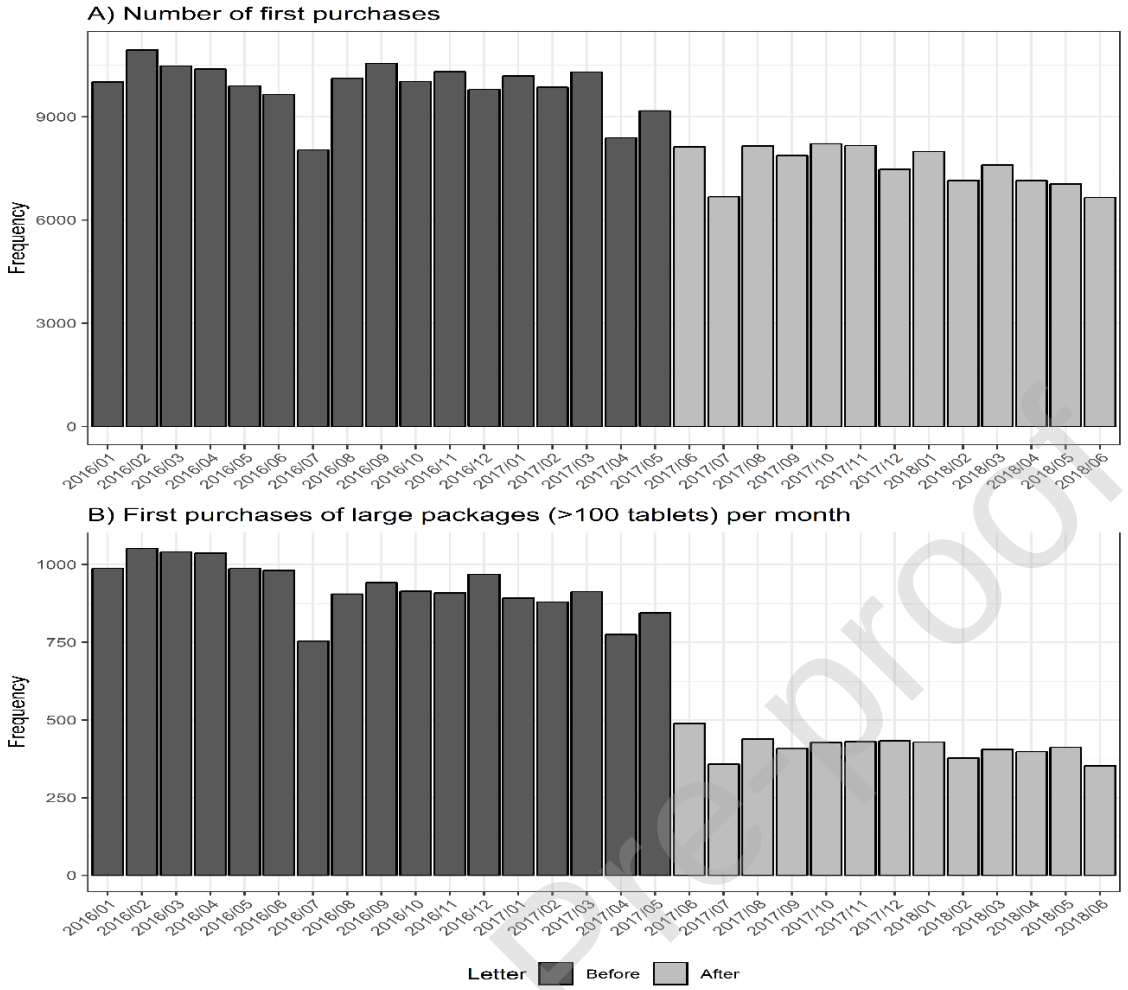
We do two additional robustness checks. First, we add group specific time trends to the models (Table A3). Second, we estimate a propensity score matching DD model following Villa (2016), where the matching is based on observed physician characteristics (Table A4). These changes in the model specification do not cause major changes to the DD coefficients.

5 RESULTS

5.1 Graphical evidence

Figure 1 shows the monthly frequencies of new patients' paracetamol-codeine purchases (Panel A) and monthly frequencies of purchases of at least 100 tablets of paracetamol-codeine (Panel B) between January 2016 and June 2018. As shown in Panel A, the number of paracetamol-codeine purchases by new patients declined during spring 2017, before the letter was sent to physicians. However, there is no substantial change after the physicians received the letter. Panel B shows a slight downward trend in the number of large purchases, continuing from January 2016 through early 2017. However, in June 2017, this frequency almost halves. This abrupt and persistent drop is coincidental with the information letter.

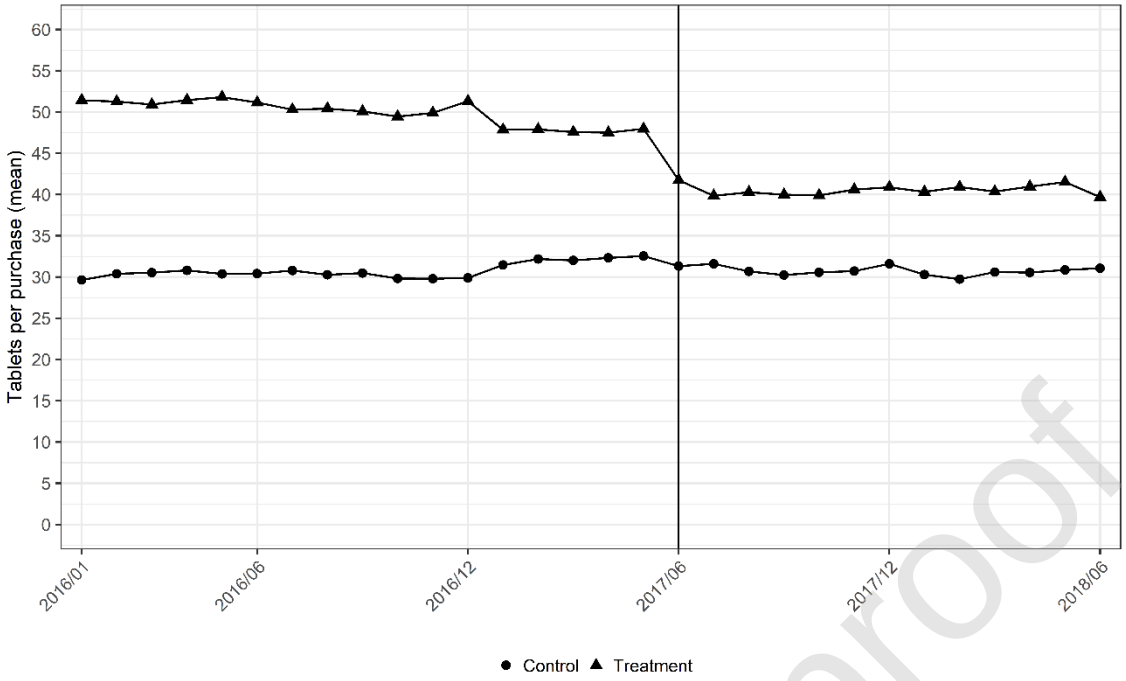
Overall, there is no substantial change in the number of all first-time paracetamol-codeine purchases around June 2017. If the number of new patients purchasing paracetamol-codeine had declined overall around June 2017, it could be expected that the number of large purchases would have decreased in the same proportion as well. The change in the number of large purchases is relatively much higher.



Notes: Panels A and B have different vertical axis scales. Panel A: monthly paracetamol-codeine purchases by new patients from January 2016 to June 2018. Panel B: monthly paracetamol-codeine purchases of at least 100 tablets by new patients from January 2016 to June 2018.

Figure 1 Monthly paracetamol-codeine purchases made by new patients from January 2016 to June 2018

Figure 2 presents trends in the mean size of first purchases separately for the treatment and control groups. From January 2016 to May 2017, the mean size of the first purchase remained around 50 tablets in the treatment group, whereas the mean was slightly over 30 in the control group. When physicians received the letter in June 2017, there was an abrupt drop in the mean size of the first purchase in the treatment group but no major changes in the control group. After June 2017, the two series remain approximately at their own constant levels. Thus, the graphical evidence suggests that the letter decreased the mean purchase size.



Notes: Triangles represent monthly averages of paracetamol-codeine purchases by new patients prescribed by doctors who received the letter. Dots represent monthly averages of paracetamol-codeine purchases by new patients prescribed by doctors who did not receive the letter. Vertical line represents the date when the letter was sent.

Figure 2 Monthly averages of tablets per first paracetamol-codeine purchases

Figure 2 also shows that there were only small changes in the trends in both groups before the letter was sent out in May 2017, the most notable change occurring in January 2017. This is most likely caused by reversion to the mean in the treatment and control groups, discussed in the Methods section. The outcome trends support the DD identification strategy, when using data from 2017 onwards. We are not aware of any other changes in the drug markets that might have caused the sudden and persistent drop in the purchase size of paracetamol-codeine in June 2017. Furthermore, it is unlikely that some other structural change would have affected only patients whose prescribing physician received the information letter. Importantly, the figure also shows that mean purchase size had similar trends in the months leading to the letter, and again after the letter.

5.2 Effect on first paracetamol-codeine purchases

We present our main results from the DD analysis, based on equation (1), in Table 2. In columns 1—4, the outcome variable is the size of the purchase measured in tablets. In columns 5—8, the outcome is an indicator for a large purchase, which takes value of 1 if the number of tablets purchased was 100 or more. Columns 1 and 5 present results without additional covariates. We add distinct sets of control variables to each of the remaining columns in order to evaluate the robustness of our results. These controls include month dummies in Columns 2 and 6. In Columns 3 and 7, we add a dummy for foreign language patients as well as patients' age, age squared and sex. Furthermore, in Columns 4 and 8 we control for physician characteristics.

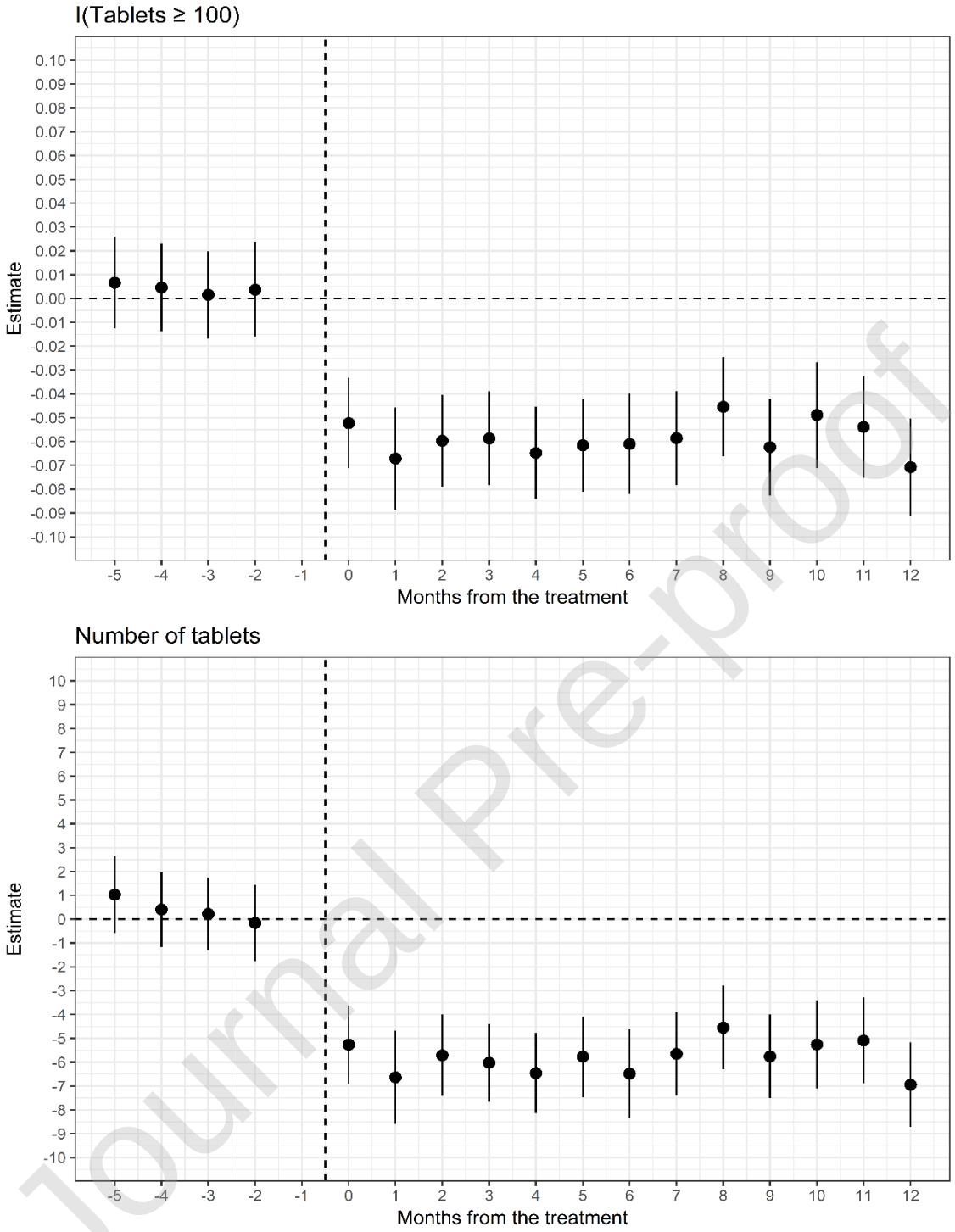
The descriptive evidence shown in Figure 2 is also reflected by the DD coefficients in Table 2. The main results show that the information letter led to a significant decrease in both the size of the first purchase and in the probability of a large purchase of paracetamol-codeine as a new patient. Columns 1—4 indicate that the letter decreased the size of the purchase by approximately six tablets on average relative to the control group. When compared to the pre-letter mean, the effect corresponds to a 12.5 percent decrease in the average purchase size in the treatment group. Results from the linear probability specifications, presented in columns 5—8, suggest that the letter decreased the probability of purchasing at least 100 tablets by six percentage points. In all specifications, the estimated coefficients are statistically significant at one percent level. Including additional control variables had only a small effect on the main parameter of interest. Male and non-Finnish speaking physicians prescribe more paracetamol-codeine for new patients compared to female and Finnish speaking physicians. Male patients' purchases are larger compared to females. The rest of the estimated coefficients are close to zero, although patients' age (Columns 3 and 4) and physicians' age (Column 4) are statistically significant in some of the specifications.

Table 2 Effect of the information letter on first paracetamol-codeine purchases

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Variables	Tablets	Tablets	Tablets	Tablets	I(Tablets ≥ 100)	I(Tablets ≥ 100)	I(Tablets ≥ 100)	I(Tablets ≥ 100)
After * Letter	-5.87***	-5.87***	-5.73***	-6.13***	-0.059***	-0.059***	-0.058***	-0.0621***
	(0.45)	(0.45)	(0.44)	(0.44)	(0.006)	(0.006)	(0.0055)	(0.0056)
After	-1.34***	-1.13***	-1.32***	-0.92**	-0.007***	-0.005	-0.007	-0.0017
	(0.20)	(0.43)	(0.42)	(0.42)	(0.002)	(0.004)	(0.0042)	(0.0043)
Letter	15.67***	15.67***	15.09***	14.65***	0.130***	0.130***	0.126***	0.1234***
	(0.59)	(0.59)	(0.58)	(0.56)	(0.007)	(0.007)	(0.0069)	(0.0065)
Age (patient)			0.18***	0.17***			0.000	0.0003
			(0.02)	(0.03)			(0.0002)	(0.0002)
Non-Finnish speaker			0.42	0.21			0.006**	0.0047
(patient)			(0.27)	(0.28)			(0.0027)	(0.0030)
Male (patient)			2.18***	1.90***			0.009***	0.0072***
			(0.16)	(0.16)			(0.0016)	(0.0016)
Comorbidity			0.73***	0.83***			0.006***	0.0068***
			(0.07)	(0.07)			(0.0007)	(0.0007)
Age (physician)				-0.08***				-0.0003
				(0.02)				(0.0002)
Non-Finnish speaker				2.33***				0.0193**
(physician)				(0.68)				(0.0076)
Male (physician)				2.90***				0.0141***
				(0.40)				(0.0038)
Specialist				5.53***				0.0431***
				(0.52)				(0.0052)
Time effects		Yes	Yes	Yes		Yes	Yes	Yes
Observations	146,178	146,178	146,158	141,415	146,178	146,178	146,158	141,415
R-squared	0.072	0.072	0.097	0.116	0.039	0.039	0.051	0.061
Treatment group base-line mean	47.76	47.76	47.76	47.76	0.165	0.165	0.165	0.165

Notes: Standard errors are clustered at the physician level and presented in parentheses. Columns 1—4 present estimates from OLS regressions, in which the dependent variable is quantity of tablets purchased. Columns 5—8 present estimates from linear probability models, in which the dependent variable is a dummy taking the value of 1 if the quantity of tablets purchased was at least 100. All models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. Columns 3, 4, 7 and 8 include patient age squared as a control variable. ** $p < 0.05$ *** $p < 0.01$.

Figure 3 shows the coefficients on the interaction of month dummies and treatment group indicator, estimated using the event study equation (2). The upper panel of the figure presents results for the large purchase outcome and the lower panel for the Number of tablets purchased. We have omitted the interaction for the first pre-treatment month, May 2017. Each estimated coefficient shows the difference in outcome between the treatment and control group for that month relative to the omitted month and conditional on control variables. These results indicate that there was no significant difference in outcome trends before June 2017. This result further supports the use of our identification strategy. The plotted estimates on the lags of the treatment interactions also suggest that the letter had an immediate and lasting effect on new patients' purchase size and on the probability of a large purchase of paracetamol-codeine.



Notes: Every dot represents a point estimate from the event study regression estimated using equation (2). Vertical lines represent 95% confidence intervals. The model is estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. The outcome is a dummy indicating a purchase of at least 100 tablets in the upper panel and the number of tablets purchased in the lower panel. The vertical axis is months from the letter. The first month leading to the treatment is omitted from the model.

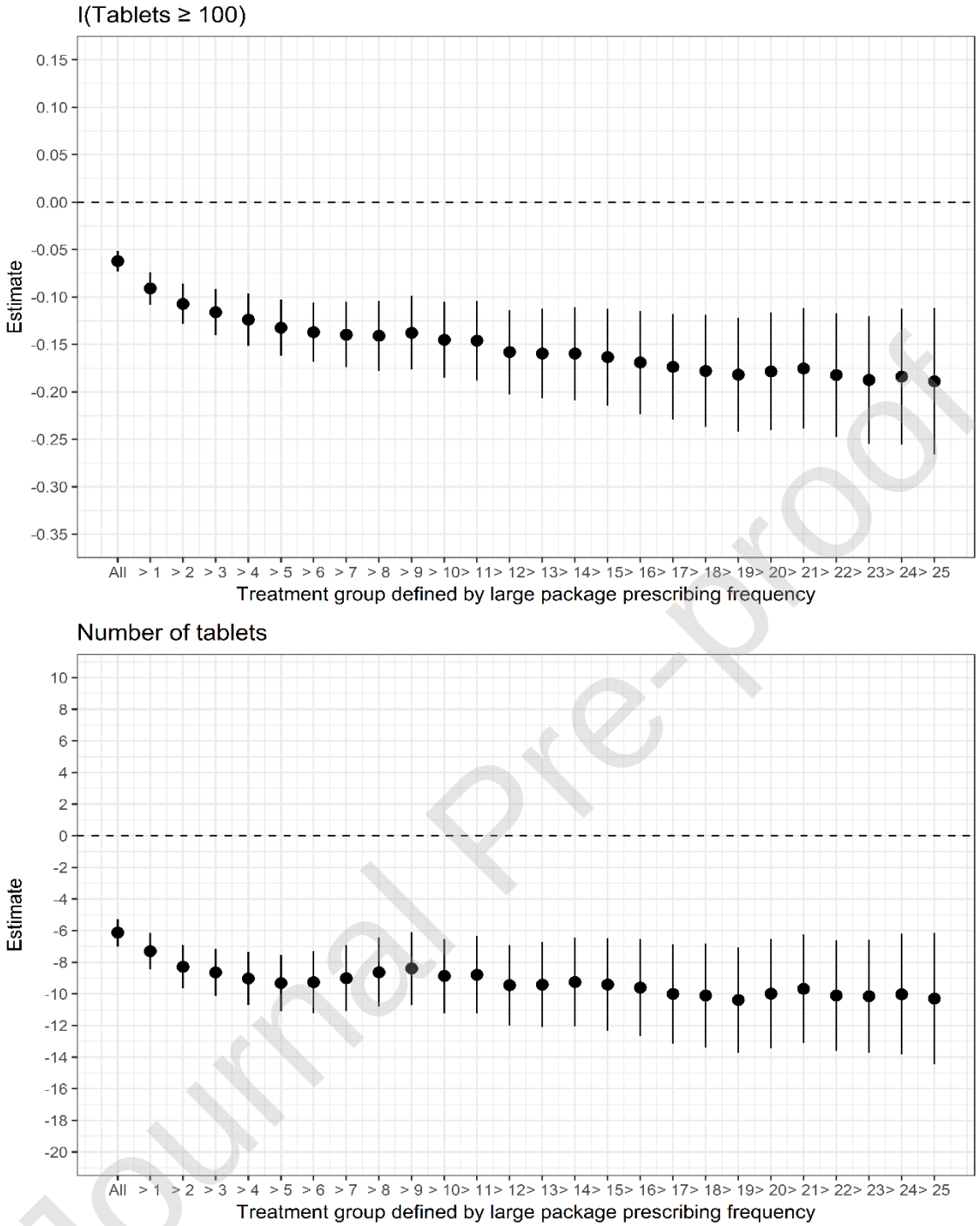
Figure 3 Effect of the information letter on first paracetamol-codeine purchases

5.3 Heterogenous treatment effects

Next, we analyze whether the information letter had different effects on different physician groups. The letter may have influenced physicians differently due to, for example, their specialty or location[6]. Also, in the treatment group there are both physicians who are consistent high prescribers and those who issue large prescriptions only incidentally. Therefore, we estimate the effects separately for a number of different treatment groups, defined by the number of new patients to whom physicians had prescribed a package of at least 100 tablets paracetamol-codeine in 2016.

In Figure 4, we plot the DD estimates from regressions, in which we omit those physicians from the treatment group whose number of large prescriptions to new patients in 2016 remained under a certain threshold value. We let this threshold vary from 1 to 25. Results from these regressions indicate that there is substantial heterogeneity in the treatment effect between consistent and coincidental high prescribers. The estimated decline in the probability of large prescriptions (Panel A) varies between 6 and 18 percentage points. When we estimate the models using the numbers of tablets as an outcome, the DD coefficients vary between -6 and -11, so that the estimated effect is larger for consistent high prescribers.

[6] Regional and physician-specific differences in medical practices are discussed, for example, in Phelps (2000).



Notes: Dots represent DD coefficients from separate regressions based on equation (1). Treatment groups are defined by the number of large prescriptions physicians issued in the pre-treatment period. Vertical lines represent 95% confidence intervals. Standard errors are clustered at the physician level. The models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. The outcome is a dummy indicating a purchase of at least 100 tablets in the upper panel and the number of tablets purchased in the lower panel.

Figure 4 Heterogeneity in the effect by the number of prescriptions to new patients

We follow McMichael et al. (2020) and estimate the effects of the letter separately for the five largest specialties and for all other physicians. The five largest specialties in the data are general practice, orthopedics and traumatology, general surgery, occupational health and orthopedics and traumatology surgery.

Results based on subsample estimations, in which the data is divided based on physician specialty, are shown in Table 3. Columns 1 and 3 show results for the five largest specialties and columns 2 and 4 for other physicians. We exclude the dummy for any specialty from the control variables, otherwise we control for the same physician and patient characteristics as before. The results suggest that the letter had similar effects on the purchase size measured in tablets among the largest specialist group and other physicians. However, the letter decreased the probability of a large purchase by 2.7 percentage points more among the largest specialist groups' patients. Corresponding event study results are presented in Figure A1.

Table 3 Effect on first paracetamol-codeine purchases, by physician specialty

Variables	(1) Tablets	(2) Tablets	(3) I(Tablets ≥ 100)	(4) I(Tablets ≥ 100)
After * Letter	-5.674***	-6.070***	-0.079***	-0.051***
	(0.798)	(0.521)	(0.011)	(0.006)
Time effects	Yes	Yes	Yes	Yes
Physician controls	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes
Observations	36,606	104,809	36,606	104,809
R-squared	0.116	0.095	0.074	0.044
Treatment group baseline mean	50.79	46.07	0.209	0.141
Sample	Largest specialties	Others	Largest specialties	Others

Notes: Standard errors are clustered at the doctor level and presented in parentheses. All regressions are based on equation (1). Coefficients in columns (1) and (3) are estimated for specialists of the 5 largest specialties in the data. Estimates in columns (2) and (4) are based on data on all other physicians. All models are estimated using data on patients' first paracetamol-codeine purchases between January 2017 and June 2018. ** p < 0.05 *** p < 0.01.

In Table 4, we show results from regressions estimated separately for physicians living in urban, semi-urban and rural municipalities. Our division of the data into these three subsamples is based on Statistics Finland's regional division.

The results indicate that the letter had a statistically significant impact on both the purchase size and the probability of a large purchase of paracetamol-codeine across all categories of physicians. The DD coefficients are more negative among physicians from semi-urban municipalities than from urban or rural municipalities. The probability of a large purchase decreased by 7.3 percentage points in semi-urban municipalities, which is 1.5 percentage points more than in rural municipalities. Compared to the baseline means, the relative effect of the letter yields a decrease in the prescribing of a large package by 38.6 percent in urban municipalities (Column 4), 34.1 percent in semi-urban municipalities (Column 5), and 31.7 percent in rural municipalities (Column 6). Corresponding

event study results are presented in Figure A2. For physicians' living in rural municipalities, the event study coefficients for the after-period do not differ statistically from zero.

Table 4 Effect on first paracetamol-codeine purchases, by degree of urbanization

Variables	(1) Tablets	(2) Tablets	(3) Tablets	(4) I(Tablets ≥ 100)	(5) I(Tablets ≥ 100)	(6) I(Tablets ≥ 100)
After * Letter	-5.966***	-7.478***	-5.947***	-0.061***	-0.073***	-0.058**
	(0.479)	(1.489)	(1.681)	(0.006)	(0.018)	(0.025)
Time effects	Yes	Yes	Yes	Yes	Yes	Yes
Physician controls	Yes	Yes	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes	Yes	Yes
Observations	123,398	10,930	6,260	123,398	10,930	6,260
R-squared	0.115	0.141	0.115	0.058	0.091	0.073
Treatment group baseline mean	47.27	51.65	48.55	0.158	0.214	0.183
Sample	Urban	Semi-urban	Rural	Urban	Semi-urban	Rural

Notes: Standard errors are clustered at the physician level and presented in parentheses. All regressions are based on equation (1). Columns (1)—(3) present estimates from OLS regressions, in which the dependent variable is quantity of tablets purchased. Columns (4)—(6) present estimates from Linear Probability Models, in which the dependent variable is a dummy taking the value of 1 if the quantity of tablets purchased was at least 100. All models are estimated using subsamples, based on whether the physicians' municipality of residence is classified as urban (Columns 1 and 4), semi-urban (Columns 2 and 5) or rural (Columns 3 and 6), on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. ** $p < 0.05$ *** $p < 0.01$.

5.4 Effect on other opioids

The aim of the information letter was to influence prescribing paracetamol-codeine to new patients. However, the letter may have also influenced the prescribing of other similar drugs. We analyze whether the letter had effects on new patients' first tramadol and oxycodone purchases between January 2017 and June 2018.

Like paracetamol-codeine, tramadol is a mild opioid that is addictive when used incorrectly, and treatment with tramadol should be started with a small package. Oxycodone is a strong opioid and its use has been increasing in Finland in the past few years (Fimea and Kela 2015, 2018). It is also one of the opioids most used for non-medical purposes in North America (OECD 2019).

Because of the similarities between these drugs, it is possible that physicians' who received the letter also changed their prescribing patterns of tramadol and oxycodone. However, it is also possible that physicians have substituted paracetamol-codeine with other opioids. This means that the information letter may lead to a decrease or increase of prescribing similar drugs.

Because there are tramadol tablets of different strengths and oxycodone prescriptions filled with other pharmaceutical dosage forms than tablets in the data, we define an additional outcome variable for tramadol and oxycodone. We calculate the number of DDDs per filled prescription, add one to each observation, apply a logarithmic transformation, and use the calculated quantity as an outcome. Furthermore, the dummy outcome for large purchases takes value 1 if the purchase was 98 tablets or more. This is because the most common large oxycodone package in Finland contains 98 tablets instead of 100 tablets like large paracetamol-codeine and tramadol packages. Otherwise, outcomes and covariates are defined in the same way as in the previous section.

Columns 1 and 2 of Table 5 show results from DD models based on data of new patients' first tramadol purchases between January 2017 and June 2018. According to these results, the letter decreased the size of the purchase in the treatment group by approximately 3 tablets on average. The probability of patients' first tramadol purchase being a large one decreased by 3.3 percentage points in the treatment group relative to the control group. Furthermore, these results indicate that the letter decreased the prescription size also when measured in the log number of DDDs. However, event study results, plotted in Figure A3 in the Appendix, are negative for pre-treatment periods as well. Although the

estimates are not statistically significant, they are of the same magnitude as the estimates after treatment time. This suggests that the point estimates in Columns 1 to 3 are driven by something else than the information letter.

Table 5 Effect on tramadol and oxycodone purchases

	(1)	(2)	(3)	(4)	(5)	(6)
Variables	Tablets	ln(DDD + 1)	I(Tablets ≥ 100)	Tablets	ln(DDD + 1)	I(Tablets ≥ 98)
After * Letter	-3.074***	-0.038**	-0.033***	0.614	0.003	0.005
	(0.789)	(0.018)	(0.010)	(1.036)	(0.022)	(0.012)
Time effects	Yes	Yes	Yes	Yes	Yes	Yes
Physician controls	Yes	Yes	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes	Yes	Yes
Observations	36,876	36,876	36,876	29,634	38,835	29,634
R-squared	0.034	0.058	0.033	0.036	0.055	0.041
Treatment group baseline mean	35.76	2.104	0.152	44.30	1.603	0.190
Data	Tramadol	Tramadol	Tramadol	Oxycodone	Oxycodone	Oxycodone

Notes: Standard errors are clustered at the physician level and presented in parentheses. All regressions are based on equation (1). In Columns (1)-(3) models are estimated using data on new patients' first tramadol purchases. In Columns (4) and (6) models are estimated using data on new patient's first oxycodone purchases between January 2017 and June 2018, in which the pharmaceutical dosage form was tablets. In Column (5) the model is estimated using data on all new patient's first oxycodone purchases between January 2017 and June 2018. Outcomes are shown in the column titles. ** $p < 0.05$ *** $p < 0.01$.

Columns 4 and 6 show results from regressions estimated using data on those new patients' first oxycodone purchases in which in the pharmaceutical dosage form was tablets. Column 5 shows the results from the model that uses information on oxycodone prescriptions filled in any dosage form. The results suggest that the letter had no impact on oxycodone prescribing. The DD coefficients are positive, but do not differ statistically from zero. These results are further supported by the event study results presented in Figure A3. None of the coefficients

on the interactions between month dummies and the treatment indicator, before or after the letter, differ statistically from zero.

5.5 Extensions

We continue by studying the impact of the information letter on the prescribing of paracetamol-codeine in any quantity to a new patient. A decline in the number of new patients receiving a paracetamol-codeine prescription could indicate that physicians are substituting prescribing with other medicines or that the patients are left without treatment.

Figure A4 plots the event study estimates for the probability of a new patient filling a paracetamol-codeine prescription. We find no effect. The point estimates are precisely estimated and close to zero.

Next, we study the effects of the treatment letter on the prescribing of other common package sizes of paracetamol-codeine. This analysis allows us to study if there was substitution of prescribing large packages, of at least 100 tablets, with prescribing smaller packages to new patients. Table 6 displays DD coefficients from estimating equation (1) for four different specifications. First, we estimate the change in the number of tablets for filled prescriptions containing fewer than 100 tablets. The parameter estimate of interest is -2.4 (Column 1). The point estimate corresponds to a relative effect size of -6.4 percent, compared to the pre-treatment mean.

Table 6 Effects on other common sized purchases

Variables	(1) Tablets	(2) I(Tablets = 50)	(3) I(Tablets = 40)	(4) I(Tablets = 20)
After * Letter	-2.396***	-0.040***	0.012***	0.091***
	(0.295)	(0.010)	(0.003)	(0.009)
Time effects	Yes	Yes	Yes	Yes
Physician controls	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes
Observations	132,117	141,415	141,415	141,415
R-squared	0.079	0.046	0.004	0.099
Treatment group baseline mean	36.93	0.457	0.0197	0.356
Sample	Tablets < 100	All	All	All

Notes: Standard errors are clustered at the physician level and presented in parentheses. Column (1) presents estimates from an OLS regression, in which the dependent variable is the quantity of tablets purchased. Columns (2)—(4) present estimates from linear probability models in which the dependent variable is a dummy taking the value of 1 if the quantity of tablets purchased was 50, 40 or 20, respectively. All models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. ** $p < 0.05$ *** $p < 0.01$.

Columns (2)–(4) show the results from specifications in which the outcomes are indicator variables taking value 1 if the number of tablets purchased was 50, 40 or 20, respectively. The results imply that physicians in the treatment group substituted prescribing from packages of 100 and 50 tablets to packages of 40 and 20 tablets. The point estimates correspond to 1.2- and 9.1-percentage-point increases in the probabilities of filling a prescription containing 40 or 20 tablets, respectively. The relative effect sizes are roughly 61 percent for the purchases of 40 tablets and 26 percent for the purchases of 20 tablets. Corresponding event study results (Figure A5) support the use of our research design with these outcomes as well.

So far, we have concentrated on new patients' first purchases of paracetamol-codeine. However, it is possible that the smaller first prescription was compensated in later prescriptions. For example, the second prescription may have been larger or prescribed sooner. To see if this was the case, we provide descriptive evidence on the average size of the second purchases and on the average time between the first and the second purchases for the same treatment and control groups as in the earlier sections of the paper. We look at a three-month time period – so that both the first and the second purchase were made in this period – before (from March 2017 to May 2017) and after (from June 2017 to August 2017) the letter was sent.

Between the aforementioned before and after periods, the number of second paracetamol-codeine purchases decreased by 387 purchases and the average size of the second purchase decreased by 2.9 tablets in the treatment group. In the control group, there was an increase of 160 purchases and a decrease of 0.2 tablets, respectively. The average time between the first and second purchase increased by 0.7 days, in both the treatment and the control group during the three-month period following the letter. These results imply that, because of the letter, physicians did not postpone prescribing to the patient's next visit, but actually prescribed less paracetamol-codeine for new patients. More detailed descriptive statistics of second purchases are shown in the Appendix in Table A5.

6 DISCUSSION

This paper provides evidence of the impact of an information letter on prescribing paracetamol-codeine to new patients. Using nationwide high-quality register data on all paracetamol-codeine purchases, before and after the letter was sent, and an identification strategy that allows us to credibly estimate the effect of the information letter on opioid prescribing, we find that the letter decreased the

probability of a physician issuing a large prescription of paracetamol-codeine to new patient by roughly six percentage points. Our results are statistically significant and robust to different model specifications. Using the event study framework, we find that the letter had an immediate and lasting effect. The impact remains until the end of the 12-month follow-up period in our data. This approach also shows no divergence in pre-treatment outcome means, which supports our main identifying assumption about equal outcome trends in the treatment and control groups in absence of the letter. The average number of tablets purchased declined by approximately six tablets, corresponding to a 12.5 percent decrease compared to the pre-letter mean. This result is in line with the results of Doctor et al. (2018) and Sacarny et al. (2018), but is in conflict with the findings of Sacarny et al. (2016). Additionally, when studying heterogenous effects of the intervention, we find larger effects for consistent high prescribers.

Six tablets make up a two-day supply of paracetamol-codeine, measured in DDDs. When not starting treatment with a package containing 100 tablets, the physician is mostly likely to prescribe one of the other common sized packages, which are 50, 40 or 20 tablets. We find, for instance, a 9.1 percentage point increase in the probability of new patient filling a prescription of 20 tablets. A shift from 100 tablets to 20 tablets means a 26.7-day reduction in the paracetamol-codeine supply available to a patient. Brat et al. (2018) estimated that for opioid naïve patients, every additional week of opioid prescription is associated with a 20-percent increase in misuse. Taken at face value, this indicates that the letter's impact was of high clinical significance.

Additionally, we studied whether the information letter had an impact on tramadol or oxycodone prescribing. We found an association between the letter and decreasing tramadol prescribing, suggesting that the letter may have decreased the average purchase size and the probability of a new patient starting treatment with a large purchase of tramadol. Although, given the results estimated using the event study specification, this evidence is not as convincing as

was the case with paracetamol-codeine. In the case of oxycodone, we find no evidence of an impact. Sacarny et al. (2018) also found no evidence of substitution to other drugs in their study.

There are at least three reasons why specialist groups consistently prescribing opioids and other physicians may have different responses to the information letter. First, consistently prescribing specialists may already have better knowledge of appropriate prescribing practices before receiving the letter. Second, some specialists may be treating patients whose treatment requires larger doses of pain medication. Third, physician training has been shown to be associated with pain treatment practices (Schnell and Curie 2018). We estimate 2.7 percentage points larger point estimate for the five largest specialties in the data. However, the relative effect sizes are similar for the most frequently prescribing specialists and for other physicians.

Phelps (2000) discusses regional differences in physicians' learning about better treatment procedures. These differences can be a result of local sources of information having lower costs or different credibility compared to non-local sources. When studying the heterogenous effects of the letter based on whether the physicians' municipality of residence is categorized as an urban, semi-urban or rural, we find no major differences in the relative effect size of the letter between urban, semi-urban or rural municipalities.

Our paper has some disadvantages. Information letters can have different effects depending on the population studied, and therefore, the external validity of the study might be limited. Also, the effect of letters can possibly decline if used continuously. The effect of continuing use, financial impacts and health outcome effects as well as mechanisms of the information letters are areas where future work is needed.

To conclude, based on the results of our paper and previous research, information letters can be an effective method to nudge physicians to reduce their opioid prescribing, and thus mitigate the possible adverse effects associated with

this prescribing. Excess prescribing of potentially addictive drugs can generate health care costs in two ways. First, there are the direct drug expenditures. Opioids are relatively inexpensive, thus the direct cost savings from decreased prescribing are probably quite small. Second, there are potentially avoidable health care costs associated with the overprescribing of addictive drugs. As the results by Shah et al. (2017) and Deyo et al. (2017) indicate, the size of the patient's first prescription is associated with the future development of continued opioid use. Therefore, the decrease in the availability of addictive drugs for patients can generate savings from future health care costs. More generally, providing personalized feedback and information on clinical guidelines can be a potentially successful policy tool as a partial solution to the overuse of medical services, discussed in, for instance, Brownlee et al. (2017) and Saini et al. (2017). However, because there are medical services that are beneficial to some patients and harmful to others (Brownlee et al. 2017), the use of these kinds of policy tools should be carefully designed and implemented.

CRediT author statement

Iiro Ahomäki: Methodology, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Funding acquisition. **Visa Pitkänen**: Methodology, Writing - Review & Editing. **Aarni Soppi**: Methodology, Software, Data Curation, Writing - Review & Editing, Visualization. **Leena Saastamoinen**: Conceptualization, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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Appendix A

Table A1 Robustness Check: Effect of the information letter on paracetamol-codeine purchases using data from January 2016 to June 2018

Variables	(1) Tablets	(2) Tablets	(3) Tablets	(4) Tablets	(5) I(Tablets ≥ 100)	(6) I(Tablets ≥ 100)	(7) I(Tablets ≥ 100)	(8) I(Tablets ≥ 100)
After * Letter	-9.362***	-9.355***	-9.015***	-9.662***	-0.107***	-0.106***	-0.104***	-0.111***
	(0.414)	(0.414)	(0.405)	(0.403)	(0.005)	(0.005)	(0.005)	(0.005)
Time effects		Yes	Yes	Yes		Yes	Yes	Yes
Patient controls			Yes	Yes			Yes	Yes
Physician controls				Yes				Yes
Observations	266,386	266,386	266,357	257,639	266,386	266,386	266,357	257,639
R-squared	0.115	0.116	0.140	0.162	0.078	0.078	0.089	0.102
Treatment group baseline mean	49.95	49.95	49.95	49.95	0.195	0.195	0.195	0.195

Notes: Standard errors are clustered at the doctor level and presented in parentheses. Columns 1–4 present estimates from OLS regressions, in which the dependent variable is quantity of tablets purchased. Columns 5–8 present estimates from linear probability models, in which the dependent variable is a dummy taking the value of 1 if the quantity of tablets purchased was at least 100. All models are estimated using data on new patients' first paracetamol-codeine purchases between January 2016 and June 2018. ** $p < 0.05$ *** $p < 0.01$.

Table A2 Robustness Check: Effect on first paracetamol-codeine prescriptions

	(1)	(2)
Variables	Tablets	I(Tablets ≥ 100)
After * Letter	-7.098***	-0.070***
	(0.546)	(0.006)
Time effects	Yes	Yes
Patient controls	Yes	Yes
Physician controls	Yes	Yes
Observations	139,457	139,457
R-squared	0.105	0.071
Treatment group baseline mean	51.36	0.190

Standard errors are clustered at the physician level and presented in parentheses. Both regressions are based on equation (1). Both models are estimated using data on new patients' first paracetamol-codeine prescriptions between January 2017 and June 2018. Prescriptions are identified and purchase data is aggregated based on information on prescription date, physician identifier, ATC code, strength and route of administration of the drug. ** $p < 0.05$ *** $p < 0.01$.

Table A3 Robustness Check: Effect of the information letter on first paracetamol-codeine purchases

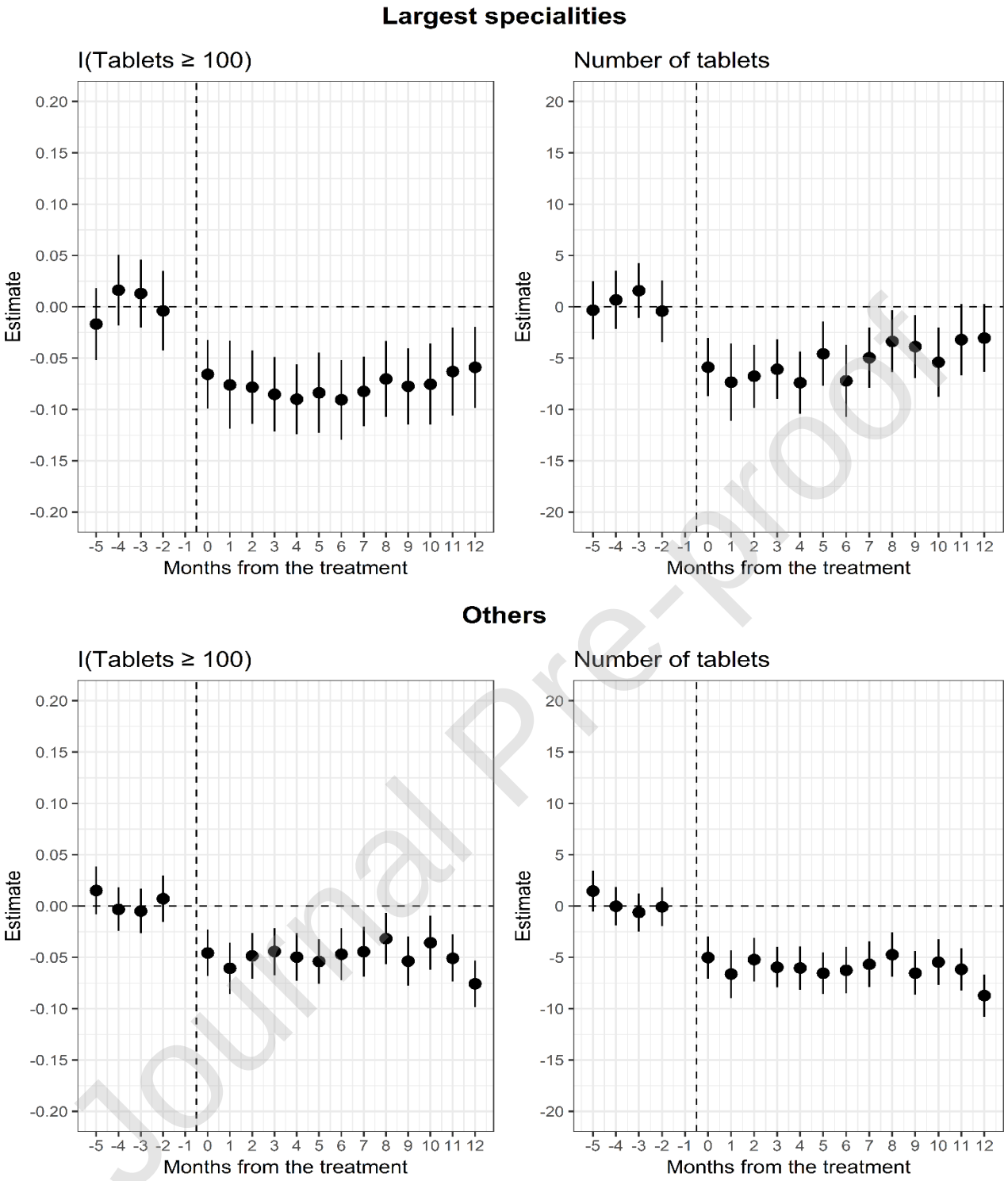
Variables	(1) Tablets	(2) Tablets	(3) I(Tablets ≥ 100)	(4) I(Tablets ≥ 100)
After * Letter	-6.128***	-6.946***	-0.062***	-0.071***
	(0.441)	(0.909)	(0.006)	(0.010)
Time effects	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes
Physician controls	Yes	Yes	Yes	Yes
Group specific time effects		Yes		Yes
Observations	141,415	141,415	141,415	141,415
R-squared	0.116	0.117	0.061	0.061
Treatment group baseline mean	47.76	47.76	0.165	0.165

Notes: Standard errors are clustered at the physician level and presented in parentheses. Columns 1 and 2 present estimates from OLS regressions, in which the dependent variable is quantity of tablets purchased. Columns 3 and 4 present estimates from linear probability models, in which the dependent variable is a dummy taking the value of 1 if the quantity of tablets purchased was at least 100. All models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. Columns 2 and 4 include controls for separate time trends for treatment and control groups. ** $p < 0.05$ *** $p < 0.01$.

Table A4: Robustness check: DD with Propensity Score Matching

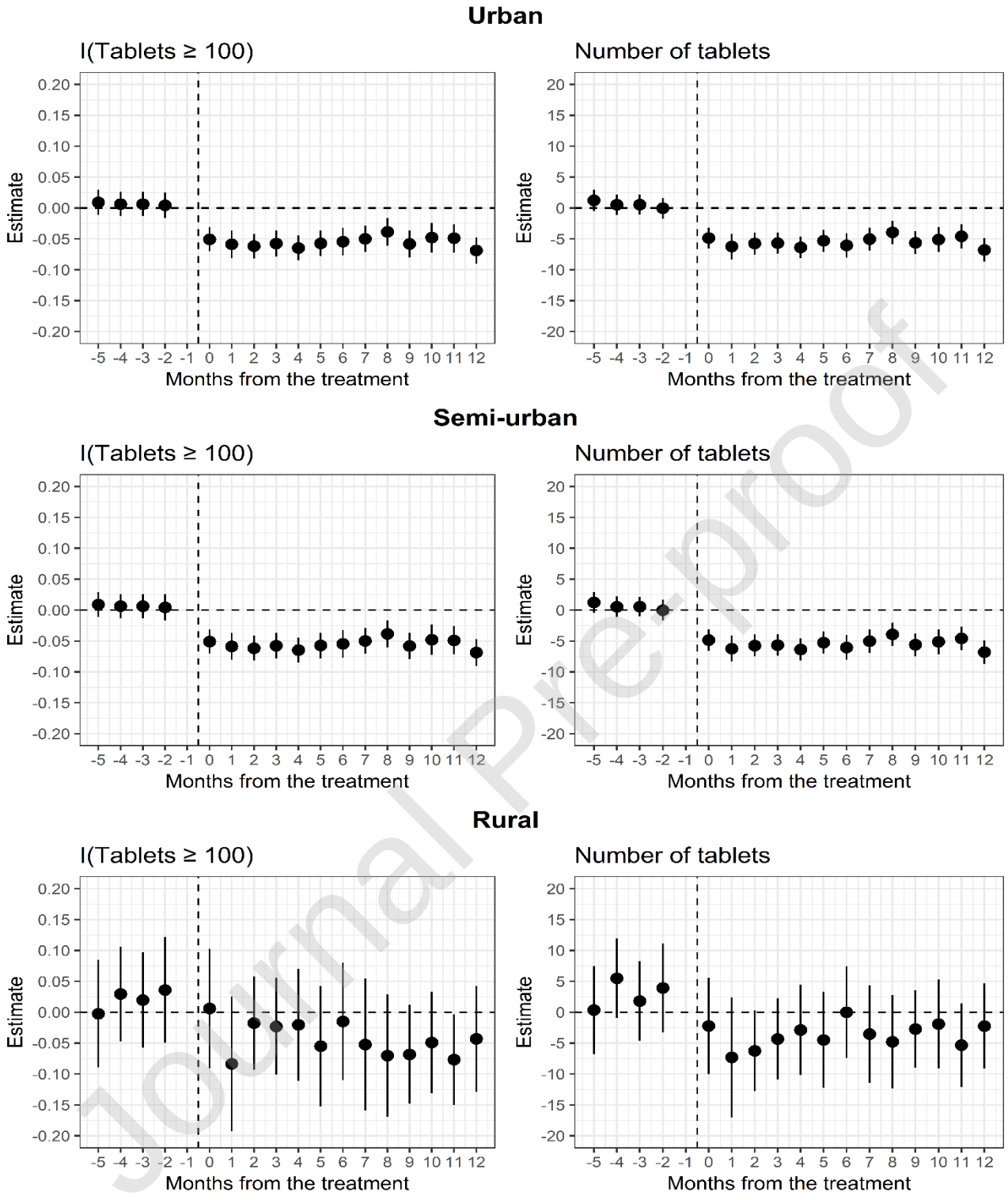
	(1)	(2)	(3)	(4)
Outcome:	Tablets	Tablets	I(Tablets ≥ 100)	I(Tablets ≥ 100)
DD	-6.163***	-6.093***	--0.061***	-0.061***
	(0.448)	(0.452)	(0.006)	
Time effects	Yes	Yes	Yes	Yes
Patient controls	Yes	Yes	Yes	Yes
Physician con-trols		Yes		Yes
Observations	141,411	141,411	141,411	141,411
R-squared	0.09	0.11	0.05	0.06

Notes: Standard errors are clustered at the physician level and presented in parentheses. Treatment effects are estimated using DD with kernel propensity score matching based on observed physician characteristics (age, dummy for Non-Finnish speakers, sex, dummy for specialists) (Villa 2016). Both models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. ** $p < 0.05$ *** $p < 0.01$.



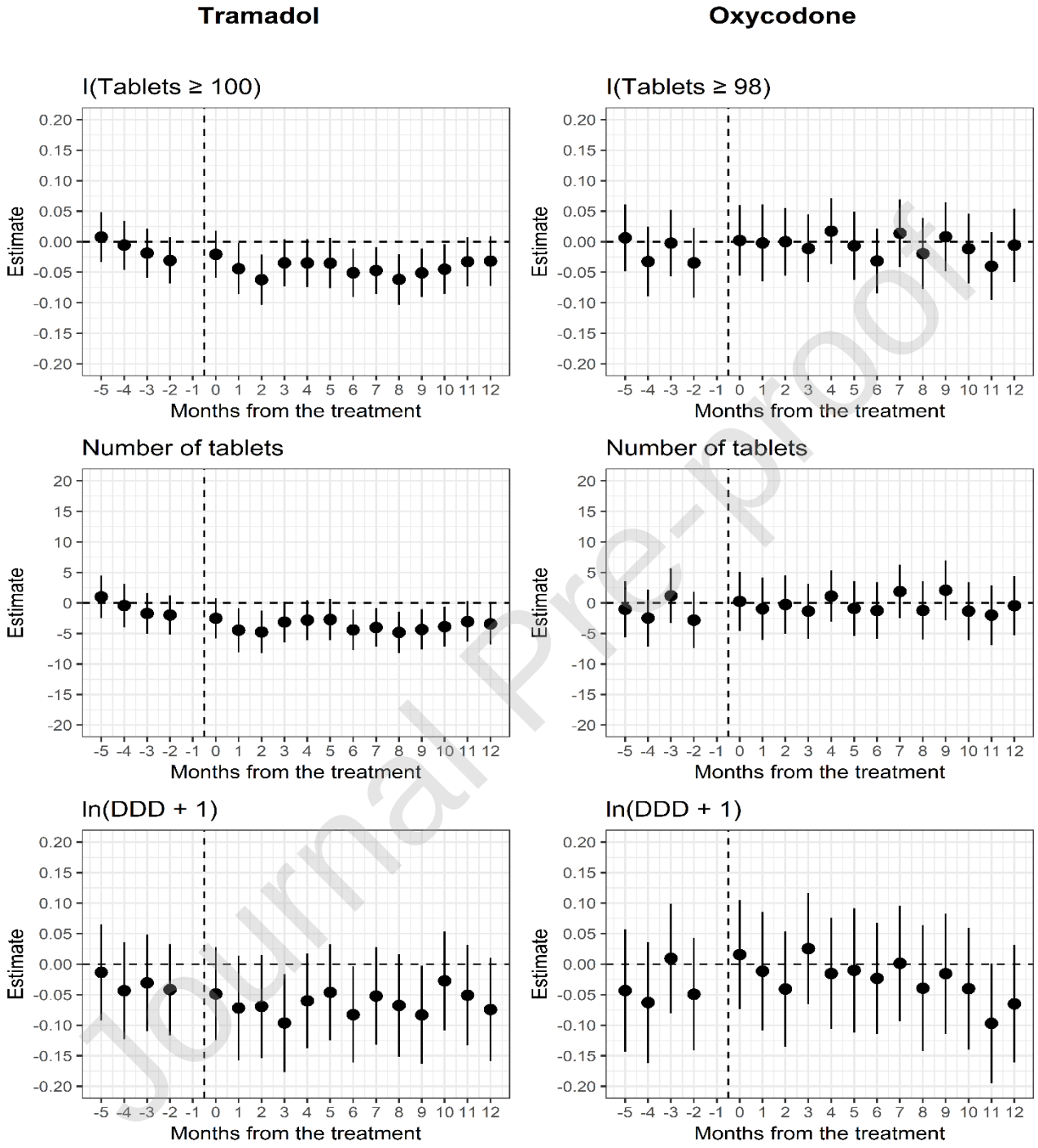
Notes: Every dot represents a point estimate from the event study regression estimated using equation (2). Vertical lines represent 95 % confidence intervals. In the upper panels, models are estimated using data on new patients' first paracetamol-codeine purchases prescribed by a specialist and in the lower panels using data on purchases prescribed by a non-specialist. The outcome is a dummy indicating if the purchase was at least 100 tablets in the left-hand side panels and number of tablets purchased in the right-hand side panels. The vertical axis is months from the letter. The first month leading to the treatment is omitted.

Figure A1 Effect on first paracetamol-codeine purchases, by physician specialty



Notes: Every dot represents a point estimate from event study regression estimated using equation (2). Vertical lines represent 95 % confidence intervals. All models are estimated using subsamples, based on whether the physicians' municipality of residence is classified as urban (upper panels), semi-urban (middle panels) or rural (lower panels), on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. The outcome is a dummy indicating if the first purchase was at least 100 tablets in the left-hand side panels and number of tablets purchased in the right-hand side panels. The vertical axis is months from the letter. The first month leading to the treatment is omitted.

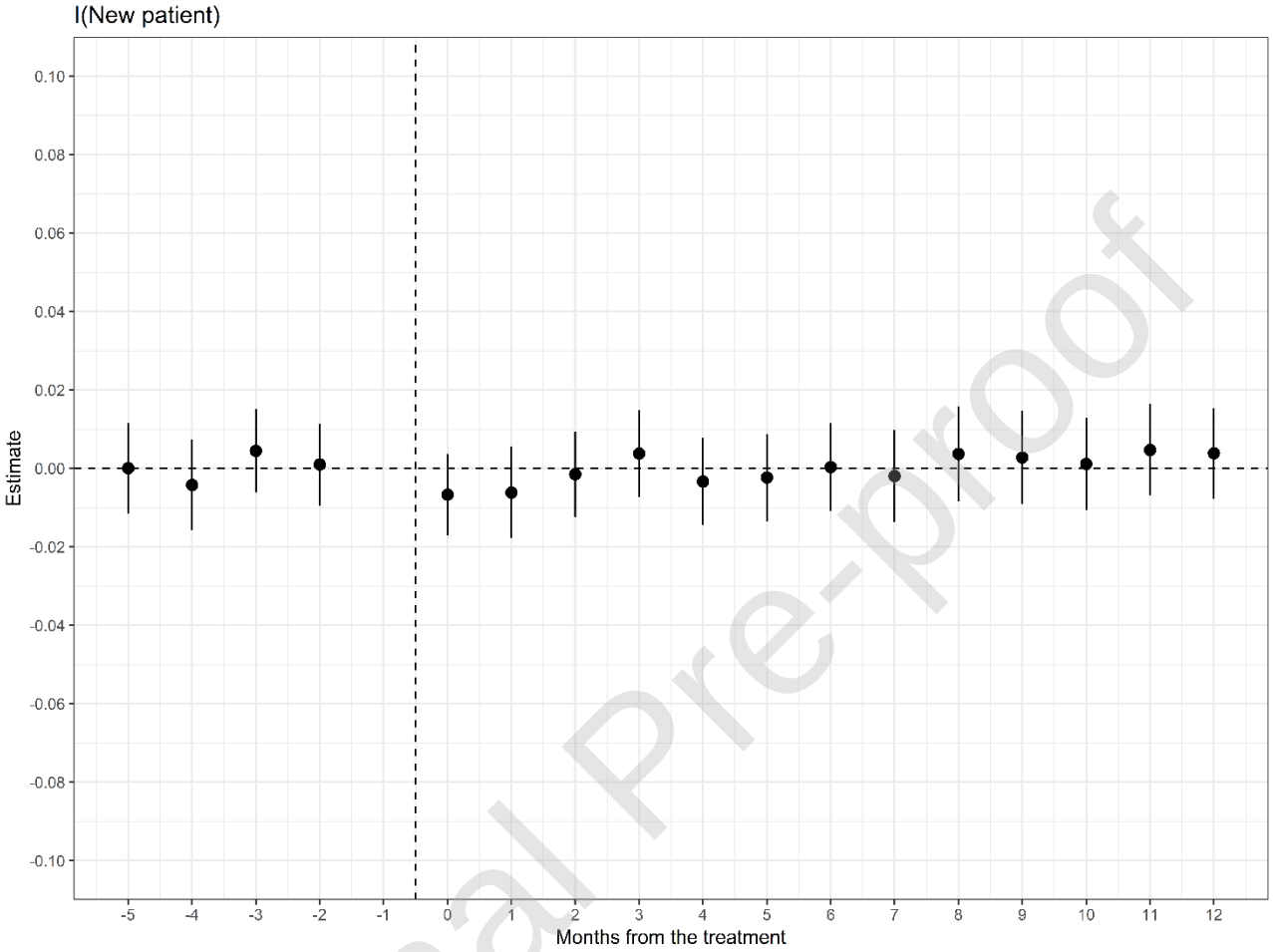
Figure A2 Effect on first paracetamol-codeine purchases, by degree of urbanization



Notes: Every dot represents a point estimate from event study regression estimated using equation (2). Vertical lines represent 95 % confidence intervals. In the upper panels, models are estimated using data on new patients' first tramadol purchases between January 2017 and June 2018 and in the lower panels using data on patients' first oxycodone purchases between January 2017 and June 2018. The outcome is a dummy indicating if the purchase was at least 100 tablets (tramadol) or 98 tablets (oxycodone) in the left-hand side panels and number of tablets purchased in the right-hand side panels. In

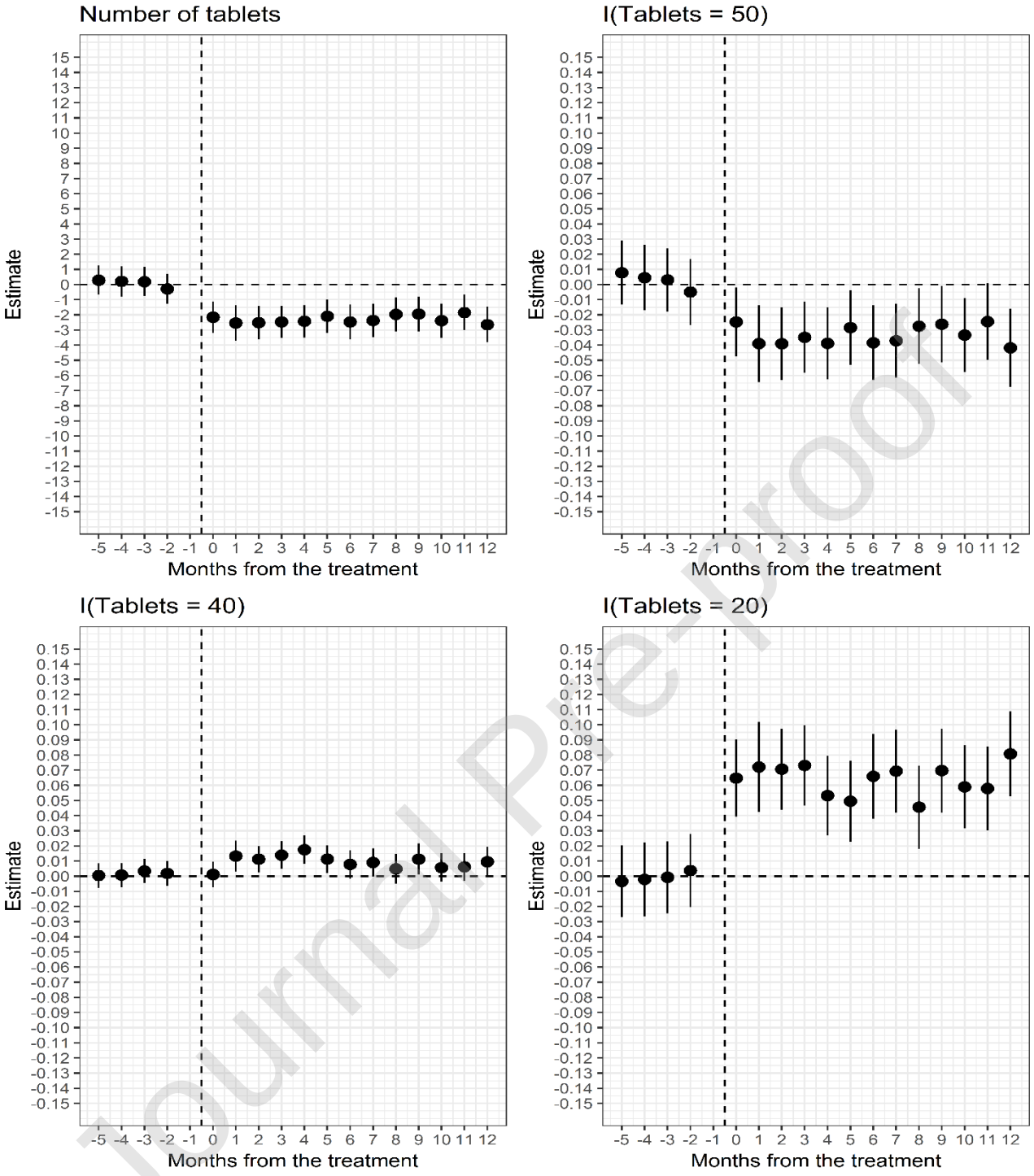
the lowest left panel, the outcome is ln (DDD + 1). The vertical axis is months from the letter. The first month leading to the treatment is omitted.

Figure A3 Effect of the information letter on tramadol and oxycodone purchases



Notes: Every dot represents a point estimate from the event study regression estimated using equation (2). Vertical lines represent 95 % confidence intervals. The model is estimated using data on paracetamol-codeine purchases between January 2017 and June 2018. The outcome is a dummy taking value 1 for patients who have no purchases in the previous 3 years. The vertical axis is months from the letter. The first month leading to the treatment is omitted from the model.

Figure A4 Effect on probability of a new patient filling a paracetamol-codeine prescription



Notes: Every dot represents a point estimate from event study regression estimated using equation (2). Vertical lines represent 95 % confidence intervals. In the upper left panel, the estimation is based on subsample, in which the number of tablets purchased is less than 100 tablets and the outcome is the number of tablets purchased. All other models are estimated using data on new patients' first paracetamol-codeine purchases between January 2017 and June 2018. In the upper right panel, the outcome is a dummy indicating if the first purchase was 50 tablets. In the lower left and right panels, the outcomes are dummies indicating if the first purchase was 40 or 20 tablets, respectively. The vertical axis is months from the letter. The first month leading to the treatment is omitted.

Figure A5 Effect on purchasing other common sized packages

Table A5 Descriptive statistics of second purchases

		Before	After	p-value [a]
A: purchase size				
Treatment	Mean	57.8	54.9	0.017
	SD	36.5	38.8	
	N	2,125	1,738	
Control	Mean	45.5	46.3	0.419
	SD	30.9	37.5	
	N	2,347	2,507	
B: time between 1st and 2nd				
Treatment	Mean	26.1	26.8	0.256
	SD	18.8	19.6	
Control	Mean	25.7	26.4	0.207
	SD	19.0	19.6	

Notes: panel A presents descriptive statistics for the second purchases of paracetamol-codeine separately for the treatment and control groups. Panel B presents the mean time intervals between first and second purchases of paracetamol-codeine. Before refers to the three months before the letter (March 2017 – May 2017), and after refers to the three months after the letter was sent (June 2017 – August 2017).

[a] p-values for a t-test of difference between before and after means.

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ONLINE APPENDIX: Translation of the information letter

Dear doctor/dentist

This letter is sent to all doctors and dentists who have prescribed, in the year 2016, at least 100 tablets of a paracetamol-codeine combination to a patient who had not used the product in two years. Prescribing paracetamol-codeine combinations for acute pain was chosen as the subject of this feedback because long-term use of these products is common and prescribing practices are known to be independent of patient characteristics or morbidity (Barnett et al. 2017). Feedback on prescribing paracetamol-combinations is sent this year as a letter to the home addresses of 4,535 doctors and 14 dentists.

For acute pain, only a package containing 10–30 tablets of paracetamol-codeine combination should be prescribed at once. There are substantial risks associated with the long-term use of these products. Attached is a text by Professor Eija Kalso on prescribing paracetamol-codeine combinations.

Kela has offered personal feedback on drugs prescribed by physicians since 1997. Feedback is sent with the common objective of rational drug treatment in mind.

This feedback is created mechanically. It is only sent personally to doctors selected into the sample. In the selection of the feedback sample, information about prescriptions of paracetamol-codeine combinations eligible for reimbursement from the health insurance are used. Therefore, information on the Panacod effervescent tablet and the ibuprofen-codeine combination Ardinex are missing from the sample. There is up-to-date information on drug prices and eligibility for reimbursement in the Kela drug search www.kela.fi/lääkehaku.

Doctors and dentists can examine their own prescribing information on the website www.kela.fi/reseptit. The electronic service allows comparing information to the preferred information by specialty or health care district. Online bank identification or an electronic ID card are used to access the system.

We are grateful for potential comments and suggestions for improvements regarding prescribing feedback. At the bottom of the page, there is an email address for sending feedback.

KANSANELÄKELAITOS (SOCIAL INSURANCE INSTITUTION OF FINLAND)

Inquiries, comments and suggestions for improvements

Laake.palaute@kela.fi

Literature

Barnett, M.L., Olenski, A.R., Jena, A.B. Opioid prescribing patterns of emergency physicians and risk of long-term use. N Engl J Med, 376(7), 663–673, 2017

Paracetamol-codeine combinations* in pain treatment

On pharmacology of paracetamol and codeine

Paracetamol-codeine combinations are Finland's most used opioid containing products. In 2016, 269 700 people purchased reimbursement eligible paracetamol-codeine combinations. The use of these products has started to slowly decline in the last few years. One tablet contains 500 mg of paracetamol and 30 mg of codeine. The maximum dose of paracetamol is 3-4 g in 24 hours. The safe daily dose of an elderly patient is considered to be 2 g. This recommendation does not tell the whole truth, because to some of the patients this can be a dangerously large dose and to others completely ineffective.

Codeine is a prodrug so it must first metabolize to active substance through CYP2D6 enzyme. In the Finnish population there is 7 % very fast, 87 % fast, 3 % semi-fast and 2,5 % slow CYP2D6 metabolizers (2). In some North-African and Middle-Eastern populations the share of very fast metabolizers can be as much as 20-40 %. On average, 6-10 % of the codeine is metabolized to morphine, if the person's CYP2D6 genotype is semi-fast metabolizer. Slow metabolizers do not produce morphine from codeine at all. Also, the use of CYP2D6 inhibitors (e.g. paroxetine, fluoxetin) slows the metabolism of codeine. Fast and very fast metabolizers convert codeine to morphine very efficiently and receive a fast and powerful opioid effect. The risk of codeine addiction for these people is high (3,4). For fast metabolizers there has been reports of serious, even fatal adverse effects together with other pharmacogenetic factors, drug interactions and kidney deficiency. Codeine is contraindicated for very fast metabolizers (2). Products containing codeine are not to be used for patients under 12 years old, during lactation, and not for patients under 18 years old, for whom tonsillectomy is made as a treatment for obstructive sleep apnea. CYP2D6 genotype can be tested but predictive gene test is not recommended.

The use of paracetamol-codeine combinations in pain treatment

Paracetamol-codeine combinations are used primarily for alleviation of acute pain. For the alleviation of pain occurring after traumas and small surgical operations (e.g. removal of wisdom tooth) analgesic is usually needed for 1-3 days. Longer-lasting intense pain requires investigation of the cause of the pain. Anti-inflammatory drugs are effective in acute conditions of pain and should be used primarily, if the effectiveness of the paracetamol is not sufficient and there are no contraindications for their use. For about every other patient at least moderate postoperative pain is halved for six hours with two tablets of paracetamol-codeine. So, for the treatment of acute pain a package of 10-30 tablets of paracetamol-codeine is sufficient.

The problems in the use of paracetamol-codeine combinations

Because some of the patients develop morphine from codeine even very efficiently, the use of codeine products is associated with the risk of developing an opioid addiction. Opioid addiction is a complex problem, but it is known that some kind of addiction can develop already in the course of few days use. In the United States in the background of the immense problems caused by physician prescribed opioids there are among other things the more widespread long-lasting postoperative

opioid use. In addition to genetics, the other factors increasing the risk of addiction are other addictions (alcohol, cigarettes, cannabis), mental health problems (anxiety, depression), previous drug addiction and certain personality traits. After the opioid addiction has developed it is difficult to end the medication for both the patient and the person giving the treatment. For this reason, it is important to avoid the formation of the problem if possible.

Five suggestion for preventing codeine addiction:

1. Think if paracetamol-codeine combination is the best option *for this patient for this acute condition of pain.*
    a. Prescribe paracetamol-codeine combination only after careful consideration to young, those who have experienced drug addiction before, intoxicant addicts, or those with increased risk of addiction.
    b. After small traumas or surgeries anti-inflammatory drug is an efficient alternative. Headache or pain related anxiety or fear is not treated with paracetamol-codeine combination.
2. Prescribe package containing only 10-30 tablets for acute pain.
3. Do not renew a paracetamol-codeine prescription for an unknown patient.
4. If your patient's use of paracetamol-codeine is prolonged, find out why, think of other possible pain treatment alternatives and other problems in the background and if necessary, start withdrawal.
5. In problematic situations consult someone specialized in pain treatment.

Eija Kalso, LKT
Professor, University of Helsinki
Chief physician, Kipuklinikka, ATeK, HYKS
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Conflict of interest statement: compensation for specialist tasks from Pierre Fabre, Gruenenthal GMBH

*At this moment the products eligible for reimbursement are *Altermol, Panacod, Paracetamol/codeine Orion, Paramax-cod*. Furthermore, there is in the market ibuprofein-codeine combination Ardinex, which is not eligible for reimbursement from the health insurance.