BMJ Open

Regional growth trajectories in antibacterial dispensing rate to 0-2 year old patients in Norway: association with area-level education

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058491
Article Type:	Original research
Date Submitted by the Author:	19-Oct-2021
Complete List of Authors:	Svalestuen, Sigbjørn; UiT The Arctic University of Norway, Department of social science Svendsen, Kristian; UiT The Arctic University of Norway, Department of pharmacy Eggen, Anne; UiT The Arctic University of Norway, Department of Community Medicine Småbrekke, Lars; UiT The Arctic University of Norway, Department of pharmacy
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Community child health < PAEDIATRICS, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Regional growth trajectories in antibacterial dispensing rate to 0-2 year old patients in Norway: association with area-level education

Sigbjørn Svalestuen[1], Kristian Svendsen [2], Anne Elise Eggen[3], Lars Småbrekke[4]

Keywords: *Drug prescriptions, Education, Geography, Health inequalities, Health Policy*

Word count: *2999 (excluding title page, abstract, headers, captions, and references)*

[1] **Dep./Inst.:** Department of social science/UiT The Arctic University of Norway

E-mail: sigbjorn.svalestuen@uit.no

Phone: +47 776 44 321

Address: UiT The Arctic University of Norway
PO Box 6050 Langnes
N-9037 Tromsø
Norway

Fax: *NA*

[2] **Dep./Inst.:** Department of pharmacy/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

[3] **Dep./Inst.:** Department of community medicine/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

[4] **Dep./Inst.:** Department of pharmacy/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

ABSTRACT

Background: Geographical variations in antibacterial use exist within and between countries and tend to vary across time. Variations in dispensed prescriptions have been linked to both individual and area-level socioeconomic factors such as education and material deprivation.

Objectives: Examine the association between area-level education and local growth trajectories in antibacterial dispensing rate between Norwegian municipalities among children 0-2 years.

Methods: Latent growth curve modelling with a linear trend variable modeled as a random effect. Cross-level interaction between linear trends and mean area-level education. Data based on the Norwegian Prescription Database (NorPD, 2006 - 2016) linked to area-level statistics on education.

Results: A significant linear negative trend can be identified in dispensing rate in children 0-2 years over the period 2006-2016. This trend varies between municipalities. A negative cross-level interaction term between population education levels and random trends show that greater reduction is more commonly observed in municipalities with high levels of population education.

Conclusion: Municipalities where a larger proportion of the local population have high educational achievements have been more successful in reducing antibacterial dispensing rates in 0–2-year-old patients. Adopting area-level strategies and addressing local community disadvantage may help standardize practice and prescribing patterns between local communities.

Strengths and limitations of this study

- Complete antibacterial dispensing data allows estimating local community dispense rate trends and their association with education at a high level of spatial resolution.
- Prescriptions to 0-2 year old patients are particularly important because of their comparatively high use and potential future consequences.
- By analyzing local communities, we can explore variation in dispensing rate under national policy guidelines for reduction.
- A limitation is that aggregate data cannot directly infer on individual level decision making and needs.
- We were not able to control for the geographical burden of infectious disease in these age groups.

INTRODUCTION

Periodic prevalence and patterns of antibiotic use varies between countries,[1] socioeconomic and demographic groups in the population,[2,3] between GP-practices,[3] within-state regions,[4,5] and geographical latitudes.[6] In addition to geographical variation, studies from Norway have shown temporal variations in dispensing of antibacterials for systemic use,[7] as well as between group variations.[8] One study found an overall reduction in the number of dispensed prescriptions among children aged 0-2 between 2005-2016, a higher prevalence among boys, and varying prevalence between counties.[9] Another study shows that among children aged 0-2, Norwegian one-year-old boys have consistently had the highest antibacterial dispense rates between 2008-2016.[10] This is a concern due to emergence of antimicrobial resistance and a possible association between high use of antibacterials in young children and elevated risks of developing chronic disease later in life.[11–14]

Several studies attribute variation in antibiotic use to socioeconomic characteristics,[3–5,15] often including an indexed area-level deprivation measurement to capture several dimensions of deprivation (e.g. education, income, barriers to housing, crime, employment). Recent findings from England suggest that area-level deprivation is linked to variation in individual trends between geographical regions.[16] Comparing antibiotic treatment in most and least deprived areas in New Zealand, one study found that children in more deprived areas receive more treatment compared to children living in less deprived areas.[17]

There are possible links between education and antibiotic use. Crowding, hygiene, lower host resistance due to poor nutrition, stress and smoking prevalence pose a greater risk of infectious illness among people of lower socioeconomic status through increased exposure to infectious agents. General practitioners treatment practice and their interaction with family attitudes towards demands for certain treatments may influence individual prescription outcomes,[2] thereby resulting in geographic and temporal variations in aggregate statistics. Sociocultural pressures from working parents may lead to preemptive antibiotic prescription, and some parents may expect antibiotic treatment for their child when visiting their physician.[18]

Awareness about proper use of antibiotics is more common in people having achieved higher education,[19–21] and high education is associated with health literacy,[22,23] that is the individual capacity to obtain, process and understand health information and services needed to make appropriate health decisions.[24,25]

Studies on variation in dispensed antibiotics in Norway have not explicitly modeled local variation in dispensing rate growth trajectories in terms of socioeconomic composition. We used longitudinal data and a latent growth curve model to investigate the association between population education levels and growth trajectories in antibacterial dispensing rates at the municipality level.

MATERIALS AND METHODS

We included all 734359 dispensed prescriptions for children aged 0-2 years from the Norwegian Prescription Registry (NorPD) between 2006-2016 aggregated to municipality level. Dispensing rates were calculated as the yearly number of prescriptions within a municipality per 100 children. We linked the aggregated prescription data to publicly available data on Norwegian municipalities. Analyses are restricted to antibacterials for systemic use.[26]

Exposure and covariates

Our exposure is the proportion of the population in a municipality having achieved tertiary education (university level ≥ 3 years).

We include a covariate on the proportion of the population in a municipality living in a household with less than 60% of national median income. This measurement is the standard definition of low income in the European Union. The link between deprivation and dispensing rates suggests that poverty may confound the relationship between dispensing rate and population education. Including this covariate serves to partial out effects that can be attributed to education, rather than material deprivation.

Municipality population size may be related to regional deprivation levels in education, regional development, and may impact access to health care services. As such, municipality size is likely to confound the link between education and dispensing rates. To compress the distribution, we use the natural logarithm of population size as an indicator of municipality size.

Lastly, we include an indicator for median travel times to the nearest pharmacy calculated by using google maps to calculate travel time between all addresses in Norway and their three nearest straight line pharmacies, picking the shortest travel time for each address before aggregating to the municipalities. A previous Norwegian study [27] has shown a link between dispensing rates and travel times to pharmacies in Norway. If education levels are geographically determined they are also likely to correlate with pharmacy access, thus serving to partial out the effect of ease-of-pharmacy access from education coefficients.

Statistical analysis

Latent growth curve models are a special case of random-coefficient models where a coefficient of time varies randomly between subjects.[28] Within variation in each municipality on the dispensing rate is modeled as a fixed growth trajectory plus a random error term. This means that parameters of individual growth can be modeled by background characteristics,[29] be they time-variant or time-invariant. Applied on our data, municipalities are repeatedly observed, such that level 1 constitutes the longitudinal part of the model (within) and level 2 captures the time-invariant (between) variance.

[FIGURE 1AND 2 ABOUT HERE]

We centered all level 1 covariates except time on their group means (centering within cluster, CWC). Covariates at level 1 are yearly measurements of poverty, education, and municipality population size (i. e. "the state" of the population). These covariates are aggregated to level 2 with simple group means (i. e. the "trait" of the population). Since we are investigating the cross-level interaction between group mean levels of education and time, both grand mean centering and group mean centering can be used to produce results of algebraic equivalence.[30] However, under grand mean centering, including level 1 covariates at both levels of analysis changes the interpretation of the level 2 coefficient. In this permutation, the level 2 coefficient is interpreted as the difference between the level 1 and level 2 main effects.[28] We therefore elect group-mean centering level 1 covariates to ease interpretation of level 2 education coefficient.

All level 2 covariates were conversely centered on their grand mean (CGM). This allows for easier interpretation of main effects in the interaction term, where the estimated trend coefficient is interpreted as the expected mean trend in municipalities at mean education trait levels. Time (L1) was not centered because we are interested in the average trend over the period (see [31] for a discussion on centering time in growth curve models).

The latent growth curve model allows inclusion of time variant covariates. However, it assumes that time variant covariates are not characterized by a systematic growth process. Including simultaneous growth processes in the latent growth curve model may lead to misspecification and biased effects.[32] Within-municipality variation in education levels are highly correlated with the trend variable ($r = .95$), providing evidence for simultaneous growth.

The two-level linear growth curve model with a cross-level interaction effect with group mean education is represented by the following equation:

$$\begin{aligned} L1{:}Y_{tj} &= \beta_{0j} + \beta_{1j}T_{tj} + \beta_2 EDU_{tj}^{CWC} + \beta_3 POP_{tj}^{CWC} + \beta_4 POV_{tj}^{CWC} + \epsilon_{tj} \\ L2{:}\beta_{0j} &= \gamma_{00} + \gamma_{01}EDU_j^{CM} + \gamma_{02}POP_j^{CM} + \gamma_{03}POV_j^{CM} + \gamma_{04}TR_j + u_{0j} \\ \beta_{1j} &= \gamma_{10} + \gamma_{11}EDU_j^{CM} + u_{1j} \\ \beta_k &= \gamma_{k0} \end{aligned}$$

Consulting the $L1$ part of the equation: β_{0j} are the random intercepts, $\beta_k X_{tj}^{CWC}$ is a vector of fixed time-variant coefficients where variables are centered on the group-mean, $\beta_{1j}T_{tj}$ is a time-variant trend variable where the first year is set to 0, and ϵ_{tj} is the level-1 error term. Moving to the $L2$ part of the equation, we find that γ_{00} is the mean municipal level intercept, $\gamma_{0k}W_j^{CM}$ is a vector of coefficients for level 1 covariate group-means, $\gamma_{04}TR_j$ is a coefficient for median travel time to nearest pharmacy, while u_{0j} is the intercept variance component. In this equation, β_k coefficients (β_2,β_3,β_4) are fixed (thus reduced to γ_{k0}), but the linear trend variable is modeled as a random effect with a following variance component u_{1j}. $\gamma_{11}\overleftarrow{EDU}_j$ is a cross-level interaction between the group-mean education level across the time-period and the random linear trend. For model 2, the term $\beta_2 EDU_{tj}^{CWC}$ is removed to address the issue of simultaneous growth.

All models are estimated with the R package `nlme` including a compound symmetric error covariance structure to deal with within-group autocorrelation.

Patient and public involvement

No patient involved.

RESULTS

Model results are available in a numeric format in table 1 along with a short discussion on simultaneous growth in the appendix. Figures 3 and 4 are based on model 2. Table 2 shows summary statistics over the type of antibacterial in the database, along with the total number of dispensed defined daily doses by year and subgroup. Table 3 contains summary statistics.

The estimated mean trend in dispensing rates at mean levels of trait education is equal to $-.608$ ($SD = .919$). This parameter is however moderated by the cross-level interaction term and must be interpreted as such. One percentage point increase in group mean education reduces the trend coefficient with $-.041$ dispensing rate, *ceteris paribus*. There is a greater reduction in dispensing rate in municipalities where a greater proportion of the population have achieved tertiary education. The predicted trends and their dependence on education are presented in figure 3 and figure 4.

Figure 3 presents the predicted linear trajectories in dispense rates based on group-mean education levels. An important observation is that trends are on average negative within the boundaries of the data. Even municipalities with the lowest levels of population education (11%) show estimated negative trends. Even though intercepts can vary, predictions are fanning out from similar intercepts due to the small and insignificant "main" effect of education (effect when $T = 0$) in the model. Consulting figure 4, several municipalities show a positive predicted trend after adjusting for the interaction with education. Most municipalities however show a predicted negative trend in the cross-level interaction model, and the size of the negative trend varies with the education "trait" in the population structure of the municipality.

[FIGURE 3 AND 4 ABOUT HERE]

Table 1: Multilevel growth curve models. Model 1 includes all level 1 covariates. Model 2 excludes the group-mean centered education (L1) covariate due to simultaneous growth issues resulting in collinearity between L1 education and trend.

	Dispensed prescriptions per 100 children	
	(1)	(2)
Level 1		
Trend	−0.271 (−0.634, 0.093)	−0.608*** (−0.750, −0.466)
Poverty	−1.064*** (−1.355, −0.772)	−1.061*** (−1.352, −0.769)
Population (ln)	16.718* (2.735, 30.701)	13.980* (0.269, 27.692)
Education	−0.621* (−1.234, −0.009)	
Level 2		
Education	0.005 (−0.261, 0.272)	0.026 (−0.239, 0.291)
Population (ln)	3.995*** (2.782, 5.207)	3.983*** (2.769, 5.197)
Poverty	−0.841*** (−1.305, −0.377)	−0.845*** (−1.310, −0.380)
Travel	−0.003*** (−0.003, −0.002)	−0.003*** (−0.003, −0.002)
Trend × Education (L2)	−0.037** (−0.062, −0.012)	−0.041*** (−0.066, −0.017)
Intercept	30.992*** (28.883, 33.101)	32.689*** (31.424, 33.953)
Var. Comp.		
Std. Dev. μ_1	.919	.918
Std. Dev. μ_0	11.61	11.54
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,499	4,503
Log Likelihood	−17,079.000	−17,097.230
Akaike Inf. Crit.	34,188.000	34,222.460
Bayesian Inf. Crit.	34,284.180	34,312.240
Note:		*p < 0.05; **p < 0.01; ***p < 0.001 95% CI in parentheses.

Table 2 Total dispensed DDD per 1000 children by ATC J01 subgroups.

Year	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
2006	0.4	1009.1	19.9	77.9	526.2	7.6	1.0	17.4
2007	0.3	923.1	16.3	58.2	453.9	2.9	1.0	11.9
2008	0.2	1158.4	19.8	73.6	504.3	9.2	0.9	13.0
2009	0.2	1057.2	18.4	69.5	418.3	6.9	0.5	10.1
2010	0.2	1296.7	22.5	74.6	502.5	0.7	0.8	9.8
2011	0.1	1170.5	21.7	70.1	566.4	2.7	1.3	8.0
2012	0.4	1195.9	17.0	68.1	484.1	1.1	1.3	7.3
2013	0.4	1001.6	20.9	66.7	355.6	0.9	2.0	5.6
2014		1104.1	24.2	71.2	367.3	1.3	1.6	7.4
2015	0.1	965.6	21.8	67.1	299.9	0.9	1.3	8.7
2016	0.0	911.2	20.1	58.3	260.8	2.0	1.8	5.2

Table 3: Pooled statistics include summary statistics for yearly observations for all municipalities before centering. The dependent variable Dispensed Rx/100 chld. under pooled statistics is the dependent variable used in the model. The within section shows descriptive statistics for all group-mean centered covariates, that is the level 1 parameters in the model. Note the mean 0 ensuring no correlation between level 1 and level 2 covariates. The between section represents the level 2 variables used in the model. These are 428 group means for all covariates excluding travel times. Travel time is presented in decimal minutes, and is time-invariant due to only being observed once.

Statistic	N	Mean	St. Dev.	Min	Max
Pooled					
Dispensed Rx/100 chld.	4,519	29.7	16.3	0.9	104.9
Education	4,515	21.2	5.9	9.1	51.9
Population	4,519	11,885.7	35,479.5	200	658,390
Poverty	4,518	10.0	2.4	3.7	21.8
Within					
Dispensed Rx/100 chld.	4,519	0.00	9.58	− 40.38	74.42
Education	4,515	0.00	1.87	− 5.25	5.97
Population	4,519	0.00	2,180.11	− 60,394.18	59,584.82
Poverty	4,518	0.00	1.07	− 3.46	5.76
Between					
Dispensed Rx/100 chld.	428	29.0	13.5	2.8	70.3
Education	428	21.0	5.6	11.2	48.2
Population	428	11,505.9	34,795.5	212.2	598,805.2
Poverty	428	10.0	2.2	5.1	18.6
Travel (min.)	426	1,674.4	1,882.8	182.0	13,129.0

DISCUSSION

While there is a national decrease in antibacterial dispense rates for 0-2 year olds in Norway,[10] this study shows that trends varies between Norwegian municipalities. Municipalities where a larger proportion of the population have attained tertiary education also tend to show a greater decrease in dispensing rates. Several efforts have been made to reduce antibacterial dispensing rates, notably through updating national guidelines for use of antibacterials[33] and intervention campaigns.[34] Considering high education levels as a form of socioeconomic advantage, the results suggest that municipalities with more socioeconomically advantaged populations have been more successful in reducing dispensing rates.

Our findings support the existing literature on the relationship between relative socioeconomic deprivation and antibacterial dispensing rate. Low parental education level has been linked to higher prescribing rates in pediatric patients,[2,5,18,35] and we expect those individual mechanisms to translate to aggregate statistics. If the lack of higher education in a community is considered a form of regional deprivation, then these inverse results are consistent with other data on the association between area-level deprivation indexes (including education in the index) and dispensing rates.[3,4,16]

We chose tertiary education as our education indicator for two reasons. Firstly, the literature states that knowledge of proper use of antibiotics is more common in people having achieved higher education specifically.[19–21] Our findings are consistent with these expectations. Secondly, the Norwegian education system ensures all youngsters the legal right to education up to and including upper secondary education. No such legal right exists for higher education. We chose higher education as our exposure because continued education past secondary education is an active choice in comparison to structured schooling in which we expect local population diversity.

Health literacy is associated with higher education.[22,23] While education and health literacy are linked, education is an inaccurate proxy for individual health literacy.[24] However, overuse of antibacterials, and the policies implemented to reduce consumption is not only an individual health issue, but a public one. Successful enactment of public health policies directed at reducing antibacterial dispense rates may partly rely on the ability of individuals and groups to obtain, process, understand, evaluate, and act upon information needed to make decisions that benefits the individual and the community; so-called public health literacy[36] It is possible that education enables an understanding of the individual and family as embedded in society as a whole, where individual decisions on antibacterial treatment are made within a framework of a greater public health issue.

The Norwegian health care system provides universal health care access, and health inequalities in care utilization have diminished over time.[37] Needs-adjusted socioeconomic differentiation in health care usage has empirically mostly been observed in use of private medical specialists and hospital outpatient care.[38] These observations do not necessarily include all differentiation in health care usage in Norway, including potential geographic variation. Importantly, these studies do not observe parental health care seeking. Assuming that parental health care seeking translates to pediatric health care seeking, a theoretical

proposition is that health care usage may not be socially determined in volume, but in kind. People from advantaged socioeconomic backgrounds interact and use health care inputs more efficiently, thus achieving the same amount of health investment with a lower amount of health care services. They may also consider the potential consequences of e. g. antibacterial use more frequently, driving the dispensing rate downward.[5]

Importantly, children are themselves not actors in this framework. Decisions on treatment are made by parents and physicians. This in turn suggests that the health care provided to children is dependent on parental socioeconomic status and *how* they seek health care for their children, as well as the physicians prescribing habits and response to different individuals and social groups. Several studies have pointed out a possible association between high use of antibacterials in young children and an increased risk of chronic disease development later in life.[11–14] Standardizing prescribing practices seems important in reducing health inequalities in future generations.

High levels of antibiotics consumption are mainly discussed with regards to threats of antimicrobial resistance. While overuse of antibiotics is associated with high prevalence of antimicrobial resistance, low dispensing rates may be a sign of underuse of health care services, potentially resulting in negative health outcomes over time.[6] Here it should be noted that dispensing rates in Norway are comparatively low in a European context,[34] but our analysis along with examples from Switzerland [5] show that low levels of overall dispensing rates do not preclude local variation.

Area level strategies rather than national level strategies for antimicrobial stewardship have been suggested in other countries.[15] Similar recommendations may be useful in Norway, given the regional variation in dispensing rate and reduction trends. The overall responsibility for health policies in Norway lies within the National Ministry of Health, and stewardship of antimicrobial resistance in Norway relies on existing administrative structures of disease prevention and control, with sectoral operative responsibility and weak coordination mechanisms.[39] National political strategies do target the primary health care service at the municipal level, but the need and potential drivers of antibacterial treatment may vary between municipalities. We expect the efficacy of national policy for reduction in antibacterial dispense rates to partially depend on local population socioeconomic composition.

Strengths, limitations, and methodological considerations

Unlike several authors who apply an indexed deprivation measurement containing a variety of deprivation indicators, we focus on education specifically as it is a common component of deprivation indexes. Deprivation based indexes present a trade-off between interpretation and capturing a more holistic concept of deprivation. It is unclear what features of a deprivation index drives empirical variations in dispensing rate. Translating theoretical mechanisms between the individual level to aggregate statistics becomes even more challenging due to the number of dimensions in a deprivation index. Effects of income and occupation deprivation have been studied separately,[4] but no such analysis is performed on an education indicator. Education is a key socioeconomic characteristic for health

determinants in Norway. By investigating education specifically, our results are more readily interpreted and more clearly relatable to specific mechanisms discussed in the literature.

A strength in this study is the completeness and specificity of the dispense rate metric. The NorPD contains all dispensed prescriptions in the period under study, excluding usage in hospitals. This means that the dispense rate metric captures primary health care dispense rates. We argue that this has two advantages. Firstly, we expect education to matter more in the context of primary health care as the parents are active participants in health care decision making. Secondly, the primary health care service is administered at the municipal level in Norway. Observed trends are likely to be a result of local community needs, behaviors, and local decision making processes.

A limitation on this study is the lack of information on the geographical burden of disease. However, regional differences in dispensing rates are unlikely to be explained by differences in severity and infection density, and more likely to be related to differences in medical practice.[9] A Welsh study similarly found no support that regional differences in prescription can be explained by chronic conditions in the adult population.[3] Regardless, if the entire variance should be explained by the burden of infections, the implication is that infections requiring antibacterial treatment is geographically unequally distributed, even between pediatric patients.

Another limitation is the limited inference that can be made on individual level outcomes based on aggregate statistics. Further research is necessary to conclude a link between parental education, individual interaction with health care services, and pediatric antibacterial dispense rates in Norway.

A methodological consideration is the correlation between the municipality dispensing rates at the beginning of the period. Larger starting dispensing rates are correlated with greater reductions, as evidenced by a correlation between the random intercepts and trends ($r = -.597$). This is partly a result of the lower bound of the dispense rate metric. Main conclusions are however unaffected. Considering the insignificant main effect of education suggests that the association between education and dispensing rate trends is unlikely to be confounded by a correlation between population education and outset dispense rate.

CONCLUSION

Our analysis shows that the ability to reduce dispensing rate over time at municipality level is associated with mean population levels of higher education. Antimicrobial stewardship should consider local needs and potential root causes of health outcomes to effectively standardize prescription patterns between municipalities. Paying attention to social demographics that may affect health behavior, preferences, and usage such as education may help further reduce dispensing rates in compliance with political ambitions.

CONTRIBUTORSHIP STATEMENT

SS conceptualized, designed, drafted the manuscript, prepared data, and performed statistical analysis. KS contributed data. LS provided ethics approval and data from the prescription registry. All authors critically revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

No funding grants to declare.

DATA SHARING STATEMENT

Data on antibacterial dispensing can be obtained by application to a third party (The Norwegian Prescription Registry) and are not publicly available. Data on covariates, sans travel times to closest pharmacy are available through Statistics Norway public data repository (Stat bank). Travel time data are available by request.

ETHICS STATEMENT

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (ref. 2018/1021) in compliance with the Norwegian Health Research Act, §10.

REFERENCES

1 Van Boeckel TP, Gandra S, Ashok A, *et al.* Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases* 2014;**14**:742–50.

2 Thrane N, Olesen C, Schønheyder HC, *et al.* Socioeconomic factors and prescription of antibiotics in 0-to 2-year-old Danish children. *Journal of Antimicrobial Chemotherapy* 2003;**51**:683–9.

3 Adekanmbi V, Jones H, Farewell D, *et al.* Antibiotic use and deprivation: An analysis of Welsh primary care antibiotic prescribing data by socioeconomic status. *Journal of Antimicrobial Chemotherapy* 2020.

4 Koller D, Hoffmann F, Maier W, *et al.* Variation in antibiotic prescriptions: Is area deprivation an explanation? Analysis of 1.2 million children in Germany. *Infection* 2013;**41**:121–7.

5 Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. *Health policy* 2006;**78**:77–92.

6 Haugen P, Simonsen GS, Primicerio R, *et al.* Antibiotics to outpatients in Norway. Assessing effect of latitude and municipality population size using quantile regression in a cross-sectional study. *Pharmaceutical statistics* 2018;**17**:4–11.

7 Sakshaug S *et al.* Legemiddelforbruket i Norge 2013–2017. Legemiddelstatistikk 2018: 1 [drug consumption in norway 2013–2017. Drug statistics 2018: 1]. 2018.

8 Blix HS, Engeland A, Litleskare I, *et al.* Age-and gender-specific antibacterial prescribing in Norway. *Journal of antimicrobial chemotherapy* 2007;**59**:971–6.

9 Stordal K, Marild K, Blix HS. Bruk av antibiotika hos barn i perioden 2005–16. *Tidsskriftet Den Norske Legeforening* 2017;**137**:1414–20.

10 Beckstrøm S, Småbrekke L. Antibacterial use by birth year and birth season in children 0-2 years in Norway. *The Norwegian Journal of Epidemiology* 2021;**29**:35–43.

11 Korpela K, Vos WM de. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. *Microbial Cell* 2016;**3**:296.

12 Mårild K, Ye W, Lebwohl B, *et al.* Antibiotic exposure and the development of coeliac disease: A nationwide case–control study. *BMC gastroenterology* 2013;**13**:1–9.

13 Risnes KR, Belanger K, Murk W, *et al.* Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *American journal of epidemiology* 2011;**173**:310–8.

14 Sander SD, Andersen A-MN, Murray JA, *et al.* Association between antibiotics in the first year of life and celiac disease. *Gastroenterology* 2019;**156**:2217–29.

15 Mölter A, Belmonte M, Palin V, *et al.* Antibiotic prescribing patterns in general medical practices in England: Does area matter? *Health & place* 2018;**53**:10–6.

16 Thomson K, Berry R, Robinson T, *et al.* An examination of trends in antibiotic prescribing in primary care and the association with area-level deprivation in England. *BMC Public Health* 2020;**20**:1–9.

17 Hobbs MR, Grant CC, Ritchie SR, *et al.* Antibiotic consumption by New Zealand children: Exposure is near universal by the age of 5 years. *Journal of Antimicrobial Chemotherapy* 2017;**72**:1832–40.

18 Pichichero ME. Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 1999;**104**:1384–8.

19 Waaseth M, Adan A, Røen IL, *et al.* Knowledge of antibiotics and antibiotic resistance among Norwegian pharmacy customers–a cross-sectional study. *BMC Public Health* 2019;**19**:1–2.

20 Agarwal S, Yewale VN, Dharmapalan D. Antibiotics use and misuse in children: A knowledge, attitude and practice survey of parents in India. *Journal of clinical and diagnostic research: JCDR* 2015;**9**:SC21.

21 Yu M, Zhao G, Lundborg CS, *et al.* Knowledge, attitudes, and practices of parents in rural china on the use of antibiotics in children: A cross-sectional study. *BMC infectious diseases* 2014;**14**:1–8.

22 Dunn-Navarra A-M, Stockwell MS, Meyer D, *et al.* Parental health literacy, knowledge and beliefs regarding upper respiratory infections (URI) in an urban Latino immigrant population. *Journal of urban health* 2012;**89**:848–60.

23 Sørensen K, Pelikan JM, Röthlin F, *et al.* Health literacy in Europe: Comparative results of the European health literacy survey (HLS-EU). *European journal of public health* 2015;**25**:1053–8.

24 Berkman ND, Davis TC, McCormack L. Health literacy: What is it? *Journal of health communication* 2010;**15**:9–19.

25 Ratzan S, Parker R. Health literacy. *National library of medicine current bibliographies in medicine Bethesda: National Institutes of Health, US Department of Health and Human Services* 2000.

26 Organization WH *et al.* ATC/DDD index 2019 https://www. Whocc. No/atc_ddd_index. 2018.

27 Svendsen K, Kongsgard H, Haugen P, *et al.* Travel time to pharmacy influence the use of antibiotics in Norway. In: *PHARMACOEPIDEMIOLOGY AND DRUG SAFETY*. WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA 2016. 641–1.

28 Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using Stata*. STATA press 2008.

29 Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis methods*. sage 2002.

30 Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: A new look at an old issue. *Psychological Methods* 2007;**12**:121–38. doi:10.1037/1082-989x.12.2.121

31 Biesanz JC, Deeb-Sossa N, Papadakis AA, *et al.* The role of coding time in estimating and interpreting growth curve models. *Psychological Methods* 2004;**9**:30–52. doi:10.1037/1082-989x.9.1.30

32 Curran PJ, Obeidat K, Losardo D. Twelve frequently asked questions about growth curve modeling. *Journal of cognition and development* 2010;**11**:121–36.

33 Eliassen KE, Fetveit A, Hjortdahl P, *et al.* New guidelines for antibiotic use in primary health care. *Tidsskriftet den Norske Legeforening: tidsskrift for praktisk medicin, ny raekke* 2008;**128**:2330–4.

34 Ministry of Health. Handlingsplan mot antibiotikaresistens i helsetjenesten. 2016.

35 Mangrio E, Wremp A, Moghaddassi M, *et al.* Antibiotic use among 8-month-old children in Malmö, Sweden–in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatrics* 2009;**9**:31.

36 Freedman DA, Bess KD, Tucker HA, *et al.* Public health literacy defined. *American journal of preventive medicine* 2009;**36**:446–51.

37 Vikum E, Bjørngaard JH, Westin S, *et al.* Socio-economic inequalities in Norwegian health care utilization over 3 decades: The HUNT study. *The European Journal of Public Health* 2013;**23**:1003–10.

38 Vikum E, Krokstad S, Westin S. Socioeconomic inequalities in health care utilisation in Norway: The population-based HUNT3 survey. *International journal for equity in health* 2012;**11**:1–9.

39 Time MS, Veggeland F. Adapting to a global health challenge: Managing antimicrobial resistance in the Nordics. *Politics and Governance* 2020;**8**:384–95.

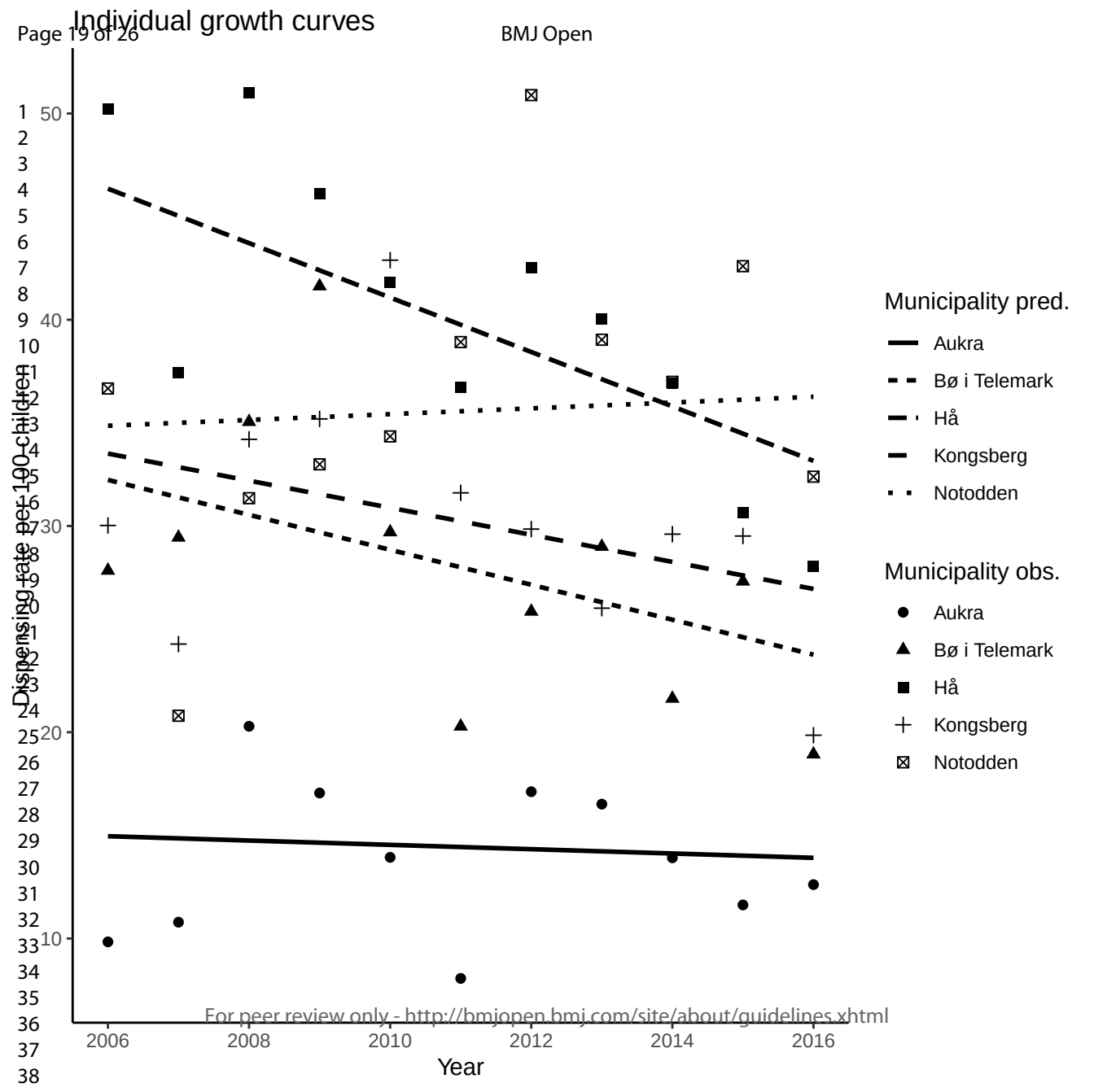
FIGURE CAPTIONS

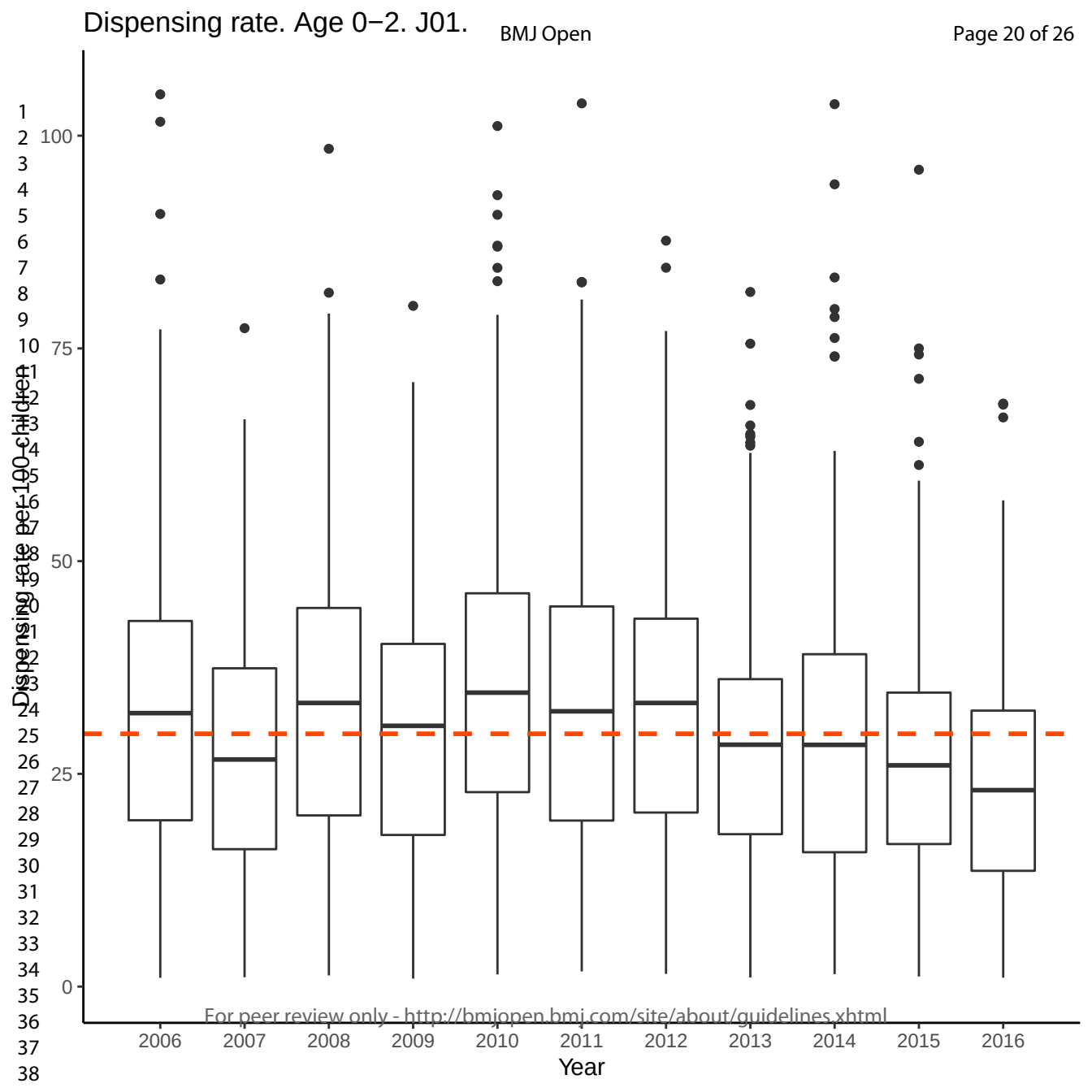
Figure 1: *Linear growth curve predictions and observations from a simple random trend null-model for five random municipalities. Municipalities were randomly sampled from a strata of slope quantiles to ensure that slope variance was represented in the figure. Note that the Y-axis is scaled by min-max observations in the subsample, not the entire distribution.*

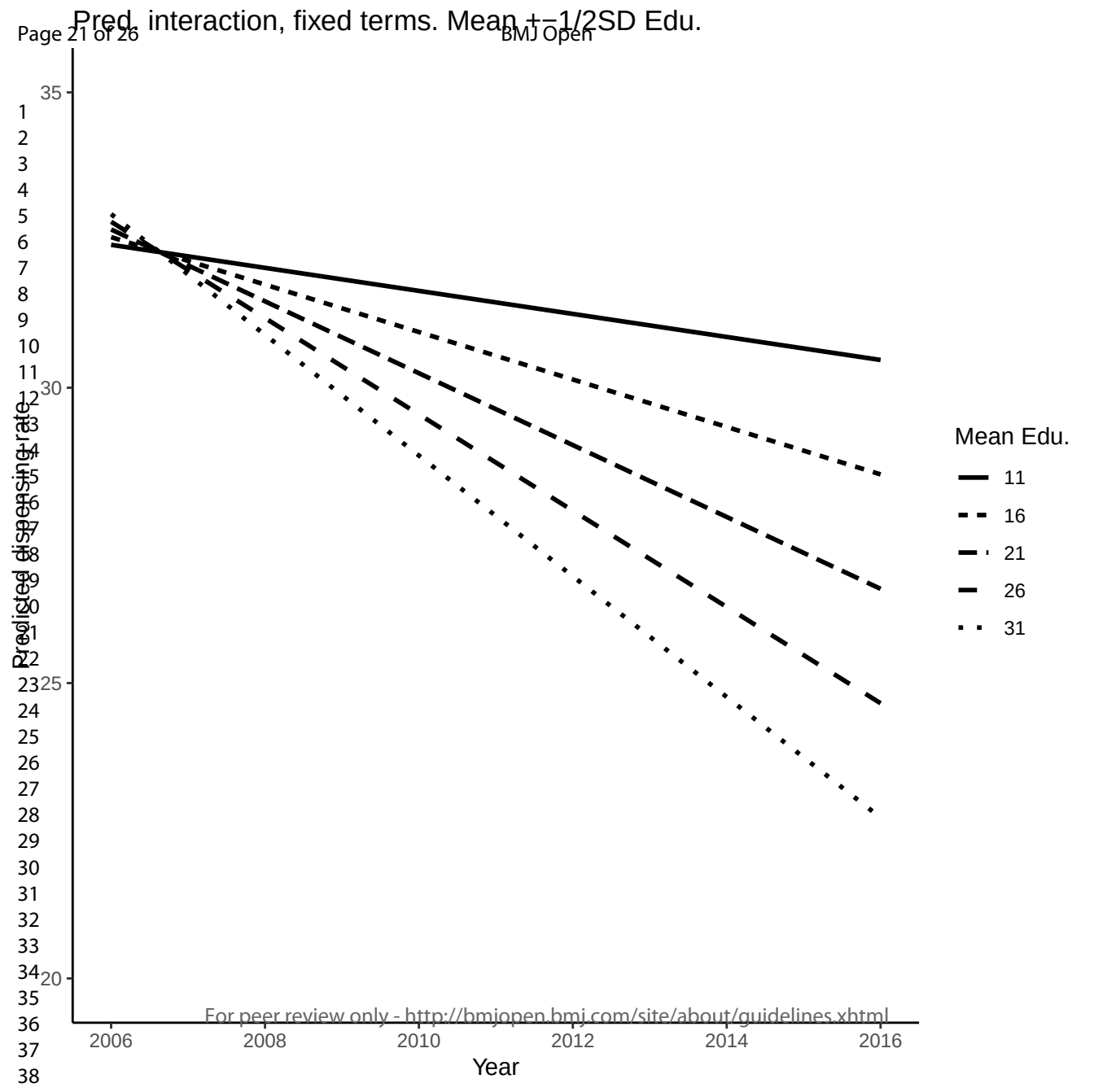
Figure 2: *Box-and-whiskers plot of dispensing rate within years. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this figure is the notable variation between municipalities within a specific year. Calculating an intraclass correlation coefficient from a null-model attributes ICC = 62.8% of the total variance to between municipalities.*

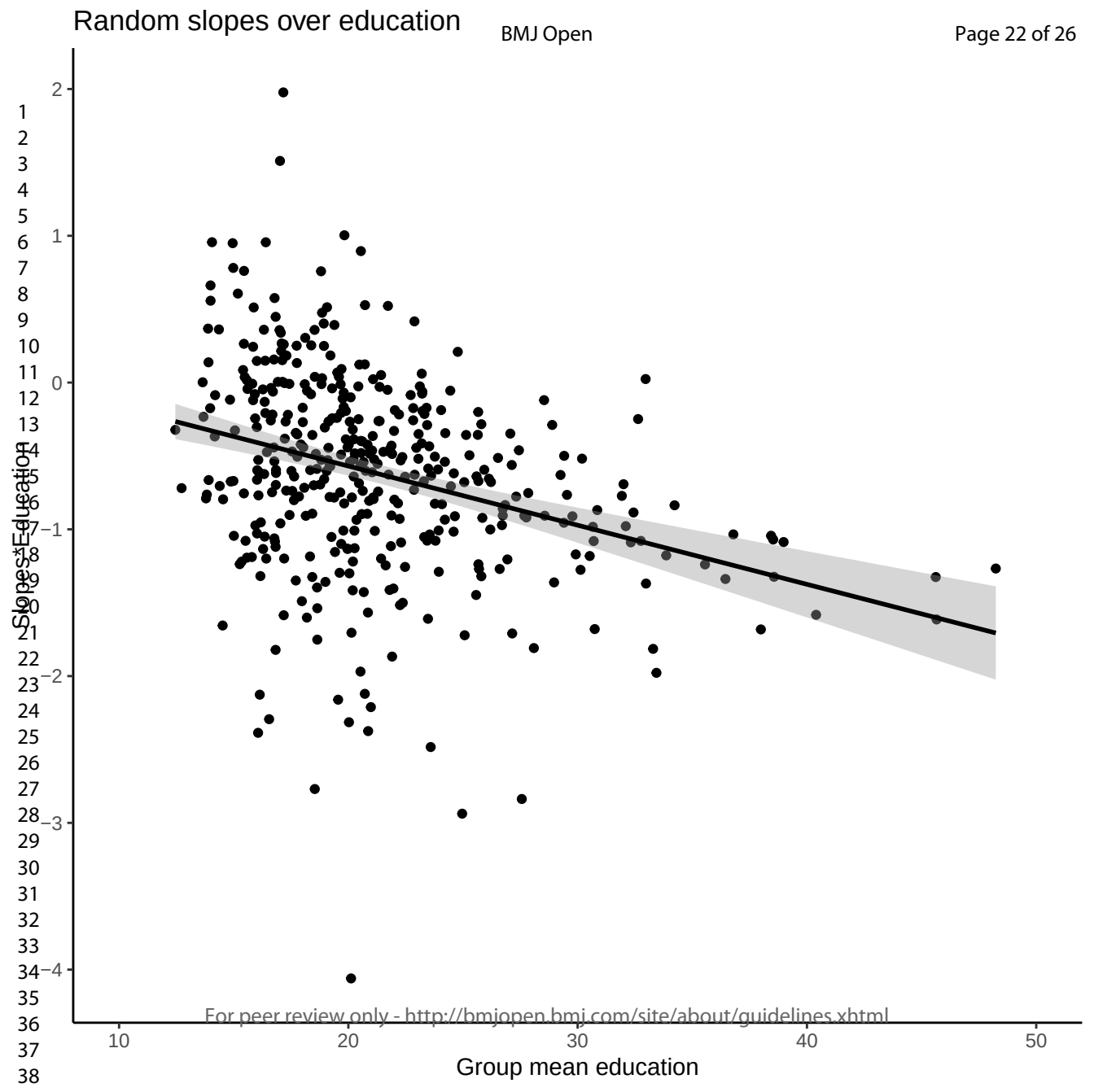
Figure 3: *Predicted slopes based on fixed components. Middle line represent the mean group level of education, bordering lines are predicted trends for +-1 standard deviation in education levels. Outer lines are predicted trends for +-2 standard deviations from mean education levels.*

Figure 4: *Random slopes over the group mean education scale. Points are individual linear trend coefficients for each municipality. Please consider Y-axis scaling when interpreting figures.*









APPENDIX

	Dispensed prescriptions per 100 children	
	(1)	(2)
Level 1		
Trend	−0.271 (−0.634, 0.093)	−0.608*** (−0.750, −0.466)
Poverty	−1.064*** (−1.355, −0.772)	−1.061*** (−1.352, −0.769)
Population (ln)	16.718* (2.735, 30.701)	13.980* (0.269, 27.692)
Education	−0.621* (−1.234, −0.009)	
Level 2		
Education	0.005 (−0.261, 0.272)	0.026 (−0.239, 0.291)
Population (ln)	3.995*** (2.782, 5.207)	3.983*** (2.769, 5.197)
Poverty	−0.841*** (−1.305, −0.377)	−0.845*** (−1.310, −0.380)
Travel	−0.003*** (−0.003, −0.002)	−0.003*** (−0.003, −0.002)
Trend×Education (L2)	−0.037** (−0.062, −0.012)	−0.041*** (−0.066, −0.017)
Intercept	30.992*** (28.883, 33.101)	32.689*** (31.424, 33.953)
Var. Comp.		
Std. Dev. μ_1	.919	.918
Std. Dev. μ_0	11.61	11.54
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,499	4,503
Log Likelihood	−17,079.000	−17,097.230
Akaike Inf. Crit.	34,188.000	34,222.460
Bayesian Inf. Crit.	34,284.180	34,312.240
Note:		*p<0.05; **p<0.01; ***p<0.001
		95% CI in parentheses.

Simultaneous growth and MLM interpretation under centering scheme

Multilevel linear growth curve models. Model 1 includes all level 1 covariates. Model 2 excludes the group-mean centered education (L1) covariate due to simultaneous growth issues resulting in collinearity between L1 education and trend.

This contrast table shows the effect of simultaneous growth on estimated parameters. The only difference between the models is the removal of the L1 group-mean centered education indicator. Confidence intervals are shown in parentheses.

Group-mean centering level 1 covariates leads to orthogonal relationships between levels; the correlations between level 1 and level 2 covariates are equal to 0. In a model without the uncentered trend variable, excluding level 1 coefficients would not affect level 2 estimates under group-mean centering. In fact, the estimates would be the same regardless of whether or not level 1 covariates were even in the model [30]. However, since the trend variable is *not* centered, some correlation will exist between levels through correlation with the trend variable, explaining the minor changes in level 2 coefficients. These changes are not substantial and only result in minor changes in L2 estimates.

Simultaneous growth leads to a very simple issue of near perfect collinearity between L1 education and the trend variable. This is the reason for the dramatic change in the trend coefficient size and confidence interval. Simply put, the trend effect in model 1 is biased due to collinearity with the L1 education covariate. While there are ways to deal with this problem through *multivariate* growth curve modeling [32], we are primarily interested in the cross-level interaction effect between education traits and the random trend. As such, we prefer the more parsimonious modeling option removing the group-mean centered education variable from the level 1 part of the equation.

Interpreting coefficients under centering scheme

Centering and cross-level interactions changes the interpretation of certain coefficients. We base the interpretation on model 2 and focus on three main coefficient interpretations a) the main trend effect and its variance, b) the main trait education effect and c) the cross level interaction term.

Due to grand-mean centering L2 covariates and the inclusion of an interaction term, the main trend effect ($-.608$) is interpreted as the expected trend for municipalities with a mean level of trait education (21.15%), *ceteris paribus*. This is a random coefficient, and its random parameter μ_1 suggests that the mean deviation from the fixed term is equal to $.919$. The main education effect ($.026$) is the expected effect of trait education at $T = 0$ (2006, remember that the trend is not centered), *ceteris paribus*. This is clearly shown by the very similar intercepts in figure 2a. Lastly, the interaction term ($.041$) is the expected decrease in trend for every pp increase in education traits. This model is the basis for figures 2a and 2b.

For other L1 coefficients (sans the trend coefficient), a one unit increase entails a one unit change from a covariates given group mean. The coefficient is thus the average effect of a one unit increase from a given group mean, *ceteris paribus*.

Centering and growth

Notably, we choose not to center the level 1 trend variable for two reasons; firstly, the the panels are only slightly imbalanced. Centering the trend variable on the group means practically results in a grand mean centered trend variable (correlation with uncentered trend indicator: $r = .97$), with no real consequences to the coefficient estimates. The only consequence is on the intercepts and the intercept variance due to the zero point being established in 2011 for all but a few groups. Secondly, the model is a linear random growth curve model. Centering the

trend covariate is more of an issue in situations where a polynomial growth curve might be fitted.

Intercept and slope correlation

Intercepts and slopes are negatively correlated at $r = -.597$. This is a natural consequence of bounded data; dispensing rate can not be less than 0. Municipalities with low starting dispensing rates will naturally not be able to reduce dispensing rates as much as those with higher starting dispensing rates. This is of no particular concern for estimating the interaction term; indeed, the non-significant main education coefficient implies that the intercept variance is not explained by mean population education levels. This is also clear when investigating figure 1a.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3-4
		(*b*) Describe any methods used to examine subgroups and interactions	3-4
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	4/B

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7-8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7-8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6/A
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of area-level education with the regional growth trajectories of rates of antibacterial dispensing to patients under 3 years in Norway: a longitudinal retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058491.R1
Article Type:	Original research
Date Submitted by the Author:	03-May-2022
Complete List of Authors:	Svalestuen, Sigbjørn; UiT The Arctic University of Norway, Department of social science Svendsen, Kristian; UiT The Arctic University of Norway, Department of pharmacy Eggen, Anne; UiT The Arctic University of Norway, Department of Community Medicine Småbrekke, Lars; UiT The Arctic University of Norway, Department of pharmacy
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Public health, Paediatrics, Pharmacology and therapeutics, Sociology
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Community child health < PAEDIATRICS, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association of area-level education with the regional growth trajectories of rates of antibacterial dispensing to patients under 3 years in Norway: a longitudinal retrospective study

Sigbjørn Svalestuen[1], Kristian Svendsen[2], Anne Elise Eggen[3], Lars Småbrekke[2]

Keywords: *Drug prescriptions, Education, Geography, Health inequalities, Health policy*

Word count: 3019 *(excluding title page, abstract, captions, references and statements)*

[1] **Dep./Inst.:** Department of Social Science/UiT The Arctic University of Norway

E-mail: *sigbjorn.svalestuen@uit.no*

Phone: *+47 776 44 321*

Address: UiT The Arctic University of Norway
PO Box 6050 Langnes
N-9037 Tromsø
Norway

Fax: *NA*

[2] **Dep./Inst.:** Department of Pharmacy/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

[3] **Dep./Inst.:** Department of Community Medicine/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

ABSTRACT

Background Antibacterial use varies within and between countries and over time, and these variations have been linked to both individual and area-level socioeconomic factors, such as education and material deprivation.

Objective To examine the association between area-level education and the local growth trajectories in antibacterial dispensing rates in Norwegian municipalities among children under 3 years old.

Methods This retrospective, longitudinal study used individual primary care prescription data from the Norwegian Prescription Database for the period 2006–2016. Data were collected on the date of dispensing, the type and amount of antibiotic, the patient's age and sex and the municipality of residence and then linked to municipality-level statistics on education available from Statistics Norway. We used multilevel growth curve modelling, with a linear trend variable modelled as a random effect and a cross-level interaction between linear trends and the proportion of the population in the municipality who had received a university or college education.

Results We identified a significant negative linear trend in the square root of the dispensing rate for children under 3 years old during the period. This trend varied between municipalities. A negative cross-level interaction term between population education levels and random trends showed that municipalities with an average level of population education saw a reduction in their square root dispensing rates of −.053 (95% CI = −.066, −.039) prescriptions per 100 children. Each additional percentage point in population education contributed a further −.0034 (95%CI = −0.006, −0.001) reduction to the square root dispensing rate.

Conclusions Municipalities in which a larger proportion of the local population have high educational achievements have been more successful in reducing antibacterial dispensing rates in children under 3 years old. Adopting area-level strategies and addressing local community disadvantages may help to optimise practices and prescribing patterns across local communities.

Strengths and limitations of this study

- Complete antibacterial dispensing data allows estimations of local community dispensing rate trends and their associations with education at a high level of spatial resolution.
- By including all Norwegian municipalities, we explored the total extent of local variations in dispensing rates under national reduction policy guidelines.
- Aggregate data cannot directly infer individual-level decision-making and needs.
- We were unable to control for the geographical burden of infectious disease in the age groups under examination.

INTRODUCTION

The periodic prevalence and patterns of antibiotic use vary between countries[1] and between socioeconomic and demographic groups within countries,[2-6] and studies have also shown temporal variations in the dispensing of antibacterials for systemic use.[7-8] One study from Norway found an overall reduction in the number of dispensed prescriptions among children aged 0–2 between 2005 and 2016, with the prevalence varying between counties.[9] Another study found that, among Norwegian children aged 0–2, one-year-olds consistently had the highest antibacterial dispensing rates between 2008 and 2016.

Several studies have attributed variations in antibacterial use to socioeconomic characteristics,[3-5,10-12] often including an indexed area-level deprivation measurement to capture several dimensions of deprivation (e.g., education, income, barriers to housing, crime, employment). Crowding, hygiene, lower host resistance due to poor nutrition, stress and smoking prevalence create a greater risk of infectious illness among people of lower socioeconomic status, but general practitioners' treatment practices and their interactions with family attitudes towards demanding certain treatments may influence prescription dispensing,[2,13] resulting in geographic and temporal variations in aggregate statistics. Education is associated with the awareness and proper use of antibacterials[14-16] and with the individual capacity to obtain, process and understand health information,[17,18] and cultural factors, such as individual vs. collective value systems, and future-oriented behaviour have also been associated with prescription patterns at multiple levels.[19]

Studies on variations in dispensed antibiotics in Norway have not explicitly modelled local variations in dispensing rate growth trajectories in terms of socioeconomic composition. The aim of this study was to investigate the association between population education levels and growth trajectories in antibacterial dispensing rates at the municipality level using longitudinal data and a multilevel growth curve model.

MATERIALS AND METHODS

The Norwegian Prescription Registry (NorPD) contains all prescriptions with a valid unique personal identifier redeemed at Norwegian pharmacies; details of the NorPD are published elsewhere.[20] We considered the period from 2006 to 2016 and included 734,359 prescriptions. We aggregated prescriptions if the same individual received two or more prescriptions for the same antibacterial drug on the same date, and we excluded records for individuals aged more than 1095 days (3 years) and those who died during the observation period. We used the following data from the NorPD: sex; year and month of birth; unique personal identifier; municipality of residence; date on which the prescription was dispensed at the pharmacy; and the Anatomical Therapeutical Chemical Classification System (ATC) code at the fifth level. As we only had information on the birth month in our data, we assigned a fictious birth date of the 15th of the birth month and calculated age as the date of dispensing minus this date.

Data in NorPD are pseudonymised, allowing longitudinal observation of an individual who is anonymous to the researcher. Individual data were aggregated at the municipality level, and

dispensing rates were calculated as the yearly number of prescriptions within a municipality per 100 children. We linked the aggregated prescription data to publicly available data on all Norwegian municipalities using the unique municipality identification number system. Analyses were restricted to ATC J01: antibacterials for systemic use.[21] The data cover the entirety of Norway at the local administrative level. Figure 1 presents a box-and-whiskers plot of the calculated local dispensing rate by year. Figure A1 (appendix) presents a sample of trends and intercepts fitted to the dispensing rate metric.

Exposure and covariates

Our exposure was the proportion of the population in a municipality who had received tertiary education (university level for 3 or more years).[22] We chose tertiary education as our education indicator for two reasons. Firstly, the literature states that knowledge of the proper use of antibiotics is more common among people who have received a higher education,[14-16] and secondly, the Norwegian education system ensures all young people the legal right to education up to and including upper secondary education, but no such right exists for higher education. Thus, continued education past the secondary level is an active choice, in contrast to structured schooling, so we would expect local population diversity.

We included a covariate for the proportion of the population in a municipality living in a household with less than 60% of the national median income,[23] which is the standard definition of low income in the European Union. The association between deprivation and dispensing rates[3-5] suggests that poverty may confound the relationship between dispensing rates and population education, and including this covariate served to partial out effects that could be attributed to education rather than to material deprivation.

The municipality population size may be related to levels of regional deprivation in education and to regional development and may therefore impact access to health care services. A previous study identified an association between municipality population size and dispensing rates in Norway,[6] and municipality size is therefore likely to confound the link between education and dispensing rates. Populations of Norwegian municipalities vary from fewer than 400 to more than 600,000 residents, and to best capture this variance, we calculated the natural logarithm of population size collected from official statistics[24] as an indicator of municipality size.

Lastly, we included an indicator for the median travel time to the nearest pharmacy, calculated using Google Maps to determine travel time between all addresses in Norway and their three nearest straight-line pharmacies, selecting the shortest travel time by car for each address before aggregating to the municipality level. A previous Norwegian study[25] found a link between dispensing rates and travel times to pharmacies in Norway. If education levels are geographically determined, they are also likely to correlate with pharmacy access, and it is thus important to partial out the effects of ease-of-pharmacy access from the educational coefficients.

Statistical analysis

Multilevel growth curve models are a special case of multilevel models in which a coefficient of time varies between units.[26] The variation in each unit of the dispensing rate is modelled

as a fixed growth trajectory plus a random error term, which means that the parameters of growth can be modelled by background characteristics.[27] Applying this to our data, the municipalities are repeatedly observed, such that level 1 constitutes the longitudinal part of the model and level 2 captures the variance between the municipalities.

[FIGURE 1 ABOUT HERE]

We centred all level 1 covariates, except time, on their cluster means—that is, centring within cluster — to achieve orthogonality between the level 1 and level 2 variables.[28] The covariates at level 1 were annual measurements of poverty, education and municipality population size, which reflect changes in the municipality by year. The same covariates were aggregated at level 2 as cluster means. These covariates reflect differences between municipalities over the period under study. All level 2 covariates were conversely centred on their grand mean. This centring scheme allows for easier interpretation of main effects in the interaction term, in which the estimated trend coefficient is interpreted as the expected mean dispensing rate trend in municipalities at average levels of population education. Time (L1) was not centred because we were interested in the average trend over the period (see [29] for a discussion on centring time in growth curve models).

The multilevel growth curve model assumes that time-variant covariates are not characterised by a systematic growth process, and the inclusion of simultaneous growth processes in a multilevel growth curve model may lead to misspecification and biased effects.[30] Within-municipality variations in education levels are highly correlated with time ($r = .95$), providing evidence for simultaneous growth and biasing the trend coefficient. We therefore removed the time-variant education predictor, as our goal was to estimate a cross-level interaction effect between the time-invariant education predictor and trends. We detail this choice further in the appendix and demonstrate the consequences of simultaneous growth on trend estimation in table A1.

We performed a square root transformation on the dispense rate metric to improve the model fit, but the coefficients on the square root scale lack the clean interpretability of coefficients on the original scale. We therefore used the square root model for predictions and for the evaluation of statistical significance but present the predicted dispensing rates using the original scale to aid in interpretation. Untransformed and square root transformed dispensing rate distributions are available in figure A2 and A3 (appendix), respectively.

The model fit was assessed using the Akaike Information Criterion, the Bayesian Information Criterion and residual diagnostic plots. Residual diagnostic plots are available in figures A4-A7 in the appendix. All models were estimated using the R package *nlme*, incorporating a compound symmetric error covariance structure to deal with within-group autocorrelation. A model equation and a parameter description are available in the appendix.

Patient and public involvement

No patients were involved.

RESULTS

The model results are shown in Table *1*, and Figures 2 and 3 are based on estimates from the model. Precise p-values and an untransformed version of the model are found in table A2 in the appendix. Table *2* shows summary statistics for the types of antibacterial in the database, together with the total number of defined daily doses (DDD) dispensed, summarised by year and subgroup. Table *3* presents summary statistics. Table A3 (appendix) includes detailed summary statistics on within and between components specifically.

From model 1 in Table 1, it can be seen that the estimated mean trend of the square root dispensing rate at mean levels of population education is equal to −.053 (SD = .0927, p = .000). A one-percentage-point increase in cluster-mean education reduces the trend coefficient of the square root dispensing rate by −.0034 (p = .0051), *ceteris paribus*. There is thus a greater reduction in the dispensing rate in municipalities in which a larger proportion of the population have received tertiary education.

Figure 2 presents the predicted trajectories in the dispensing rates based on cluster-mean education levels. An important observation is that the trends are, on average, negative within the boundaries of the data. Even the municipalities with the lowest levels of population education (11%) show predicted reductions in dispensing rates. The predictions fan out from similar intercepts due to the small and insignificant 'main' effect of education (the effect when $T = 0$, p = .892) in the model. The Figure shows that the municipalities with low levels of population education have predicted reductions of approximately two prescriptions per 100 children, while municipalities with comparatively high levels of population education have predicted reductions approximately equal to ten prescriptions per 100 children over the period. In Figure 3, several municipalities can be seen to have a positive predicted trend after adjusting for the interaction with education. Most municipalities, however, show a predicted negative trend in the cross-level interaction model, and the size of the negative trend varies with population education in the municipality.

[FIGURES 2 AND 3 ABOUT HERE]

Table 1: Multilevel linear growth curve model. The model uses the square roots of the transformed dispensing rates as outcomes. This model is used for the prediction (Figures 2 and 3) and evaluation of statistical significance and rates of change. Complete information is missing only for two municipalities due to municipality mergers during the period.

Coefficient	$\sqrt{\text{Dispensed Rx per 100 children}}$
Level 1	
Trend	−0.053** (−0.066, −0.039)
Poverty	−0.098** (−0.125, −0.070)
Population (ln)	1.265 (−0.061, 2.592)
Level 2	
Education	−0.002 (−0.027, 0.023)
Population (ln)	0.408** (0.290, 0.525)
Poverty	−0.085** (−0.130, −0.041)
Travel	−0.0003* (−0.0004, −0.0003)
Trend × Education (L2)	−0.0034* (−0.006, −0.001)
Intercept	5.459** (5.340, 5.578)
Var. Comp.	
Std. Dev. μ_1	.0927
Std. Dev. μ_0	.8647
Misc.	
ρ Comp. Symm.	.000
Groups	426
Observations	4,503
Log Likelihood	−6,442.764
Akaike Inf. Crit.	12,913.53
Bayesian Inf. Crit.	13,003.3
Note:	*p<.01; **p<.001
	95% CI in parentheses

Table 2: Total dispensed DDD per 1,000 children by ATC J01 subgroups.

Year	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
2006	0.4	1009.1	19.9	77.9	526.2	7.6	1.0	17.4
2007	0.3	923.1	16.3	58.2	453.9	2.9	1.0	11.9
2008	0.2	1158.4	19.8	73.6	504.3	9.2	0.9	13.0
2009	0.2	1057.2	18.4	69.5	418.3	6.9	0.5	10.1
2010	0.2	1296.7	22.5	74.6	502.5	0.7	0.8	9.8
2011	0.1	1170.5	21.7	70.1	566.4	2.7	1.3	8.0
2012	0.4	1195.9	17.0	68.1	484.1	1.1	1.3	7.3
2013	0.4	1001.6	20.9	66.7	355.6	0.9	2.0	5.6
2014		1104.1	24.2	71.2	367.3	1.3	1.6	7.4
2015	0.1	965.6	21.8	67.1	299.9	0.9	1.3	8.7
2016	0.0	911.2	20.1	58.3	260.8	2.0	1.8	5.2

Table 3: Pooled statistics, including summary statistics for yearly observations for all municipalities, before centring. The variable Dispensed Rx/100 child *is the dependent variable used in the model. Travel time is presented in decimal minutes and is time-invariant due to only being observed once. An extended table of summary statistics, including both centred and non-centred values, is available in the appendix.*

Statistic	**N**	**Mean**	**St. Dev.**	**Min.**	**Max.**
Dispensed Rx/100 children	4,519	29.7	16.3	0.9	104.9
Education	4,515	21.2	5.9	9.1	51.9
Population	4,519	11,885	35,479	200	658,390
Poverty	4,518	10.0	2.4	3.7	21.8
Trend	4519	5.01	3.16	0	10
Travel time (sec.)	426	1,674	1,882	182	13,129

DISCUSSION

While there has been a national decrease in antibacterial dispensing rates in Norway,[31] the current study shows that trends vary between Norwegian municipalities for patients below 3 years of age, with municipalities in which more of the population has received tertiary education showing larger decreases in dispensing rates. Several efforts have been made to reduce antibacterial dispensing rates, notably by updating national guidelines for the use of antibacterials [32] and through intervention campaigns.[33] If one views high education levels as a form of socioeconomic advantage, the results suggest that municipalities with socioeconomically advantaged populations have been more successful in reducing dispensing rates.

Our findings support the existing literature on the relationship between relative socioeconomic deprivation and antibacterial dispensing rates. Low parental education has been linked to higher prescribing rates in paediatric patients,[2,5,13,34] and we would expect the same individual mechanisms to translate to aggregate statistics. If a lack of higher education in a community is considered a form of regional deprivation, then these results are consistent with other data on the association between area-level deprivation indexes (which include education in the index) and dispensing rates.[3,4,11]

We chose tertiary education as our education indicator because proper use of antibiotics is more common in people who have received higher education,[14-16] and our findings are consistent with these expectations. In addition, the Norwegian education system ensures all young people the legal right to education up to and including the upper secondary level, but no such right exists for higher education. Thus, continued education past secondary level is an active choice in which we would expect local population diversity, in contrast to structured schooling.

Health literacy is also associated with higher education,[17,18] but education is an inaccurate proxy for individual health literacy.[35] However, the overuse of antibacterials and policies implemented to reduce consumption are not only an issue of individual health, but also of public health. Successful enactment of public health policies directed at reducing antibacterial dispensing rates may rely in part on the ability of individuals and groups to obtain, process, understand, evaluate and act upon information needed to make decisions that benefit the individual and the community[36], allowing collectivist and long-term values to outweigh individualist short-term decision-making. It is possible that education enables an understanding of the individual and family as being embedded in society, such that individual decisions on antibacterial treatment are more likely to be made within the framework of a greater public health concern.

The Norwegian health care system provides universal health care access, and health inequalities in care utilisation have diminished over time.[37] Needs-adjusted socioeconomic differentiation in health care usage has empirically been observed mostly in the use of private medical specialists and hospital outpatient care.[38] However, these observations do not necessarily include all differentiation in health care usage in Norway, such as potential geographic variations, and importantly, these studies do not include parental health care–seeking. If parental health care–seeking translates to paediatric health care–seeking, health

care usage may, hypothetically, not be socially determined in volume, but rather in kind. People from advantaged socioeconomic backgrounds may interact and use health care inputs more efficiently, thus achieving the same amount of health investment with less health care services. They may also consider the potential consequences of antibacterial use more frequently, driving the dispensing rate downward.[5]

Importantly, children are themselves not actors in this framework. Decisions on treatment are made by physicians and parents, which suggests that the health care provided to children is dependent on parental socioeconomic status and how they seek health care for their children, as well as the physician's prescribing habits and responses to different individuals and social groups. Several studies have identified an association between the high use of antibacterials in young children and an increased risk of chronic disease development later in life,[31,39-43] so optimising prescribing practices would seem important for reducing health inequalities in future generations.

Area-level strategies, as opposed to national-level strategies, for antimicrobial stewardship have been suggested in other countries;[10] given the local and regional variations in dispensing rates and reduction trends in Norway, we agree with previous authors[19] that effective antimicrobial stewardship requires that the issue be addressed from a multilevel systems perspective and that social, structural and cultural determinants also be considered when implementing policy at the local administrative level. The overall responsibility for health policies in Norway lies with the National Ministry of Health, and stewardship of antimicrobial resistance in Norway relies on existing administrative structures of disease prevention and control, with sectoral operative responsibility and weak coordination mechanisms.[44] National political strategies do target primary health care services at the municipal level, but the need for and potential drivers of antibacterial treatment may vary between municipalities. We expect the efficacy of national policies for reducing antibacterial dispensing rates to partially depend on the local population's socioeconomic composition.

Strengths, limitations and methodological considerations

Unlike several authors who have applied indexed deprivation measures containing a variety of deprivation indicators, we focused on education specifically because it is a common component of deprivation indexes, which present a trade-off between interpretation and capturing a holistic concept of deprivation. It is thus unclear which features of such deprivation indexes drive empirical variations in dispensing rates, and translating theoretical mechanisms from the individual level to aggregate statistics then becomes even more challenging due to the number of dimensions in such indexes. The effects of income and occupation deprivation have been studied separately,[4] but no such analysis has been performed using an education indicator. Education is a key socioeconomic characteristic for health determinants, and by investigating education specifically, our results are more readily interpreted and more clearly relatable to the specific mechanisms discussed in the literature.

A strength of this study is the completeness of the dispensing rate metric. The NorPD contains all prescriptions dispensed in the period under examination, excluding usage in hospitals. We argue that this has two advantages. Firstly, we expect education to matter more in the context of primary health care, because parents are active participants in health care decision-

making, and secondly, the primary health care service is administered at the municipal level in Norway. Observed trends are therefore likely to be a result of local community needs and behaviours and local decision-making processes.

A limitation of this study is the lack of information on the geographical burden of disease, although regional differences in dispensing rates are unlikely to be explained by differences in the severity and density of infections and more likely to be related to differences in medical practices.[9] A Welsh study similarly found no support for regional differences in prescriptions being explainable by chronic conditions in the adult population.[3] Indeed, if the entire variance could be explained by the burden of infections, the implication would be that infections requiring antibacterial treatment are geographically unequally distributed, even between paediatric patients.

Another limitation is the limited inferences that can be made regarding individual outcomes based on aggregate statistics. Further research is necessary to conclude an association between parental education, individual interactions with health care services and paediatric antibacterial dispensing rates in Norway.

CONCLUSION

Our analysis shows that the ability to reduce dispensing rates over time at the municipality level is associated with mean population levels of higher education. Local needs and potential root causes of health outcomes should be considered in antimicrobial stewardship to optimise prescription patterns, and attention should be paid to social demographics, like education, that may affect health behaviour, preferences and usage, which may help to further reduce dispensing rates in accordance with political goals.

CONTRIBUTORSHIP STATEMENT

SS conceptualised, designed and drafted the manuscript; prepared data; and performed the statistical analysis. KS contributed data. LS provided ethics approval and data from the prescription registry. SS, KS, AEE, and LS critically revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

There are no funding grants to declare.

DATA SHARING STATEMENT

Data on antibacterial dispensing can be obtained by application to a third party (The Norwegian Prescription Registry) and are not publicly available. Travel time data are available from the corresponding author upon request. Data collected from Statistics Norway are licensed under the Creative Commons Attribution 4.0 International (*https://www.ssb.no/en/diverse/lisens*) which permits others to share, copy, redistribute, and adapt the material for any purpose and are available from the corresponding author upon request.

ETHICS STATEMENT

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (ref. 2018/1021) in compliance with the Norwegian Health Research Act, §10. Data were anonymised before the authors accessed them for the purposes of this study.

REFERENCES

1 Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014;**14**:742–50.

2 Thrane N, Olesen C, Schønheyder HC, et al. Socioeconomic factors and prescription of antibiotics in 0-to 2-year-old Danish children. *J Antimicrob Chemother* 2003;**51**:683–9.

3 Adekanmbi V, Jones H, Farewell D, et al. Antibiotic use and deprivation: an analysis of Welsh primary care antibiotic prescribing data by socioeconomic status. *J Antimicrob Chemother* 2020;**75**:2363–71.

4 Koller D, Hoffmann F, Maier W, et al. Variation in antibiotic prescriptions: is area deprivation an explanation? Analysis of 1.2 million children in Germany. *Infection* 2013;**41**:121–7.

5 Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: evidence from Switzerland. *Health Policy* 2006;**78**:77–92.

6 Haugen P, Simonsen GS, Primicerio R, et al. Antibiotics to outpatients in Norway. Assessing effect of latitude and municipality population size using quantile regression in a cross-sectional study. *Pharm Stat* 2018;**17**:4–11.

7 Sakshaug S, Strøm H, Berg C, et al. Legemiddelforbruket i Norge 2013–2017. Legemiddelstatistikk 2018: 1 [Drug consumption in Norway 2013–2017. Drug statistics 2018: 1]. Oslo: Norwegian Institute of Public Health 2018.

8 Blix HS, Engeland A, Litleskare I, et al. Age-and gender-specific antibacterial prescribing in Norway. *J Antimicrob Chemother* 2007;**59**:971–6.

9 Stordal K, Marild K, Blix HS. Bruk av antibiotika hos barn i perioden 2005–16. *Tidsskriftet Den Norske Legeforening* 2017;**137**:1414–20.

10 Mölter A, Belmonte M, Palin V, et al. Antibiotic prescribing patterns in general medical practices in England: does area matter? *Health Place* 2018;**53**:10–6.

11 Thomson K, Berry R, Robinson T, et al. An examination of trends in antibiotic prescribing in primary care and the association with area-level deprivation in England. *BMC Public Health* 2020;**20**:1–9.

12 Hobbs MR, Grant CC, Ritchie SR, et al. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5 years. *J Antimicrob Chemother* 2017;**72**:1832–40.

13 Pichichero ME. Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 1999;**104**:1384–8.

14 Waaseth M, Adan A, Røen IL, et al. Knowledge of antibiotics and antibiotic resistance among Norwegian pharmacy customers–a cross-sectional study. *BMC Public Health* 2019;**19**:1–2.

15 Agarwal S, Yewale VN, Dharmapalan D. Antibiotics use and misuse in children: A knowledge, attitude and practice survey of parents in India. *J Clin Diagn Res* 2015;**9**:SC21.

16 Yu M, Zhao G, Lundborg CS, et al. Knowledge, attitudes, and practices of parents in rural china on the use of antibiotics in children: a cross-sectional study. *BMC Infect Dis* 2014;**14**:1–8.

17 Dunn-Navarra A-M, Stockwell MS, Meyer D, et al. Parental health literacy, knowledge and beliefs regarding upper respiratory infections (URI) in an urban Latino immigrant population. *J Urban Health* 2012;**89**:848–60.

18 Sørensen K, Pelikan JM, Röthlin F, et al. Health literacy in Europe: Comparative results of the European health literacy survey (HLS-EU). *Eur J Public Health* 2015;**25**:1053–8.

19 Blaser MJ, Melby MK, Lock M, et al. Accounting for variation in and overuse of antibiotics among humans. *BioEssays* 2021;43:e2000163.

20 Furu, K. Establishment of the nationwide Norwegian prescription database (NorPD)–new opportunities for research in pharmacoepidemiology in Norway. *Nor Epidemiol* 2008;18:129–36.

21 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2019 [Date accessed: April 2022]. https://www.whocc.no/atc_ddd_index

22 Statistics Norway. Educational attainment of the population, Source table 09429: Educational attainment, by municipality and sex (M), 1970–2020 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/09429/

23 Statistics Norway. Income and wealth statistics for households, Source table: 06947: Persons in private households with annual after-tax income per consumption unit, below different distances to the median income. EU-scale and OECD-scale (M) (UD) 2005–2020 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/06947

24 Statistics Norway. Population count, Source table 07459: Population, by sex and one-year age groups (M) 1986–2022 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/07459

25 Svendsen K, Kongsgard H, Haugen P, et al. Travel time to pharmacy influence the use of antibiotics in Norway. *Pharmacoepidemiol Drug Saf* 2016;25(Suppl 3):641.

26 Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using Stata*. College Station, TX: Stata Press 2008.

27 Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis methods*. Thousand Oaks, CA: Sage 2002.

28 Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: A new look at an old issue. *Psychol Methods* 2007;**12**:121–38.

29 Biesanz JC, Deeb-Sossa N, Papadakis AA, et al. The role of coding time in estimating and interpreting growth curve models. *Psychol Methods* 2004;**9**:30–52.

30 Curran PJ, Obeidat K, Losardo D. Twelve frequently asked questions about growth curve modeling. *J Cogn Dev* 2010;**11**:121–36.

31 Beckstrøm S, Småbrekke L. Antibacterial use by birth year and birth season in children 0-2 years in Norway. *Nor Epidemiol* 2021;**29**:35–43.

32 Eliassen KE, Fetveit A, Hjortdahl P, et al. New guidelines for antibiotic use in primary health care. *Tidsskriftet den Norske Legeforening: tidsskrift for praktisk medicin, ny raekke* 2008;**128**:2330–4.

33 Ministry of Health. Handlingsplan mot antibiotikaresistens i helsetjenesten. 2016.

34 Mangrio E, Wremp A, Moghaddassi M, et al. Antibiotic use among 8-month-old children in Malmö, Sweden – in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatr* 2009;**9**:31.

35 Berkman ND, Davis TC, McCormack L. Health literacy: What is it? *J Health Commun* 2010;**15**:9–19.

36 Freedman DA, Bess KD, Tucker HA, et al. Public health literacy defined. *Am J Prev Med* 2009;**36**:446–51.

37 Vikum E, Bjørngaard JH, Westin S, et al. Socio-economic inequalities in Norwegian health care utilization over 3 decades: the HUNT study. *Eur J Public Health* 2013;**23**:1003–10.

38 Vikum E, Krokstad S, Westin S. Socioeconomic inequalities in health care utilisation in Norway: the population-based HUNT3 survey. *Int J Equity Health* 2012;**11**:1–9.

39 Korpela K, Vos WM de. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. *Microb Cell* 2016;**3**:296.

40 Mårild K, Ye W, Lebwohl B, et al. Antibiotic exposure and the development of coeliac disease: A nationwide case–control study. *BMC Gastroenterol* 2013;**13**:1–9.

41 Risnes KR, Belanger K, Murk W, et al. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;**173**:310–8.

42 Sander SD, Andersen A-MN, Murray JA, et al. Association between antibiotics in the first year of life and celiac disease. *Gastroenterology* 2019;**156**:2217–29.

43 Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science* 2016;352:544–5.

44 Time MS, Veggeland F. Adapting to a global health challenge: managing antimicrobial resistance in the Nordics. *Politics Gov* 2020;**8**:384–95.

FIGURE CAPTIONS

Figure 1: *Box-and-whisker plot of dispensing rates by year. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this Figure is the notable variation between municipalities within a specific year. The intraclass correlation coefficient of the null model indicates that 62.8% of the total variance is between municipalities.*

Figure 2: *Predicted cross-level interaction effect between trends and education. The Y-axis displays the dispensing rate on the original scale. The middle line represents the average cluster level of education, while the outer lines are predicted trends for ±2 standard deviations from the mean education levels. Predictions fan out from similar intercepts due to the insignificant main effect of education (effect when T = 0).*

Figure 3: *Predicted slopes by population education. The points are the predicted square roots of the dispensing rate trends for each municipality. All 426 estimated trends are presented and plotted against education on the X-axis. The Figure shows that the leaders in dispensing rate reductions also tend to have higher proportions of people with tertiary education and, conversely, that low performers tend to have lower levels of tertiary education. Please note the Y-axis scaling when interpreting the figures.*

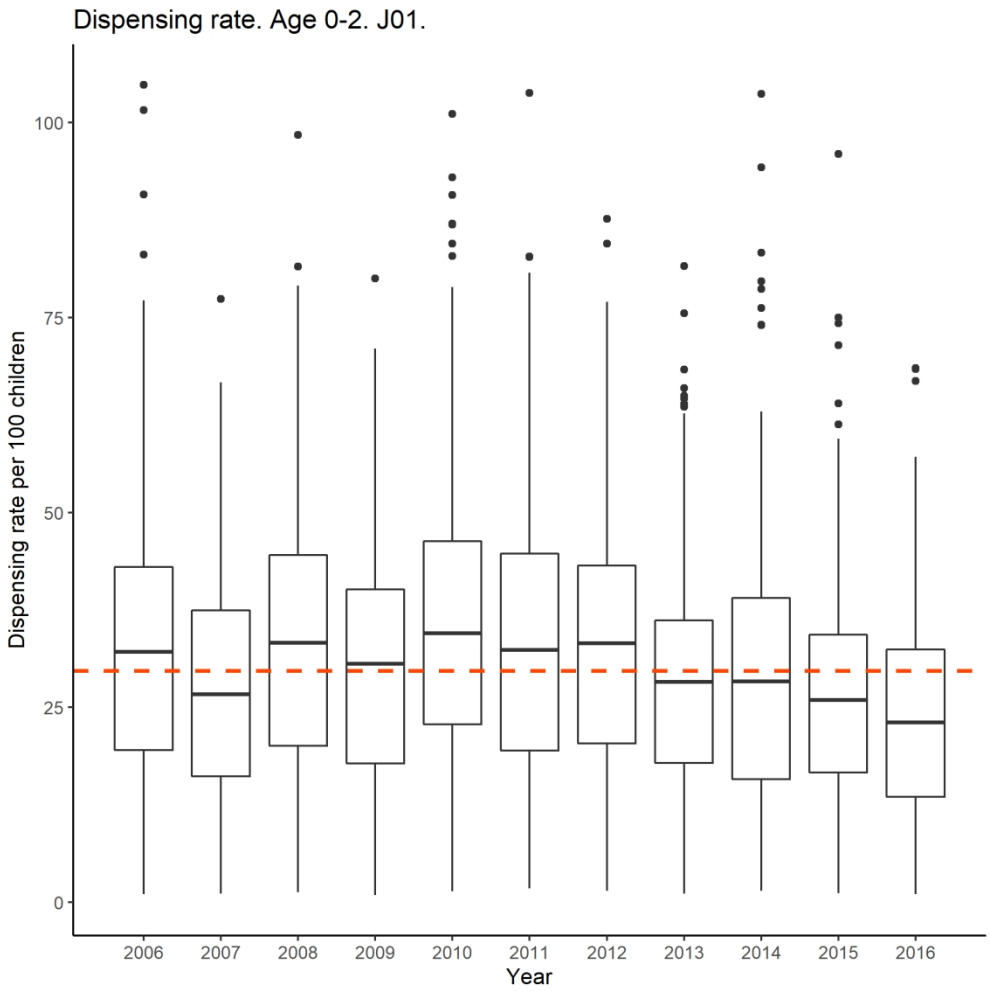


Figure 1: Box-and-whisker plot of dispensing rates by year. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this Figure is the notable variation between municipalities within a specific year. The intraclass correlation coefficient of the null model indicates that 62.8% of the total variance is between municipalities.

452x451mm (118 x 118 DPI)

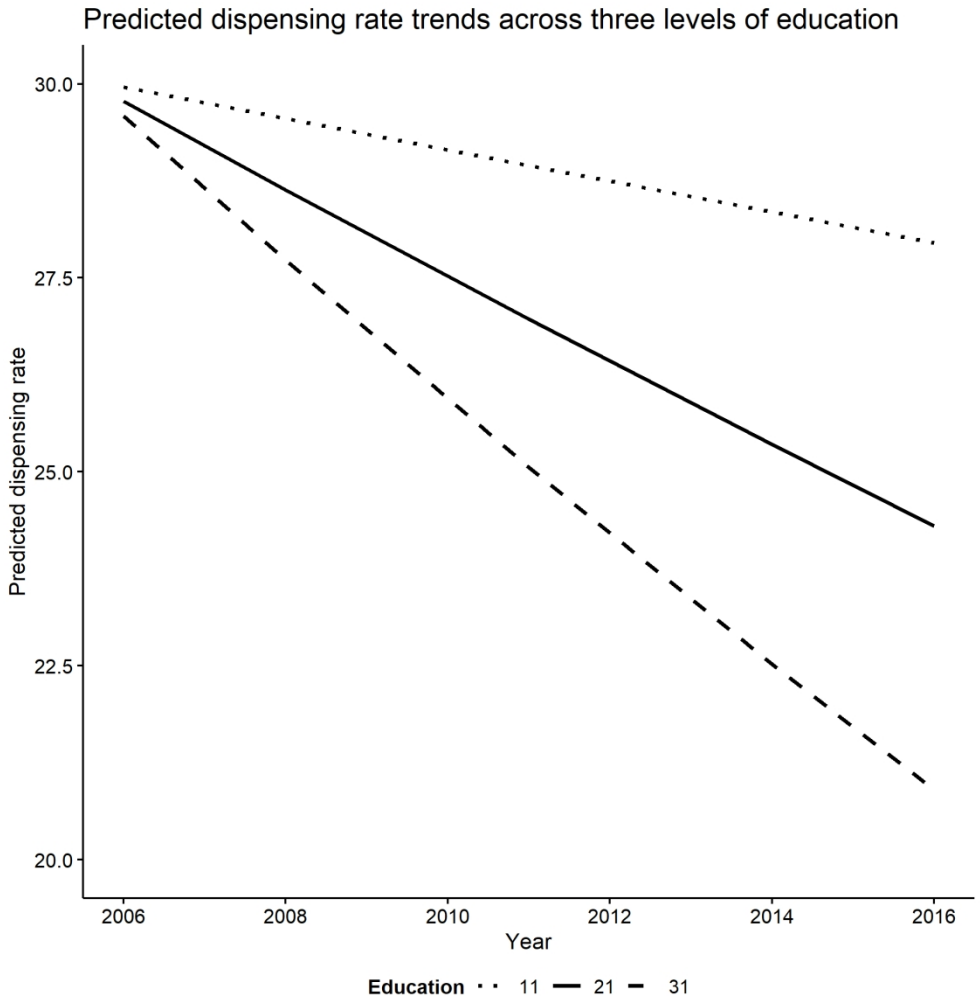


Figure 2: Predicted cross-level interaction effect between trends and education. The Y-axis displays the dispensing rate on the original scale. The middle line represents the average cluster level of education, while the outer lines are predicted trends for ±2 standard deviations from the mean education levels. Predictions fan out from similar intercepts due to the insignificant main effect of education (effect when T = 0).

452x452mm (118 x 118 DPI)

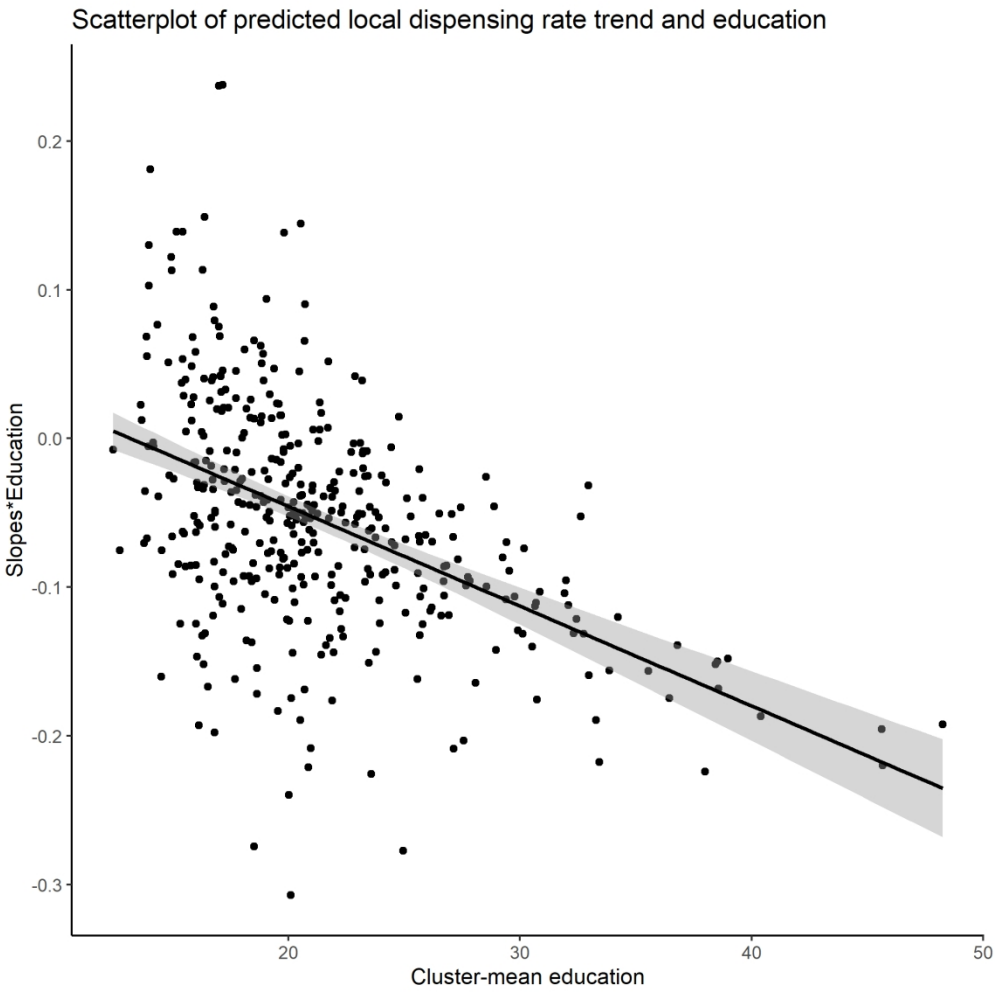


Figure 3: Predicted slopes by population education. The points are the predicted square roots of the dispensing rate trends for each municipality. All 426 estimated trends are presented and plotted against education on the X-axis. The Figure shows that the leaders in dispensing rate reductions also tend to have higher proportions of people with tertiary education and, conversely, that low performers tend to have lower levels of tertiary education. Please note the Y-axis scaling when interpreting the figures.

452x451mm (118 x 118 DPI)

APPENDIX

Model description

The two-level linear growth curve model with a cross-level interaction effect with cluster-mean education is represented by the following equation:

$$\begin{aligned} L1: \sqrt{Y_{tj}} &= \beta_{0j} + \beta_{1j}T_{tj} + \beta_2 EDU_{tj}^{CWC} + \beta_3 lnPOP_{tj}^{CWC} + \beta_4 POV_{tj}^{CWC} + \epsilon_{tj} \\ L2: \beta_{0j} &= \gamma_{00} + \gamma_{01}EDU_j^{CM} + \gamma_{02}lnPOP_j^{CM} + \gamma_{03}POV_j^{CM} + \gamma_{04}TR_j + \mu_{0j} \\ \beta_{1j} &= \gamma_{10} + \gamma_{11}EDU_j^{CM} + \mu_{1j} \end{aligned}$$

Error terms are all assumed normally distributed:

$$\begin{aligned} \epsilon_{tj} &\sim \mathrm{N}(0, \sigma_\epsilon^2) \\ \mu_{0j} &\sim \mathrm{N}(0, \sigma_{\mu_0}^2) \\ \mu_{1j} &\sim \mathrm{N}(0, \sigma_{\mu_1}^2) \end{aligned}$$

Consulting the $L1$ part of the equation: β_{0j} are random intercepts, $\gamma_k X_{tj}^{CWC}$ are the fixed time-variant coefficients where variables are centered-within-cluster, $\beta_{1j}T_{tj}$ is a time-variant trend variable where the first year is set to 0, and ϵ_{tj} is the level-1 error term. In the $L2$ part of the equation, γ_{00} is the mean municipal level intercept, $\gamma_{0k}X_j^{CM}$ are coefficients for level 1 covariate cluster-means (CM), $\gamma_{04}TR_j$ is a coefficient for median travel time to nearest pharmacy, while μ_{0j} is the intercept variance component. The linear trend variable is modeled as a random effect with μ_{1j} variance component $\gamma_{11}EDU_j^{CM}$. $\beta_2 EDU_{tj}^{CWC}$ is a cross-level interaction between the cluster-mean education level across the time-period and the random linear trend. The term $\beta_2 EDU_{tj}^{CWC}$ was removed in the final model to address the issue of simultaneous growth.

Table A1: Model 1 includes the time-variant education predictor, model 2 is the same as the in-text model. This table aims to show the consequences of simultaneous growth on the estimated trend coefficient and confidence intervals.

	$\sqrt{Dispensed\ prescriptions\ per\ 100\ children}$	
	~~(1)~~Model 1	~~(2)~~Model 2
Level 1		
Trend	−0.015 (−0.050, 0.019)	−0.053*** (−0.066, −0.039)
Poverty	−0.098*** (−0.125, −0.071)	−0.098*** (−0.125, −0.070)
Population (ln)	1.562* (0.210, 2.914)	1.265 (−0.061, 2.592)
Education	−0.069* (−0.127, −0.010)	
Level 2		
Education	-0.004 (−0.029, 0.021)	−0.002 (−0.027, 0.023)
Population (ln)	0.409*** (0.292, 0.527)	0.408*** (0.290, 0.525)
Poverty	−0.085*** (−0.130, −0.040)	−0.085*** (−0.130, −0.041)
Travel	−0.0003*** (−0.0004, −0.0003)	−0.0003** (−0.0004, −0.0003)
Trend×Education (L2)	−0.003** (−0.005, −0.0005)	−0.0034** (−0.006, −0.001)
Intercept	5.271*** (28.883, 33.101)	5.459*** (5.340, 5.578)
Var. Comp.		
Std. Dev. μ_1	.0929	.0927
Std. Dev. μ_0	1.0912	.8647
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,499	4,503
Log Likelihood	−6,431.018	−6,442.764
Akaike Inf. Crit.	12,892.04	12,913.53
Bayesian Inf. Crit.	12,988.21	13,003.3
Note:	*p<0.05; **p<0.01; ***p<0.001	
	95% CI in parentheses.	

Simultaneous growth and MLM interpretation under centering scheme

Model 1 includes all level 1 covariates. Model 2 excludes the group-mean centered education (L1) covariate due to simultaneous growth issues resulting in collinearity between L1 education and trend.

This contrast table shows the effect of simultaneous growth on estimated parameters. The only difference between the models is the removal of the L1 group-mean centered education indicator. Confidence intervals are shown in parentheses.

Group-mean centering level 1 covariates leads to orthogonal relationships between levels; the correlations between level 1 and level 2 covariates are equal to 0. In a model without the uncentered trend variable, excluding level 1 coefficients would not affect level 2 estimates under group-mean centering. In fact, the estimates would be the same regardless of whether level 1 covariates were even in the model [30]. However, since the trend variable is *not* centered, some correlation will exist between levels through correlation with the trend variable, explaining the minor changes in level 2 coefficients. These changes are unsubstantial and only result in minor changes in L2 estimates.

Simultaneous growth leads to a very simple issue of near perfect collinearity between L1 education and the trend variable. This is the reason for the dramatic change in the trend coefficient size and confidence interval. Simply put, the trend effect in model 1 is biased due to collinearity with the L1 education covariate. While there are ways to deal with this problem through *multivariate* growth curve modeling [32], we are primarily interested in the cross-level interaction effect between education traits and the random trend. As such, we prefer the more parsimonious modeling option removing the cluster-mean centered education variable from the level 1 part of the equation.

Interpreting coefficients under centering scheme

Centering and cross-level interactions changes the interpretation of certain coefficients. We base the interpretation on model 2 and focus on three main coefficient interpretations a) the main trend effect and its variance, b) the main trait education effect and c) the cross level interaction term.

Due to grand-mean centering L2 covariates and the inclusion of an interaction term, the main trend effect ($-.015$) is interpreted as the expected square root dispense rate trend for municipalities with a mean level of trait education (21.15%), *ceteris paribus*. This is a random coefficient, and its random parameter μ_1 suggests that the standard deviation from the fixed term is equal to $.919$. The main education effect ($-.002$) is the expected effect of education at $T = 0$ (2006, trend is not centered). This is clearly shown by the very similar intercepts in figure 2 and 3. Lastly, the interaction term (-0034.) is the expected decrease in trend for every pp increase in education traits. This model is the basis for figures 2 and 3.

For other L1 coefficients (sans the trend coefficient), a one-unit increase entails a one unit change from a covariates given group mean. The coefficient is thus the average effect of a one unit increase from a given group mean, *ceteris paribus*.

Centering and growth

Notably, we choose not to center the level 1 trend variable for two reasons; firstly, the panels are only slightly imbalanced. Centering the trend variable on the group means practically results in a grand mean centered trend variable (correlation with uncentered trend indicator: $r = .97$), with

no real consequences to the coefficient estimates. The only consequence is on the intercepts and the intercept variance due to the zero point being established in 2011 for all but a few groups. Secondly, the model is a linear random growth curve model. Centering the trend covariate is more of an issue in situations where a polynomial growth curve might be fitted.

Intercept and slope correlation

Intercepts and slopes are negatively correlated at $r = -.597$. This is a natural consequence of bounded data; dispensing rate cannot be less than 0. Municipalities with low starting dispensing rates will naturally not be able to reduce dispensing rates as much as those with higher starting dispensing rates. This is of no particular concern for estimating the interaction term; indeed, the non-significant main education coefficient implies that the intercept variance is not explained by mean population education levels. This is also clear when investigating figure 2 in the main text.

SUPPLEMENTARY FIGURES AND TABLES

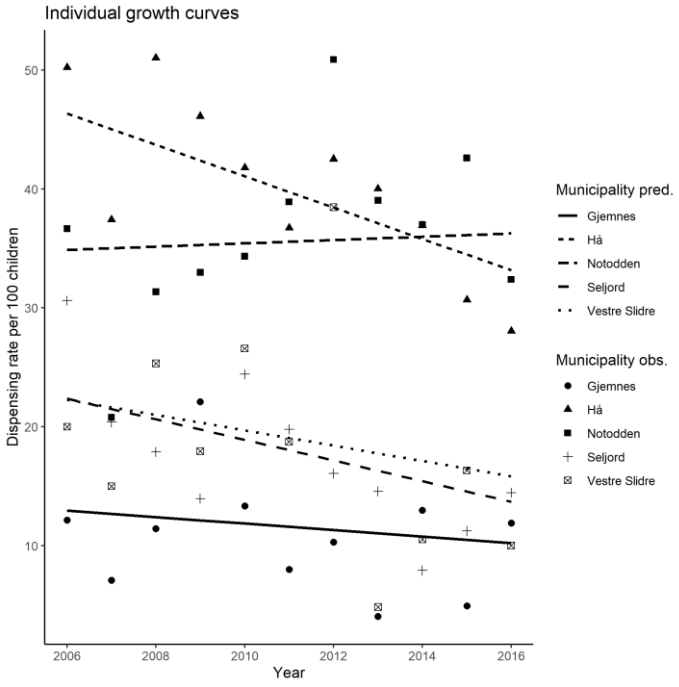


Figure A1: *Linear growth curve predictions and observations from a simple random trend null-model for five random municipalities. Municipalities were randomly sampled from a strata of slope quantiles to ensure that slope variance was represented in the figure. Note that the Y-axis is scaled by min-max observations in the subsample, not the entire distribution.*

Table with exact p-values for all parameters

Table A2: Multilevel growth curve models. Both models include all covariates. Model 1 uses the square-root transformed dispense rates as outcomes. This model is used for prediction (figures 2 and 3) and evaluation of statistical significance. Model 2 uses the dispense rate as the outcome.

	$\sqrt{\text{Dispensed Rx per 100 children}}$	Dispensed Rx per 100 children
	(1)	(2)
Level 1		
Trend	-0.053^{***} (.0000)	-0.608^{***} (.0000)
Poverty	-0.098^{***} (.0000)	-1.061^{***} (.0000)
Population (ln)	1.265 (.0617)	13.980^{*} (.0457)
Level 2		
Education	−0.002 (.8922)	0.026 (.8479)
Population (ln)	0.408^{***} (.0000)	3.983^{***} (.0000)
Poverty	-0.085^{***} (.0002)	-0.845^{***} (.0004)
Travel	-0.0003^{**} (.0000)	-0.003^{***} (.0000)
Trend×Education (L2)	-0.003^{**} (.0051)	-0.041^{***} (.0010)
Intercept	5.459^{***} (.0000)	32.689^{***} (.0000)
Var. Comp.		
Std. Dev. μ_1	.0927	.918
Std. Dev. μ_0	.8647	11.54
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,503	4,503
Log Likelihood	−6,442.764	−17,097.230
Akaike Inf. Crit.	12,913.53	34,222.460
Bayesian Inf. Crit.	13,003.3	34,312.240
Note:	*p<0.05; **p<0.01; ***p<0.001	
	p-values in parentheses.	

Dependent variable distribution before and after square root transformation

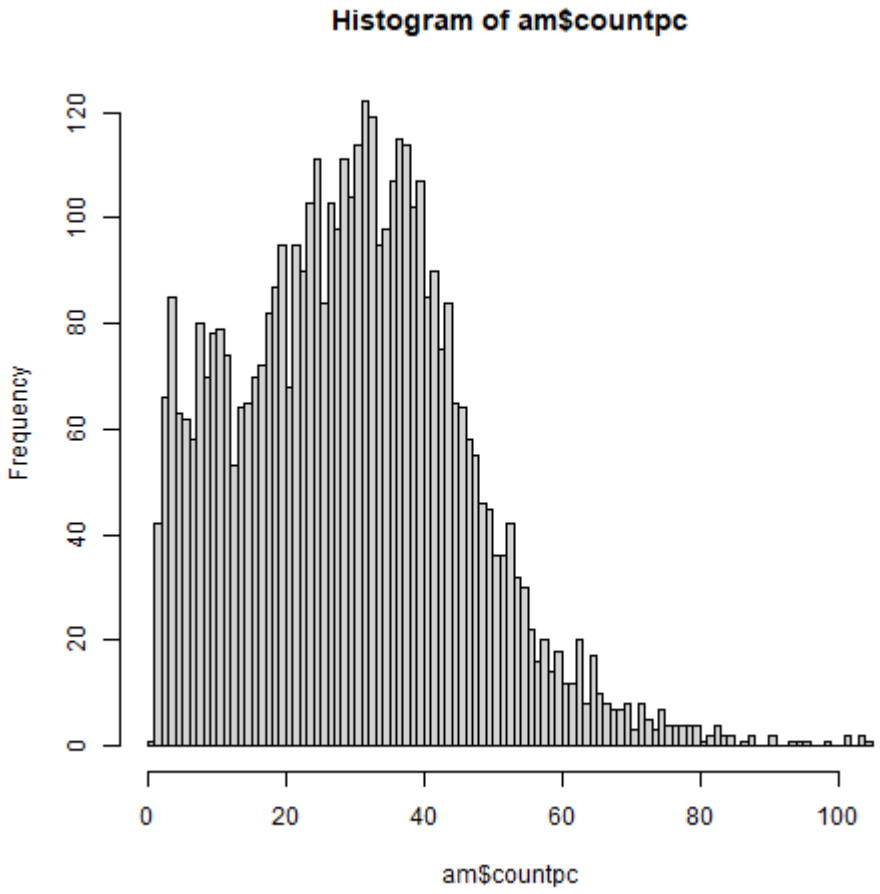


Figure A2: Dispense rate distribution before square root transformation. The distribution is closer to a Poisson distribution, due to the natural bounds of the data.

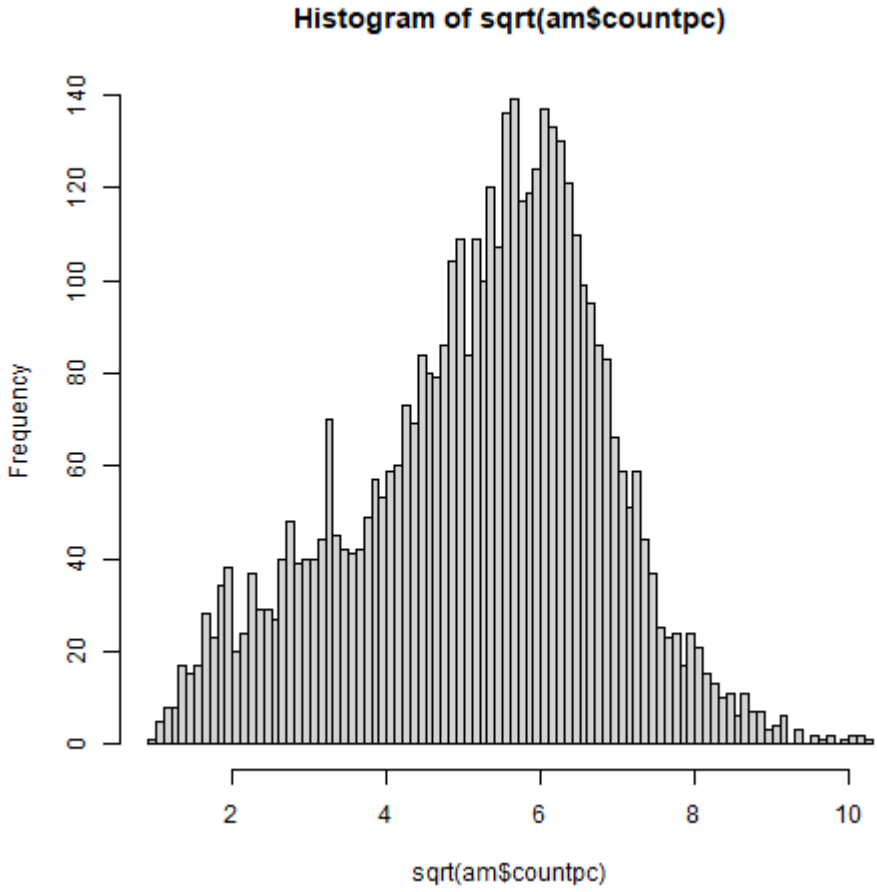


Figure A3: Dispense rate after square root transformation. Where the log-transformation (not shown) aggressively overcorrects the issue, leading to a worse fit than the untransformed version of the model, the square root transformation only moderately corrects the distribution, making residuals more well-behaved than the untransformed model. We emphasize that we performed this transformation to solve a statistical issue particularly present when investigating the residuals vs. the fitted values, and as such were guided by the data rather than theory. However, as the prediction plots, significance tests, and coefficients show, these modeling changes do not affect results in a significant way.

Residual plots main model

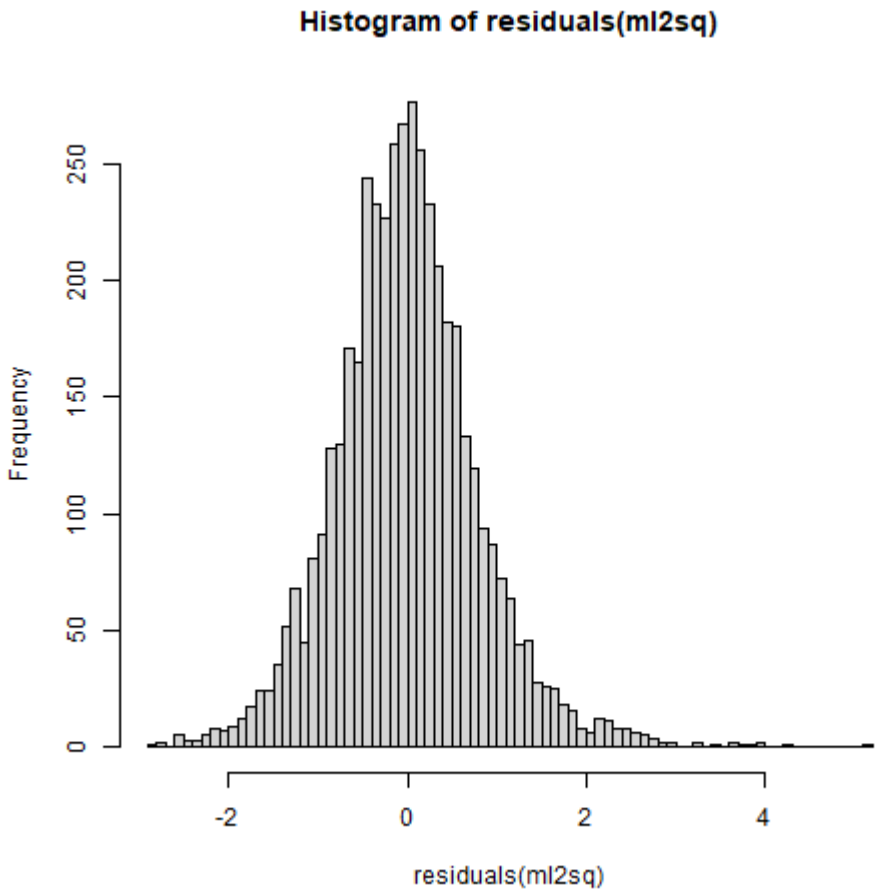


Figure A4: Level 1 Residual distribution after square root transformation of the dependent variable. While a marginally longer tail on positive residuals, we find no particular issues with this distribution.

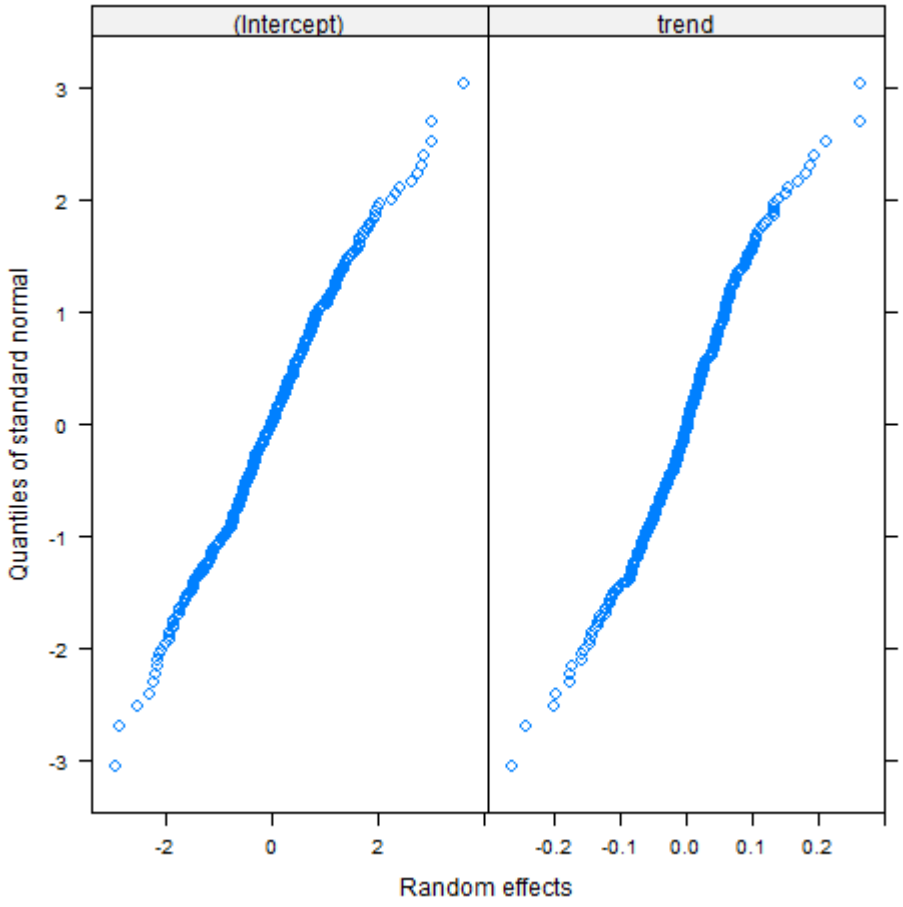


Figure A5: QQ-plot of the random terms in the model. We find that these are approximately normally distributed.

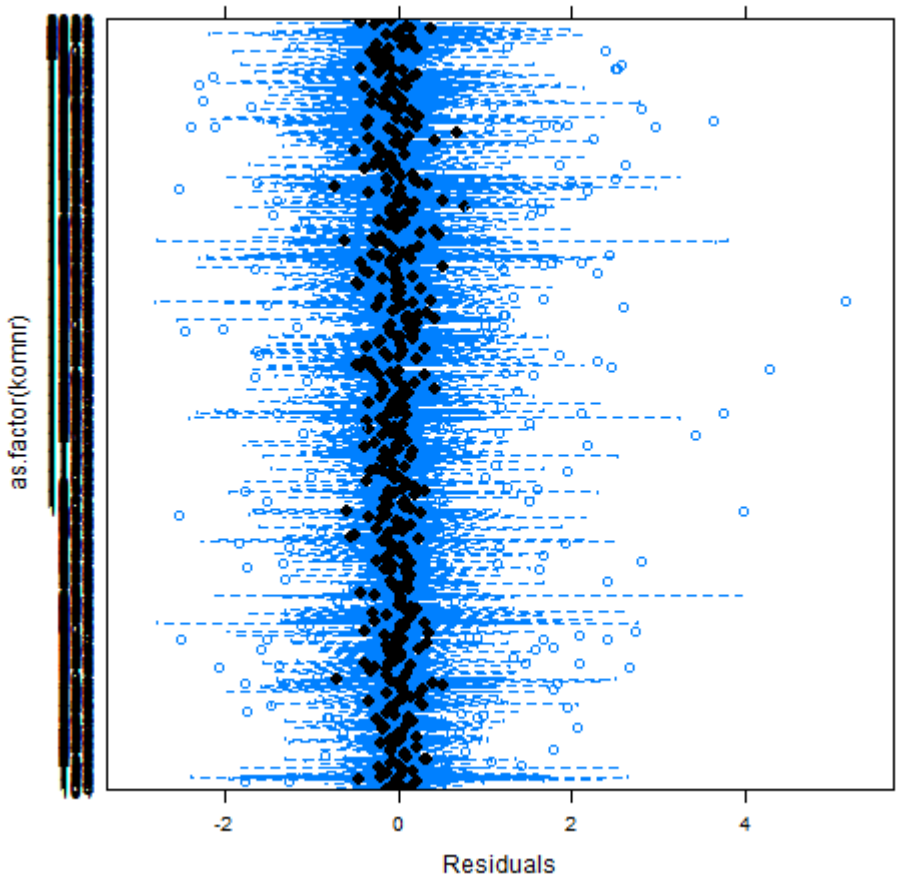


Figure A6: Level-1 residuals by municipality. Residuals seem overall to be centered at 0 with random deviation from this mean. Some differences in variance between municipalities is expected, as the number of repeat observations is relatively small (11).

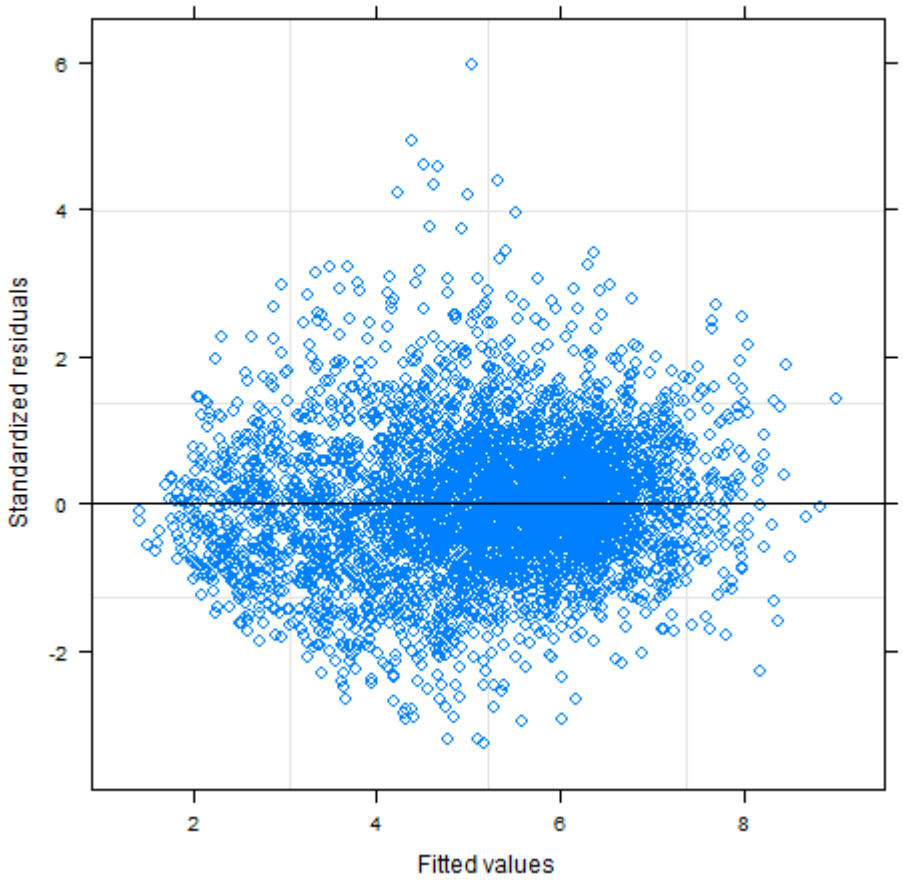


Figure A7: Standardized residuals vs. fitted values plot. We saw some problems with heteroskedasticity in the unadjusted model. While logarithmic transformation aggressively overcorrected the issue, the square root transformation adjusts for the moderate skewness and provides confidence to estimated standard errors.

Full version of summary statistics table

Statistics	N	Mean	St. Dev.	Min	Max
Pooled					
Dispensed Rx/100 chld.	4,519	29.7	16.3	0.9	104.9
Education	4,515	21.2	5.9	9.1	51.9
Population	4,519	11,885	35,479	200	658,390
Poverty	4,518	10.0	2.4	3.7	21.8
Within					
Dispensed Rx/100 child	4,519	0.00	9.58	−40.38	74.42
Education	4,515	0.00	1.87	−5.25	5.97
Population	4,519	0.00	2,180	−60,394	59,5842
Poverty	4,518	0.00	1.07	−3.46	5.76
Between					
Dispensed Rx/100 chld.	428	29.0	13.5	2.8	70.3
Education	428	21.0	5.6	11.2	48.2
Population	428	11,505	34,795	212	598,805
Poverty	428	10.0	2.2	5.1	18.6
Travel (sec.)	426	1,674	1,882	182.0	13,129

Table A3: Summary statistics grouped by levels. Pooled statistics include summary statistics for yearly observations for all municipalities before centering. The dependent variable. The within section shows descriptive statistics for all cluster-mean centered covariates, that is the level 1 parameters in the model. Note the mean 0 ensuring no correlation between level 1 and level 2 covariates. The between section represents the level 2 variables used in the model. These are 428 cluster-means for all covariates excluding travel times, due to municipality mergers before data collection.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1,3
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3-4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	3-4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	5/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3-4
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7/A
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of area-level education with the regional growth trajectories of rates of antibacterial dispensing to patients under 3 years in Norway: a longitudinal retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058491.R2
Article Type:	Original research
Date Submitted by the Author:	21-Jul-2022
Complete List of Authors:	Svalestuen, Sigbjørn; UiT The Arctic University of Norway, Department of social science Svendsen, Kristian; UiT The Arctic University of Norway, Department of pharmacy Eggen, Anne; UiT The Arctic University of Norway, Department of Community Medicine Småbrekke, Lars; UiT The Arctic University of Norway, Department of pharmacy
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Public health, Paediatrics, Pharmacology and therapeutics, Sociology
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Community child health < PAEDIATRICS, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Association of area-level education with the regional growth trajectories of rates of antibacterial dispensing to patients under 3 years in Norway: a longitudinal retrospective study

Sigbjørn Svalestuen[1], Kristian Svendsen[2], Anne Elise Eggen[3], Lars Småbrekke[2]

Keywords: *Drug prescriptions, Education, Geography, Health inequalities, Health policy*

Word count: 3019 *(excluding title page, abstract, captions, references and statements)*

[1] **Corresponding author**

Dep./Inst.: Department of Social Science/UiT The Arctic University of Norway

E-mail: *sigbjorn.svalestuen@uit.no*

Phone: *+47 776 44 321*

Address: UiT The Arctic University of Norway
PO Box 6050 Langnes
N-9037 Tromsø
Norway

Fax: *NA*

[2] **Dep./Inst.:** Department of Pharmacy/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

[3] **Dep./Inst.:** Department of Community Medicine/UiT The Arctic University of Norway

City/Country: Tromsø/Norway

ABSTRACT

Objective To examine the association between area-level education and the local growth trajectories in antibacterial dispensing rates in Norwegian municipalities among children under 3 years old.

Design Retrospective, longitudinal study using individual primary care prescription data from the Norwegian Prescription Database for the period 2006–2016. Data were collected on the date of dispensing, the type and amount of antibiotic, the patient's age, sex and municipality of residence and linked to municipality-level statistics on education available from Statistics Norway. We used multilevel growth curve modelling, with a linear trend variable modelled as a random effect and a cross-level interaction between linear trends and the proportion of the population in the municipality having received a university or college education.

Setting The local government level in Norway. The sample includes all municipalities over the study period.

Outcome measure Number of dispensed antibacterial prescriptions per 100 children in individual primary care by municipality and year.

Results We identified a significant negative linear trend in the square root of the dispensing rate for children under 3 years old during the period. This trend varied between municipalities. A negative cross-level interaction term between population education levels and random trends showed that municipalities with an average level of population education saw a reduction in their square root dispensing rates of −.053 (95% CI = −.066, −.039) prescriptions per 100 children. Each additional percentage point in population education contributed a further −.0034 (95%CI = −0.006, −0.001) reduction to the square root dispensing rate.

Conclusions Municipalities in which a larger proportion of the local population have high educational achievements have been more successful in reducing antibacterial dispensing rates in children under 3 years old. Adopting area-level strategies and addressing local community disadvantages may help to optimise practices and prescribing patterns across local communities.

Strengths and limitations of this study

- Complete antibacterial dispensing data allows estimations of local community dispensing rate trends and their associations with education at a high level of spatial resolution.
- By including all Norwegian municipalities, we explored the total extent of local variations in dispensing rates under national reduction policy guidelines.
- Aggregate data cannot directly infer individual-level decision-making and needs.
- We were unable to control for the geographical burden of infectious disease in the age groups under examination.

INTRODUCTION

The periodic prevalence and patterns of antibiotic use vary between countries[1] and between socioeconomic and demographic groups within countries,[2-6] and studies have also shown temporal variations in the dispensing of antibacterials for systemic use.[7-8] One study from Norway found an overall reduction in the number of dispensed prescriptions among children aged 0–2 between 2005 and 2016, with the prevalence varying between counties.[9] Another study found that, among Norwegian children aged 0–2, one-year-olds consistently had the highest antibacterial dispensing rates between 2008 and 2016.

Several studies have attributed variations in antibacterial use to socioeconomic characteristics,[3-5,10-12] often including an indexed area-level deprivation measurement to capture several dimensions of deprivation (e.g., education, income, barriers to housing, crime, employment). Crowding, hygiene, lower host resistance due to poor nutrition, stress and smoking prevalence create a greater risk of infectious illness among people of lower socioeconomic status, but general practitioners' treatment practices and their interactions with family attitudes towards demanding certain treatments may influence prescription dispensing,[2,13] resulting in geographic and temporal variations in aggregate statistics. Education is associated with the awareness and proper use of antibacterials[14-16] and with the individual capacity to obtain, process and understand health information,[17,18] and cultural factors, such as individual vs. collective value systems, and future-oriented behaviour have also been associated with prescription patterns at multiple levels.[19]

Studies on variations in dispensed antibiotics in Norway have not explicitly modelled local variations in dispensing rate growth trajectories in terms of socioeconomic composition. The aim of this study was to investigate the association between population education levels and growth trajectories in antibacterial dispensing rates at the municipality level using longitudinal data and a multilevel growth curve model.

MATERIALS AND METHODS

The Norwegian Prescription Registry (NorPD) contains all prescriptions with a valid unique personal identifier redeemed at Norwegian pharmacies; details of the NorPD are published elsewhere.[20] We considered the period from 2006 to 2016 and included 734,359 prescriptions. We aggregated prescriptions if the same individual received two or more prescriptions for the same antibacterial drug on the same date, and we excluded records for individuals aged more than 1095 days (3 years) and those who died during the observation period. We used the following data from the NorPD: sex; year and month of birth; unique personal identifier; municipality of residence; date on which the prescription was dispensed at the pharmacy; and the Anatomical Therapeutical Chemical Classification System (ATC) code at the fifth level. As we only had information on the birth month in our data, we assigned a fictious birth date of the 15th of the birth month and calculated age as the date of dispensing minus this date.

Data in NorPD are pseudonymised, allowing longitudinal observation of an individual who is anonymous to the researcher. Individual data were aggregated at the municipality level, and

dispensing rates were calculated as the yearly number of prescriptions within a municipality per 100 children. We linked the aggregated prescription data to publicly available data on all Norwegian municipalities using the unique municipality identification number system. Analyses were restricted to ATC J01: antibacterials for systemic use.[21] The data cover the entirety of Norway at the local administrative level. Figure 1 presents a box-and-whiskers plot of the calculated local dispensing rate by year. Figure A1 (appendix) presents a sample of trends and intercepts fitted to the dispensing rate metric.

Exposure and covariates

Our exposure was the proportion of the population in a municipality who had received tertiary education (university level for 3 or more years).[22] We chose tertiary education as our education indicator for two reasons. Firstly, the literature states that knowledge of the proper use of antibiotics is more common among people who have received a higher education,[14-16] and secondly, the Norwegian education system ensures all young people the legal right to education up to and including upper secondary education, but no such right exists for higher education. Thus, continued education past the secondary level is an active choice, in contrast to structured schooling, so we would expect local population diversity.

We included a covariate for the proportion of the population in a municipality living in a household with less than 60% of the national median income,[23] which is the standard definition of low income in the European Union. The association between deprivation and dispensing rates[3-5] suggests that poverty may confound the relationship between dispensing rates and population education, and including this covariate served to partial out effects that could be attributed to education rather than to material deprivation.

The municipality population size may be related to levels of regional deprivation in education and to regional development and may therefore impact access to health care services. A previous study identified an association between municipality population size and dispensing rates in Norway,[6] and municipality size is therefore likely to confound the link between education and dispensing rates. Populations of Norwegian municipalities vary from fewer than 400 to more than 600,000 residents, and to best capture this variance, we calculated the natural logarithm of population size collected from official statistics[24] as an indicator of municipality size.

Lastly, we included an indicator for the median travel time to the nearest pharmacy, calculated using Google Maps to determine travel time between all addresses in Norway and their three nearest straight-line pharmacies, selecting the shortest travel time by car for each address before aggregating to the municipality level. A previous Norwegian study[25] found a link between dispensing rates and travel times to pharmacies in Norway. If education levels are geographically determined, they are also likely to correlate with pharmacy access, and it is thus important to partial out the effects of ease-of-pharmacy access from the educational coefficients.

Statistical analysis

Multilevel growth curve models are a special case of multilevel models in which a coefficient of time varies between units.[26] The variation in each unit of the dispensing rate is modelled

as a fixed growth trajectory plus a random error term, which means that the parameters of growth can be modelled by background characteristics.[27] Applying this to our data, the municipalities are repeatedly observed, such that level 1 constitutes the longitudinal part of the model and level 2 captures the variance between the municipalities.

[FIGURE 1 ABOUT HERE]

We centred all level 1 covariates, except time, on their cluster means—that is, centring within cluster — to achieve orthogonality between the level 1 and level 2 variables.[28] The covariates at level 1 were annual measurements of poverty, education and municipality population size, which reflect changes in the municipality by year. The same covariates were aggregated at level 2 as cluster means. These covariates reflect differences between municipalities over the period under study. All level 2 covariates were conversely centred on their grand mean. This centring scheme allows for easier interpretation of main effects in the interaction term, in which the estimated trend coefficient is interpreted as the expected mean dispensing rate trend in municipalities at average levels of population education. Time (L1) was not centred because we were interested in the average trend over the period (see [29] for a discussion on centring time in growth curve models).

The multilevel growth curve model assumes that time-variant covariates are not characterised by a systematic growth process, and the inclusion of simultaneous growth processes in a multilevel growth curve model may lead to misspecification and biased effects.[30] Within-municipality variations in education levels are highly correlated with time ($r = .95$), providing evidence for simultaneous growth and biasing the trend coefficient. We therefore removed the time-variant education predictor, as our goal was to estimate a cross-level interaction effect between the time-invariant education predictor and trends. We detail this choice further in the appendix and demonstrate the consequences of simultaneous growth on trend estimation in table A1.

We performed a square root transformation on the dispense rate metric to improve the model fit, but the coefficients on the square root scale lack the clean interpretability of coefficients on the original scale. We therefore used the square root model for predictions and for the evaluation of statistical significance but present the predicted dispensing rates using the original scale to aid in interpretation. Untransformed and square root transformed dispensing rate distributions are available in figure A2 and A3 (appendix), respectively.

The model fit was assessed using the Akaike Information Criterion, the Bayesian Information Criterion and residual diagnostic plots. Residual diagnostic plots are available in figures A4-A7 in the appendix. All models were estimated using the R package *nlme*, incorporating a compound symmetric error covariance structure to deal with within-group autocorrelation. A model equation and a parameter description are available in the appendix.

Patient and public involvement

No patients were involved.

RESULTS

The model results are shown in Table *1*, and Figures 2 and 3 are based on estimates from the model. An untransformed version of the model is available in table A2 in the appendix. Table *2* shows summary statistics for the types of antibacterial in the database, together with the total number of defined daily doses (DDD) dispensed, summarised by year and subgroup. Table *3* presents summary statistics. Table A3 (appendix) includes detailed summary statistics on within and between components specifically.

From model 1 in Table 1, it can be seen that the estimated mean trend of the square root dispensing rate at mean levels of population education is equal to −.053 (SD = .0927, $p < .001$). A one-percentage-point increase in cluster-mean education reduces the trend coefficient of the square root dispensing rate by −.0034 ($p = .0051$), *ceteris paribus*. There is thus a greater reduction in the dispensing rate in municipalities in which a larger proportion of the population have received tertiary education.

Figure 2 presents the predicted trajectories in the dispensing rates based on cluster-mean education levels. An important observation is that the trends are, on average, negative within the boundaries of the data. Even the municipalities with the lowest levels of population education (11%) show predicted reductions in dispensing rates. The predictions fan out from similar intercepts due to the small and insignificant 'main' effect of education (the effect when $T = 0$, $p = .892$) in the model. The Figure shows that the municipalities with low levels of population education have predicted reductions of approximately two prescriptions per 100 children, while municipalities with comparatively high levels of population education have predicted reductions approximately equal to ten prescriptions per 100 children over the period. In Figure 3, several municipalities can be seen to have a positive predicted trend after adjusting for the interaction with education. Most municipalities, however, show a predicted negative trend in the cross-level interaction model, and the size of the negative trend varies with population education in the municipality.

[FIGURES 2 AND 3 ABOUT HERE]

Table 1: Multilevel linear growth curve model. The model uses the square root of the transformed dispensing rates as outcomes. This model is used for the prediction (Figures 2 and 3) and evaluation of statistical significance and rates of change. Complete information is missing only for two municipalities due to municipality mergers during the period.

Coefficient	$\sqrt{\text{Dispensed Rx per 100 children}}$	*p*-values
Level 1		
Trend	−0.053 (−0.066, −0.039)	<. 001
Poverty	−0.098 (−0.125, −0.070)	<. 001
Population (ln)	1.265 (−0.061, 2.592)	.062
Level 2		
Education	−0.002 (−0.027, 0.023)	.892
Population (ln)	0.408 (0.290, 0.525)	< .001
Poverty	−0.085 (−0.130, −0.041)	< .001
Travel	−0.0003 (−0.0004, −0.0003)	< .001
Trend × Education (L2)	−0.0034 (−0.006, −0.001)	.005
Intercept	5.459 (5.340, 5.578)	< .001
Var. Comp.		
Std. Dev. μ_1	.0927	
Std. Dev. μ_0	.8647	
Misc.		
ρ Comp. Symm.	.000	
Groups	426	
Observations	4,503	
Log Likelihood	−6,442.764	
Akaike Inf. Crit.	12,913.53	
Bayesian Inf. Crit.	13,003.3	

Note: 95% CI in parentheses.

Table 2: Total dispensed DDD per 1,000 children by ATC J01 subgroups

Year	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
2006	0.4	1009.1	19.9	77.9	526.2	7.6	1.0	17.4
2007	0.3	923.1	16.3	58.2	453.9	2.9	1.0	11.9
2008	0.2	1158.4	19.8	73.6	504.3	9.2	0.9	13.0
2009	0.2	1057.2	18.4	69.5	418.3	6.9	0.5	10.1
2010	0.2	1296.7	22.5	74.6	502.5	0.7	0.8	9.8
2011	0.1	1170.5	21.7	70.1	566.4	2.7	1.3	8.0
2012	0.4	1195.9	17.0	68.1	484.1	1.1	1.3	7.3
2013	0.4	1001.6	20.9	66.7	355.6	0.9	2.0	5.6
2014		1104.1	24.2	71.2	367.3	1.3	1.6	7.4
2015	0.1	965.6	21.8	67.1	299.9	0.9	1.3	8.7
2016	0.0	911.2	20.1	58.3	260.8	2.0	1.8	5.2

Note: J01A tetracyclines; J01C beta-lactam antibacterials, penicillins; J01D other beta-lactam antibacterials; J01E sulfonamides and trimethoprim; J01F macrolides, lincosamides and streptogramins; J01G aminoglycoside antibacterials; J01M quinolone antibacterials; J01X other antibacterials.

Table 3: Pooled statistics, including summary statistics for yearly observations for all municipalities, before centring. The variable Dispensed Rx/100 child *is the dependent variable used in the model. Travel time is presented in decimal minutes and is time-invariant due to only being observed once. An extended table of summary statistics, including both centred and non-centred values, is available in the appendix.*

Statistic	**N**	**Mean**	**St. Dev.**	**Min.**	**Max.**
Dispensed Rx/100 children	4,519	29.7	16.3	0.9	104.9
Education	4,515	21.2	5.9	9.1	51.9
Population	4,519	11,885	35,479	200	658,390
Poverty	4,518	10.0	2.4	3.7	21.8
Trend	4519	5.01	3.16	0	10
Travel time (sec.)	426	1,674	1,882	182	13,129

DISCUSSION

While there has been a national decrease in antibacterial dispensing rates in Norway,[31] the current study shows that trends vary between Norwegian municipalities for patients below 3 years of age, with municipalities in which more of the population has received tertiary education showing larger decreases in dispensing rates. Several efforts have been made to reduce antibacterial dispensing rates, notably by updating national guidelines for the use of antibacterials [32] and through intervention campaigns.[33] If one views high education levels as a form of socioeconomic advantage, the results suggest that municipalities with socioeconomically advantaged populations have been more successful in reducing dispensing rates.

Our findings support the existing literature on the relationship between relative socioeconomic deprivation and antibacterial dispensing rates. Low parental education has been linked to higher prescribing rates in paediatric patients,[2,5,13,34] and we would expect the same individual mechanisms to translate to aggregate statistics. If a lack of higher education in a community is considered a form of regional deprivation, then these results are consistent with other data on the association between area-level deprivation indexes (which include education in the index) and dispensing rates.[3,4,11]

We chose tertiary education as our education indicator because proper use of antibiotics is more common in people who have received higher education,[14-16] and our findings are consistent with these expectations. In addition, the Norwegian education system ensures all young people the legal right to education up to and including the upper secondary level, but no such right exists for higher education. Thus, continued education past secondary level is an active choice in which we would expect local population diversity, in contrast to structured schooling.

Health literacy is also associated with higher education,[17,18] but education is an inaccurate proxy for individual health literacy.[35] However, the overuse of antibacterials and policies implemented to reduce consumption are not only an issue of individual health, but also of public health. Successful enactment of public health policies directed at reducing antibacterial dispensing rates may rely in part on the ability of individuals and groups to obtain, process, understand, evaluate and act upon information needed to make decisions that benefit the individual and the community[36], allowing collectivist and long-term values to outweigh individualist short-term decision-making. It is possible that education enables an understanding of the individual and family as being embedded in society, such that individual decisions on antibacterial treatment are more likely to be made within the framework of a greater public health concern.

The Norwegian health care system provides universal health care access, and health inequalities in care utilisation have diminished over time.[37] Needs-adjusted socioeconomic differentiation in health care usage has empirically been observed mostly in the use of private medical specialists and hospital outpatient care.[38] However, these observations do not necessarily include all differentiation in health care usage in Norway, such as potential geographic variations, and importantly, these studies do not include parental health care–seeking. If parental health care–seeking translates to paediatric health care–seeking, health

care usage may, hypothetically, not be socially determined in volume, but rather in kind. People from advantaged socioeconomic backgrounds may interact and use health care inputs more efficiently, thus achieving the same amount of health investment with less health care services. They may also consider the potential consequences of antibacterial use more frequently, driving the dispensing rate downward.[5]

Importantly, children are themselves not actors in this framework. Decisions on treatment are made by physicians and parents, which suggests that the health care provided to children is dependent on parental socioeconomic status and how they seek health care for their children, as well as the physician's prescribing habits and responses to different individuals and social groups. Several studies have identified an association between the high use of antibacterials in young children and an increased risk of chronic disease development later in life,[31,39-43] so optimising prescribing practices would seem important for reducing health inequalities in future generations.

Area-level strategies, as opposed to national-level strategies, for antimicrobial stewardship have been suggested in other countries;[10] given the local and regional variations in dispensing rates and reduction trends in Norway, we agree with previous authors[19] that effective antimicrobial stewardship requires that the issue be addressed from a multilevel systems perspective and that social, structural and cultural determinants also be considered when implementing policy at the local administrative level. The overall responsibility for health policies in Norway lies with the National Ministry of Health, and stewardship of antimicrobial resistance in Norway relies on existing administrative structures of disease prevention and control, with sectoral operative responsibility and weak coordination mechanisms.[44] National political strategies do target primary health care services at the municipal level, but the need for and potential drivers of antibacterial treatment may vary between municipalities. We expect the efficacy of national policies for reducing antibacterial dispensing rates to partially depend on the local population's socioeconomic composition.

Strengths, limitations and methodological considerations

Unlike several authors who have applied indexed deprivation measures containing a variety of deprivation indicators, we focused on education specifically because it is a common component of deprivation indexes, which present a trade-off between interpretation and capturing a holistic concept of deprivation. It is thus unclear which features of such deprivation indexes drive empirical variations in dispensing rates, and translating theoretical mechanisms from the individual level to aggregate statistics then becomes even more challenging due to the number of dimensions in such indexes. The effects of income and occupation deprivation have been studied separately,[4] but no such analysis has been performed using an education indicator. Education is a key socioeconomic characteristic for health determinants, and by investigating education specifically, our results are more readily interpreted and more clearly relatable to the specific mechanisms discussed in the literature.

A strength of this study is the completeness of the dispensing rate metric. The NorPD contains all prescriptions dispensed in the period under examination, excluding usage in hospitals. We argue that this has two advantages. Firstly, we expect education to matter more in the context of primary health care, because parents are active participants in health care decision-

making, and secondly, the primary health care service is administered at the municipal level in Norway. Observed trends are therefore likely to be a result of local community needs and behaviours and local decision-making processes.

A limitation of this study is the lack of information on the geographical burden of disease, although regional differences in dispensing rates are unlikely to be explained by differences in the severity and density of infections and more likely to be related to differences in medical practices.[9] A Welsh study similarly found no support for regional differences in prescriptions being explainable by chronic conditions in the adult population.[3] Indeed, if the entire variance could be explained by the burden of infections, the implication would be that infections requiring antibacterial treatment are geographically unequally distributed, even between paediatric patients.

Another limitation is the limited inferences that can be made regarding individual outcomes based on aggregate statistics. Further research is necessary to conclude an association between parental education, individual interactions with health care services and paediatric antibacterial dispensing rates in Norway.

CONCLUSION

Our analysis shows that the ability to reduce dispensing rates over time at the municipality level is associated with mean population levels of higher education. Local needs and potential root causes of health outcomes should be considered in antimicrobial stewardship to optimise prescription patterns, and attention should be paid to social demographics, like education, that may affect health behaviour, preferences and usage, which may help to further reduce dispensing rates in accordance with political goals.

CONTRIBUTORSHIP STATEMENT

SS conceptualised, designed and drafted the manuscript; prepared data; and performed the statistical analysis. KS contributed data. LS provided ethics approval and data from the prescription registry. SS, KS, AEE, and LS critically revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

There are no funding grants to declare.

DATA SHARING STATEMENT

Data on antibacterial dispensing can be obtained by application to a third party (The Norwegian Prescription Registry) and are not publicly available. Travel time data are available from the corresponding author upon request. Data collected from Statistics Norway are licensed under the Creative Commons Attribution 4.0 International (*https://www.ssb.no/en/diverse/lisens*) which permits others to share, copy, redistribute, and adapt the material for any purpose and are available from the corresponding author upon request.

ETHICS STATEMENT

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (ref. 2018/1021) in compliance with the Norwegian Health Research Act, §10. Data were anonymised before the authors accessed them for the purposes of this study.

REFERENCES

1 Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014;**14**:742–50.

2 Thrane N, Olesen C, Schønheyder HC, et al. Socioeconomic factors and prescription of antibiotics in 0-to 2-year-old Danish children. *J Antimicrob Chemother* 2003;**51**:683–9.

3 Adekanmbi V, Jones H, Farewell D, et al. Antibiotic use and deprivation: an analysis of Welsh primary care antibiotic prescribing data by socioeconomic status. *J Antimicrob Chemother* 2020;**75**:2363–71.

4 Koller D, Hoffmann F, Maier W, et al. Variation in antibiotic prescriptions: is area deprivation an explanation? Analysis of 1.2 million children in Germany. *Infection* 2013;**41**:121–7.

5 Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: evidence from Switzerland. *Health Policy* 2006;**78**:77–92.

6 Haugen P, Simonsen GS, Primicerio R, et al. Antibiotics to outpatients in Norway. Assessing effect of latitude and municipality population size using quantile regression in a cross-sectional study. *Pharm Stat* 2018;**17**:4–11.

7 Sakshaug S, Strøm H, Berg C, et al. Legemiddelforbruket i Norge 2013–2017. Legemiddelstatistikk 2018: 1 [Drug consumption in Norway 2013–2017. Drug statistics 2018: 1]. Oslo: Norwegian Institute of Public Health 2018.

8 Blix HS, Engeland A, Litleskare I, et al. Age-and gender-specific antibacterial prescribing in Norway. *J Antimicrob Chemother* 2007;**59**:971–6.

9 Stordal K, Marild K, Blix HS. Bruk av antibiotika hos barn i perioden 2005–16. *Tidsskriftet Den Norske Legeforening* 2017;**137**:1414–20.

10 Mölter A, Belmonte M, Palin V, et al. Antibiotic prescribing patterns in general medical practices in England: does area matter? *Health Place* 2018;**53**:10–6.

11 Thomson K, Berry R, Robinson T, et al. An examination of trends in antibiotic prescribing in primary care and the association with area-level deprivation in England. *BMC Public Health* 2020;**20**:1–9.

12 Hobbs MR, Grant CC, Ritchie SR, et al. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5 years. *J Antimicrob Chemother* 2017;**72**:1832–40.

13 Pichichero ME. Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 1999;**104**:1384–8.

14 Waaseth M, Adan A, Røen IL, et al. Knowledge of antibiotics and antibiotic resistance among Norwegian pharmacy customers–a cross-sectional study. *BMC Public Health* 2019;**19**:1–2.

15 Agarwal S, Yewale VN, Dharmapalan D. Antibiotics use and misuse in children: A knowledge, attitude and practice survey of parents in India. *J Clin Diagn Res* 2015;**9**:SC21.

16 Yu M, Zhao G, Lundborg CS, et al. Knowledge, attitudes, and practices of parents in rural china on the use of antibiotics in children: a cross-sectional study. *BMC Infect Dis* 2014;**14**:1–8.

17 Dunn-Navarra A-M, Stockwell MS, Meyer D, et al. Parental health literacy, knowledge and beliefs regarding upper respiratory infections (URI) in an urban Latino immigrant population. *J Urban Health* 2012;**89**:848–60.

18 Sørensen K, Pelikan JM, Röthlin F, et al. Health literacy in Europe: Comparative results of the European health literacy survey (HLS-EU). *Eur J Public Health* 2015;**25**:1053–8.

19 Blaser MJ, Melby MK, Lock M, et al. Accounting for variation in and overuse of antibiotics among humans. *BioEssays* 2021;43:e2000163.

20 Furu, K. Establishment of the nationwide Norwegian prescription database (NorPD)–new opportunities for research in pharmacoepidemiology in Norway. *Nor Epidemiol* 2008;18:129–36.

21 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2019 [Date accessed: April 2022]. https://www.whocc.no/atc_ddd_index

22 Statistics Norway. Educational attainment of the population, Source table 09429: Educational attainment, by municipality and sex (M), 1970–2020 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/09429/

23 Statistics Norway. Income and wealth statistics for households, Source table: 06947: Persons in private households with annual after-tax income per consumption unit, below different distances to the median income. EU-scale and OECD-scale (M) (UD) 2005–2020 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/06947

24 Statistics Norway. Population count, Source table 07459: Population, by sex and one-year age groups (M) 1986–2022 [Date accessed: April 2022]. https://www.ssb.no/en/statbank/table/07459

25 Svendsen K, Kongsgard H, Haugen P, et al. Travel time to pharmacy influence the use of antibiotics in Norway. *Pharmacoepidemiol Drug Saf* 2016;25(Suppl 3):641.

26 Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using Stata*. College Station, TX: Stata Press 2008.

27 Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis methods*. Thousand Oaks, CA: Sage 2002.

28 Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: A new look at an old issue. *Psychol Methods* 2007;**12**:121–38.

29 Biesanz JC, Deeb-Sossa N, Papadakis AA, et al. The role of coding time in estimating and interpreting growth curve models. *Psychol Methods* 2004;**9**:30–52.

30 Curran PJ, Obeidat K, Losardo D. Twelve frequently asked questions about growth curve modeling. *J Cogn Dev* 2010;**11**:121–36.

31 Beckstrøm S, Småbrekke L. Antibacterial use by birth year and birth season in children 0-2 years in Norway. *Nor Epidemiol* 2021;**29**:35–43.

32 Eliassen KE, Fetveit A, Hjortdahl P, et al. New guidelines for antibiotic use in primary health care. *Tidsskriftet den Norske Legeforening: tidsskrift for praktisk medicin, ny raekke* 2008;**128**:2330–4.

33 Ministry of Health. Handlingsplan mot antibiotikaresistens i helsetjenesten. 2016.

34 Mangrio E, Wremp A, Moghaddassi M, et al. Antibiotic use among 8-month-old children in Malmö, Sweden – in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatr* 2009;**9**:31.

35 Berkman ND, Davis TC, McCormack L. Health literacy: What is it? *J Health Commun* 2010;**15**:9–19.

36 Freedman DA, Bess KD, Tucker HA, et al. Public health literacy defined. *Am J Prev Med* 2009;**36**:446–51.

37 Vikum E, Bjørngaard JH, Westin S, et al. Socio-economic inequalities in Norwegian health care utilization over 3 decades: the HUNT study. *Eur J Public Health* 2013;**23**:1003–10.

38 Vikum E, Krokstad S, Westin S. Socioeconomic inequalities in health care utilisation in Norway: the population-based HUNT3 survey. *Int J Equity Health* 2012;**11**:1–9.

39 Korpela K, Vos WM de. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. *Microb Cell* 2016;**3**:296.

40 Mårild K, Ye W, Lebwohl B, et al. Antibiotic exposure and the development of coeliac disease: A nationwide case–control study. *BMC Gastroenterol* 2013;**13**:1–9.

41 Risnes KR, Belanger K, Murk W, et al. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;**173**:310–8.

42 Sander SD, Andersen A-MN, Murray JA, et al. Association between antibiotics in the first year of life and celiac disease. *Gastroenterology* 2019;**156**:2217–29.

43 Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science* 2016;352:544–5.

44 Time MS, Veggeland F. Adapting to a global health challenge: managing antimicrobial resistance in the Nordics. *Politics Gov* 2020;**8**:384–95.

FIGURE CAPTIONS

Figure 1: *Box-and-whisker plot of dispensing rates by year. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this Figure is the notable variation between municipalities within a specific year. The intraclass correlation coefficient of the null model indicates that 62.8% of the total variance is between municipalities.*

Figure 2: *Predicted cross-level interaction effect between trends and education. The Y-axis displays the dispensing rate on the original scale. The middle line represents the average cluster level of education, while the outer lines are predicted trends for ±2 standard deviations from the mean education levels. Predictions fan out from similar intercepts due to the insignificant main effect of education (effect when T = 0).*

Figure 3: *Predicted slopes by population education. The points are the predicted square roots of the dispensing rate trends for each municipality. All 426 estimated trends are presented and plotted against education on the X-axis. The Figure shows that the leaders in dispensing rate reductions also tend to have higher proportions of people with tertiary education and, conversely, that low performers tend to have lower levels of tertiary education. Please note the Y-axis scaling when interpreting the figures.*

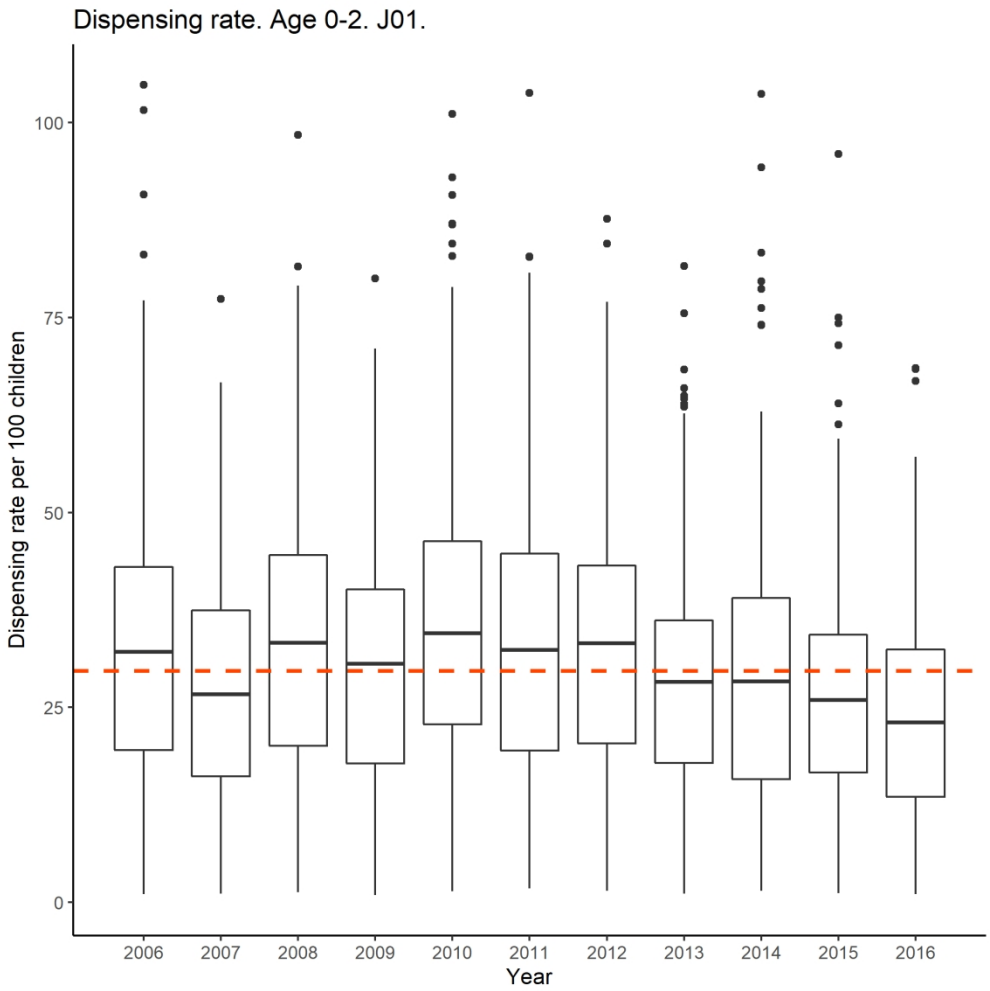


Figure 1: Box-and-whisker plot of dispensing rates by year. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this Figure is the notable variation between municipalities within a specific year. The intraclass correlation coefficient of the null model indicates that 62.8% of the total variance is between municipalities.

452x451mm (118 x 118 DPI)

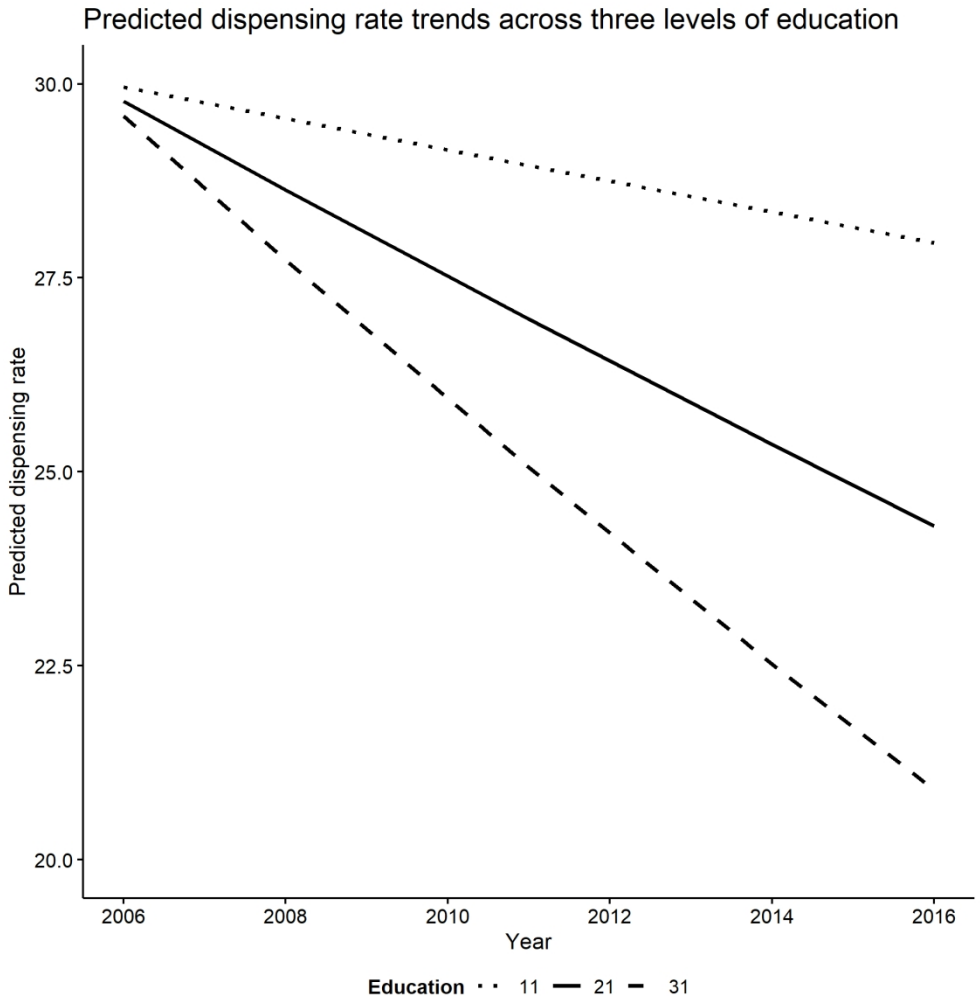


Figure 2: Predicted cross-level interaction effect between trends and education. The Y-axis displays the dispensing rate on the original scale. The middle line represents the average cluster level of education, while the outer lines are predicted trends for ±2 standard deviations from the mean education levels. Predictions fan out from similar intercepts due to the insignificant main effect of education (effect when T = 0).

452x452mm (118 x 118 DPI)

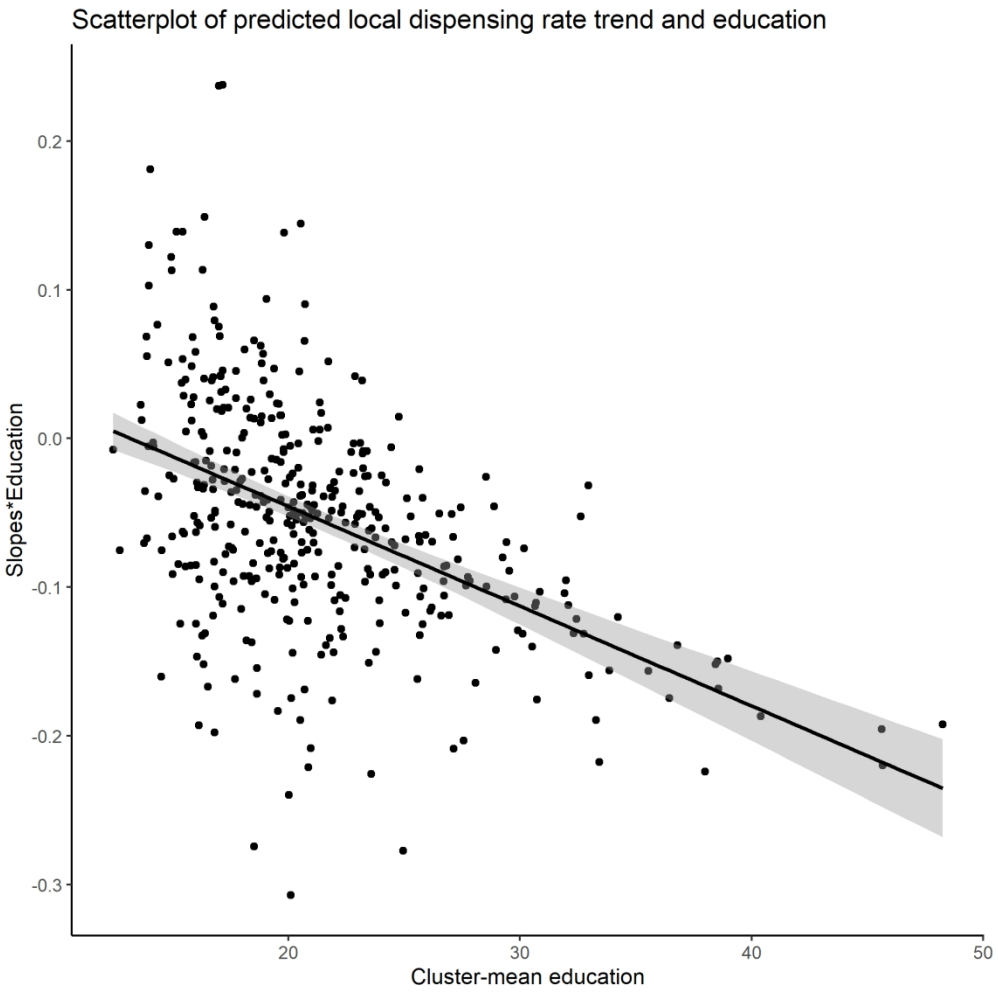


Figure 3: Predicted slopes by population education. The points are the predicted square roots of the dispensing rate trends for each municipality. All 426 estimated trends are presented and plotted against education on the X-axis. The Figure shows that the leaders in dispensing rate reductions also tend to have higher proportions of people with tertiary education and, conversely, that low performers tend to have lower levels of tertiary education. Please note the Y-axis scaling when interpreting the figures.

452x451mm (118 x 118 DPI)

APPENDIX

Model description

The two-level linear growth curve model with a cross-level interaction effect with cluster-mean education is represented by the following equation:

$$\begin{aligned} L1: \sqrt{Y_{tj}} &= \beta_{0j} + \beta_{1j}T_{tj} + \beta_2 EDU_{tj}^{CWC} + \beta_3 lnPOP_{tj}^{CWC} + \beta_4 POV_{tj}^{CWC} + \epsilon_{tj} \\ L2: \beta_{0j} &= \gamma_{00} + \gamma_{01}EDU_j^{CM} + \gamma_{02}lnPOP_j^{CM} + \gamma_{03}POV_j^{CM} + \gamma_{04}TR_j + \mu_{0j} \\ \beta_{1j} &= \gamma_{10} + \gamma_{11}EDU_j^{CM} + \mu_{1j} \end{aligned}$$

Error terms are all assumed normally distributed:

$$\begin{aligned} \epsilon_{tj} &\sim \mathrm{N}(0, \sigma_\epsilon^2) \\ \mu_{0j} &\sim \mathrm{N}(0, \sigma_{\mu_0}^2) \\ \mu_{1j} &\sim \mathrm{N}(0, \sigma_{\mu_1}^2) \end{aligned}$$

Consulting the $L1$ part of the equation: β_{0j} are random intercepts, $\beta_k X_{tj}^{CWC}$ are the fixed time-variant coefficients where variables are centered-within-cluster, $\beta_{1j}T_{tj}$ is a time-variant trend variable where the first year is set to 0, and ϵ_{tj} is the level-1 error term. In the $L2$ part of the equation, γ_{00} is the mean municipal level intercept, $\gamma_{0k}X_j^{CM}$ are coefficients for level 1 covariate cluster-means (CM), $\gamma_{04}TR_j$ is a coefficient for median travel time to nearest pharmacy, while μ_{0j} is the intercept variance component. The linear trend variable is modeled as a random effect with μ_{1j} variance component $\gamma_{11}EDU_j^{CM}$. $\beta_2 EDU_{tj}^{CWC}$ is a cross-level interaction between the cluster-mean education level across the time-period and the random linear trend. The term $\beta_2 EDU_{tj}^{CWC}$ was removed in the final model to address the issue of simultaneous growth.

Table A1: Model 1 includes the time-variant education predictor, model 2 is the same as the in-text model. This table aims to show the consequences of simultaneous growth on the estimated trend coefficient and confidence intervals.

	$\sqrt{Dispensed\ prescriptions\ per\ 100\ children}$	
	Model 1	Model 2
Level 1		
Trend	−0.015 (−0.050, 0.019) [.385]	−0.053 (−0.066, −0.039) [<.001]
Poverty	−0.098 (−0.125, −0.071) [<.001]	−0.098 (−0.125, −0.070) [<.001]
Population (ln)	1.562 (0.210, 2.914) [.024]	1.265 (−0.061, 2.592) [.062]
Education	−0.069 (−0.127, −0.010) [.021]	
Level 2		
Education	-0.004 (−0.029, 0.021) [.751]	−0.002 (−0.027, 0.023) [.892]
Population (ln)	0.409 (0.292, 0.527) [<.001]	0.408 (0.290, 0.525) [<.001]
Poverty	−0.085 (−0.130, −0.040) [<.001]	−0.085 (−0.130, −0.041) [<.001]
Travel	−0.0003 (−0.0004, −0.0003) [<.001]	−0.0003 (−0.0004, −0.0003) [<.001]
Trend×Education (L2)	−0.003 (−0.005, −0.0005) [.019]	−0.0034 (−0.006, −0.001) [.005]
Intercept	5.271 (5.072, 5.471) [<.001]	5.459 (5.340, 5.578) [<.001]
Var. Comp.		
Std. Dev. μ_1	.0929	.0927
Std. Dev. μ_0	1.0912	.8647
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,499	4,503
Log Likelihood	−6,431.018	−6,442.764
Akaike Inf. Crit.	12,892.04	12,913.53
Bayesian Inf. Crit.	12,988.21	13,003.3
Note:	95% CI in parentheses. P-values in square brackets.	

Simultaneous growth and MLM interpretation under centering scheme

Model 1 includes all level 1 covariates. Model 2 excludes the group-mean centered education (L1) covariate due to simultaneous growth issues resulting in collinearity between L1 education and trend.

This contrast table shows the effect of simultaneous growth on estimated parameters. The only difference between the models is the removal of the L1 group-mean centered education indicator. Confidence intervals are shown in parentheses.

Group-mean centering level 1 covariates leads to orthogonal relationships between levels; the correlations between level 1 and level 2 covariates are equal to 0. In a model without the uncentered trend variable, excluding level 1 coefficients would not affect level 2 estimates under group-mean centering. In fact, the estimates would be the same regardless of whether level 1 covariates were even in the model [30]. However, since the trend variable is *not* centered, some correlation will exist between levels through correlation with the trend variable, explaining the minor changes in level 2 coefficients. These changes are unsubstantial and only result in minor changes in L2 estimates.

Simultaneous growth leads to a very simple issue of near perfect collinearity between L1 education and the trend variable. This is the reason for the dramatic change in the trend coefficient size and confidence interval. Simply put, the trend effect in model 1 is biased due to collinearity with the L1 education covariate. While there are ways to deal with this problem through *multivariate* growth curve modeling [32], we are primarily interested in the cross-level interaction effect between education traits and the random trend. As such, we prefer the more parsimonious modeling option removing the cluster-mean centered education variable from the level 1 part of the equation.

Interpreting coefficients under centering scheme

Centering and cross-level interactions changes the interpretation of certain coefficients. We base the interpretation on model 2 and focus on three main coefficient interpretations a) the main trend effect and its variance, b) the main trait education effect and c) the cross level interaction term.

Due to grand-mean centering L2 covariates and the inclusion of an interaction term, the main trend effect ($-.015$) is interpreted as the expected square root dispense rate trend for municipalities with a mean level of trait education (21.15%), *ceteris paribus*. This is a random coefficient, and its random parameter μ_1 suggests that the standard deviation from the fixed term is equal to $.919$. The main education effect ($-.002$) is the expected effect of education at $T = 0$ (2006, trend is not centered). This is clearly shown by the very similar intercepts in figure 2 and 3. Lastly, the interaction term (-0034.) is the expected decrease in trend for every pp increase in education traits. This model is the basis for figures 2 and 3.

For other L1 coefficients (sans the trend coefficient), a one-unit increase entails a one unit change from a covariates given group mean. The coefficient is thus the average effect of a one unit increase from a given group mean, *ceteris paribus*.

Centering and growth

Notably, we choose not to center the level 1 trend variable for two reasons; firstly, the panels are only slightly imbalanced. Centering the trend variable on the group means practically results in a grand mean centered trend variable (correlation with uncentered trend indicator: $r = .97$), with

no real consequences to the coefficient estimates. The only consequence is on the intercepts and the intercept variance due to the zero point being established in 2011 for all but a few groups. Secondly, the model is a linear random growth curve model. Centering the trend covariate is more of an issue in situations where a polynomial growth curve might be fitted.

Intercept and slope correlation

Intercepts and slopes are negatively correlated at $r = -.597$. This is a natural consequence of bounded data; dispensing rate cannot be less than 0. Municipalities with low starting dispensing rates will naturally not be able to reduce dispensing rates as much as those with higher starting dispensing rates. This is of no particular concern for estimating the interaction term; indeed, the non-significant main education coefficient implies that the intercept variance is not explained by mean population education levels. This is also clear when investigating figure 2 in the main text.

SUPPLEMENTARY FIGURES AND TABLES

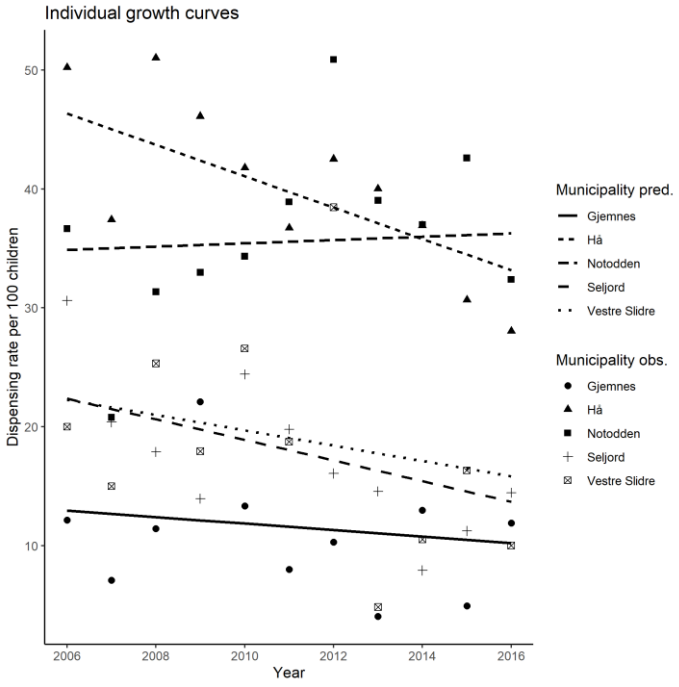


Figure A1: *Linear growth curve predictions and observations from a simple random trend null-model for five random municipalities. Municipalities were randomly sampled from a strata of slope quantiles to ensure that slope variance was represented in the figure. Note that the Y-axis is scaled by min-max observations in the subsample, not the entire distribution.*

Table with transformed and untransformed dispense rates

Table A2: Multilevel growth curve models. Both models include all covariates. Model 1 uses the square-root transformed dispense rates as outcomes. This model is used for prediction (figures 2 and 3) and evaluation of statistical significance. Model 2 uses the dispense rate as the outcome.

	$\sqrt{\text{Dispensed Rx per 100 children}}$	Dispensed Rx per 100 children
	(1)	(2)
Level 1		
Trend	−0.053 (−0.066, −0.039) [<. 001]	−0.608 (-.750, -.466) [< . 001]
Poverty	−0.098 (−0.125, −0.070) [<. 001]	−1.061 (-1.352, -.769) [< . 001]
Population (ln)	1.265 (−0.061, 2.592) [.062]	13.980 (.278, 27.683) [.046]
Level 2		
Education	−0.002 (−0.027, 0.023) [.892]	0.026 (-.239, .291) [. 848]
Population (ln)	0.408 (0.290, 0.525) [< .001]	3.983 (2.767, 5.199) [< .001]
Poverty	−0.085 (−0.130, −0.041) [< .001]	−0.845 (-1.311, -.379) [. 001]
Travel	−0.0003 (−0.0004, −0.0003) [< .001]	−0.003 (-.003, -.002) [< . 001]
Trend × Education (L2)	−0.0034 (−0.006, −0.001) [.005]	−0.041 (-.066, -.017) [. 001]
Intercept	5.459 (5.340, 5.578) [< .001]	32.689 (31.425, 33.952) [< .001]
Var. Comp.		
Std. Dev. μ_1	.0927	.918
Std. Dev. μ_0	.8647	11.54
Misc.		
ρ Comp. Symm.	.000	.000
Groups	426	426
Observations	4,503	4,503
Log Likelihood	−6,442.764	−17,097.230
Akaike Inf. Crit.	12,913.53	34,222.460
Bayesian Inf. Crit.	13,003.3	34,312.240
Note:	*p<0.05; **p<0.01; ***p<0.001	
	95% CI in parentheses. P-values in square brackets.	

Dependent variable distribution before and after square root transformation

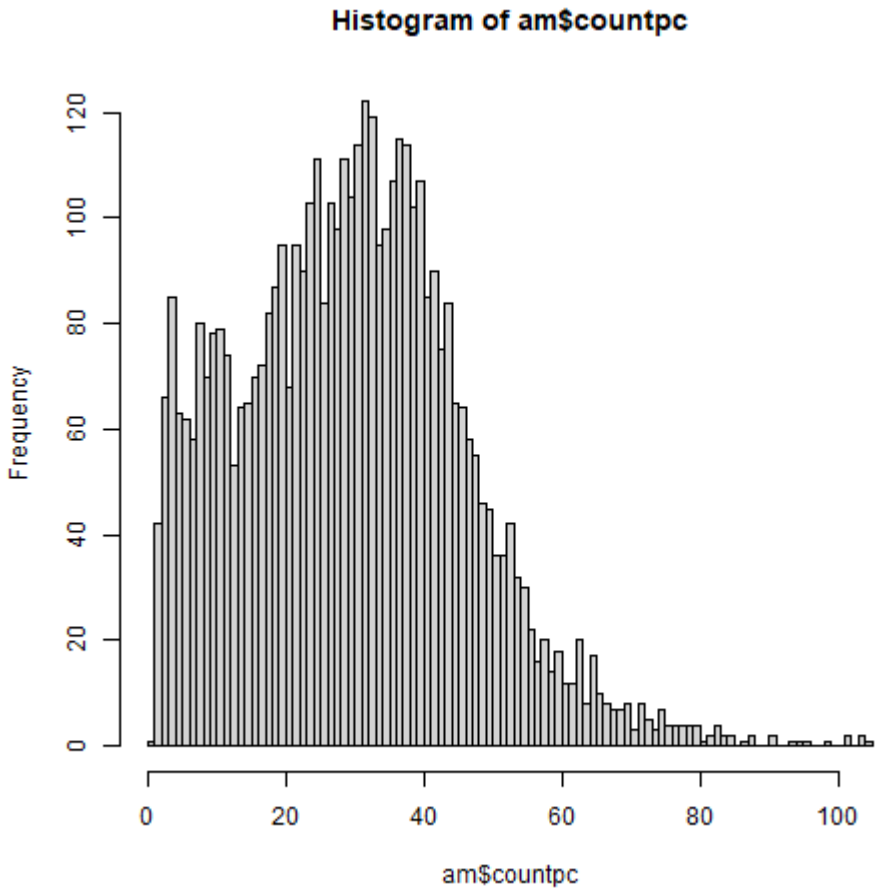


Figure A2: Dispense rate distribution before square root transformation. The distribution is closer to a Poisson distribution, due to the natural bounds of the data.

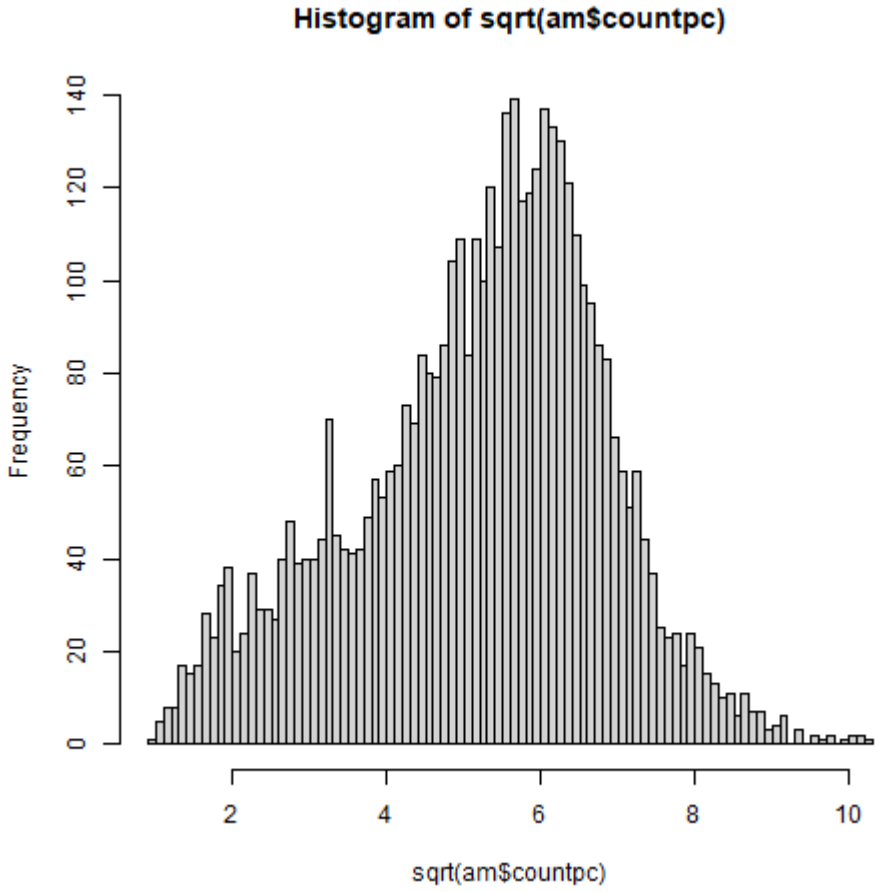


Figure A3: Dispense rate after square root transformation. Where the log-transformation (not shown) aggressively overcorrects the issue, leading to a worse fit than the untransformed version of the model, the square root transformation only moderately corrects the distribution, making residuals more well-behaved than the untransformed model. We emphasize that we performed this transformation to solve a statistical issue particularly present when investigating the residuals vs. the fitted values, and as such were guided by the data rather than theory. However, as the prediction plots, significance tests, and coefficients show, these modeling changes do not affect results in a significant way.

Residual plots main model

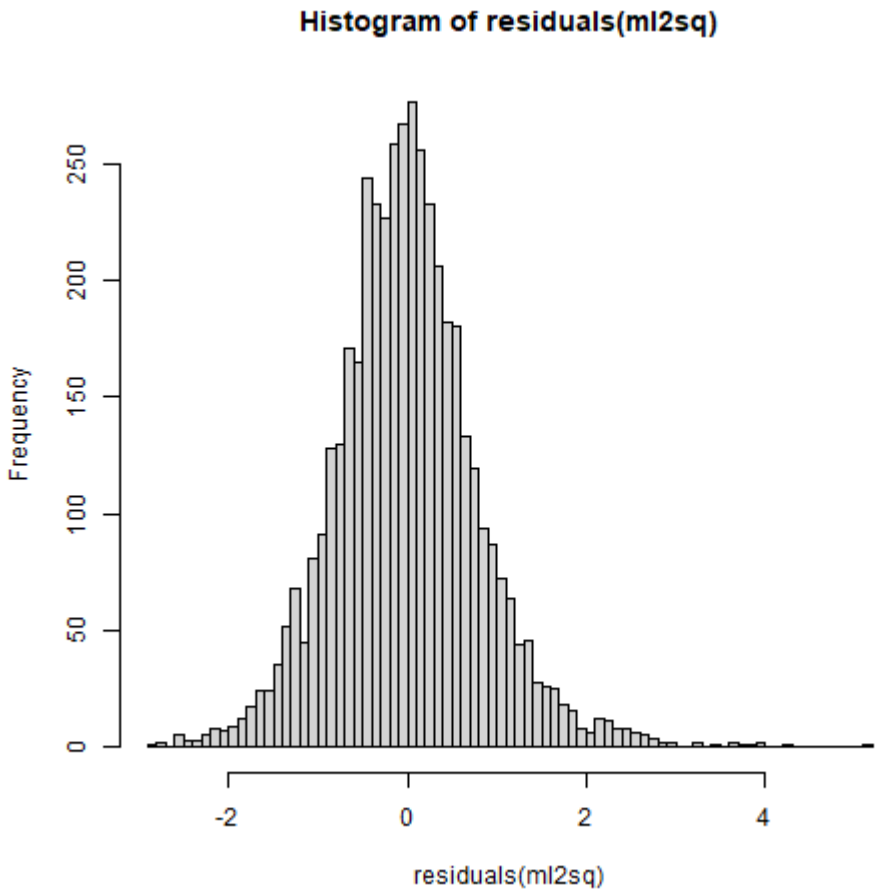


Figure A4: Level 1 Residual distribution after square root transformation of the dependent variable. While a marginally longer tail on positive residuals, we find no particular issues with this distribution.

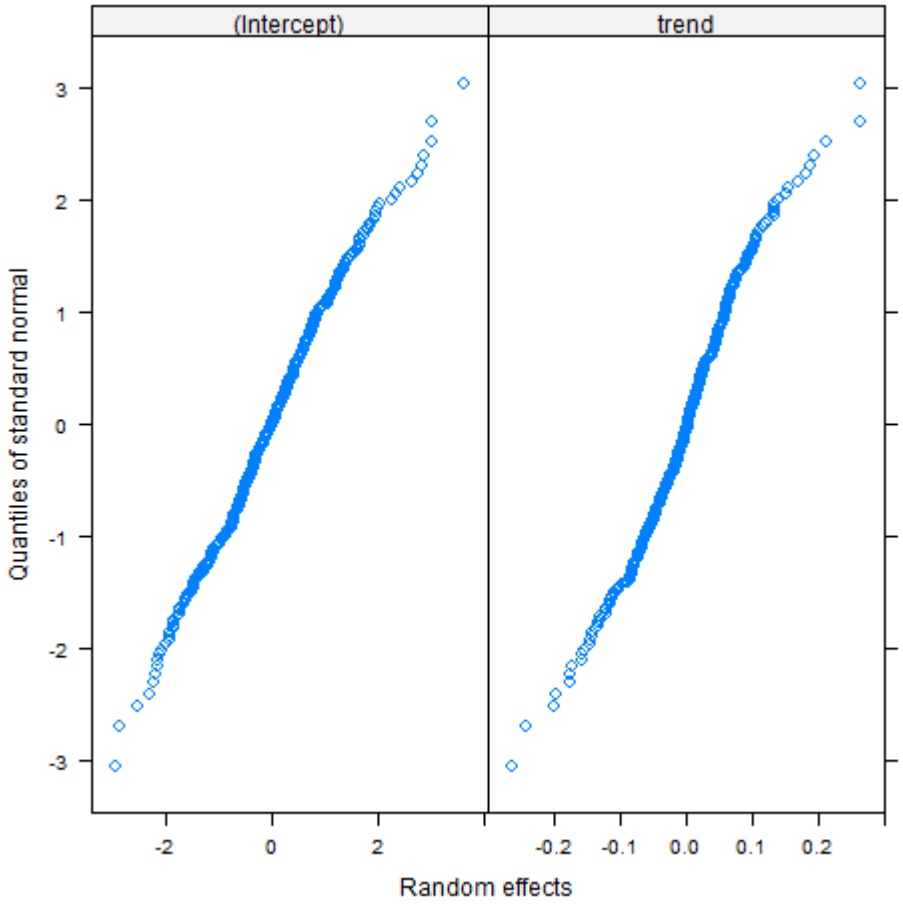


Figure A5: QQ-plot of the random terms in the model. We find that these are approximately normally distributed.

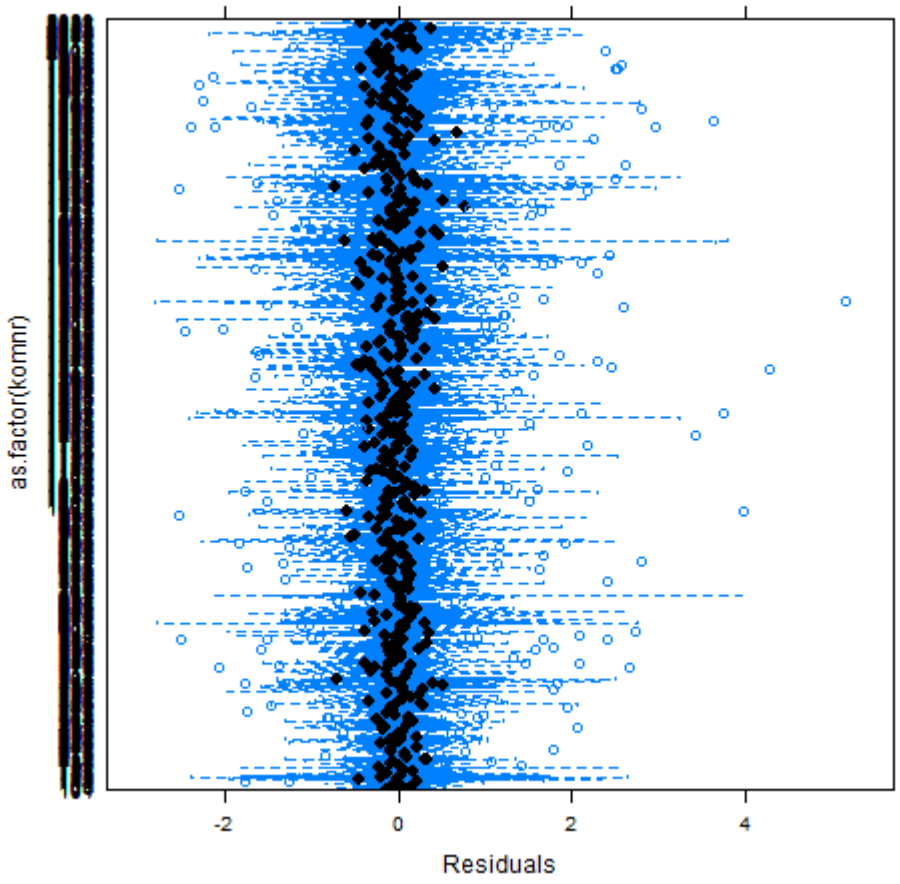


Figure A6: Level-1 residuals by municipality. Residuals seem overall to be centered at 0 with random deviation from this mean. Some differences in variance between municipalities is expected, as the number of repeat observations is relatively small (11).

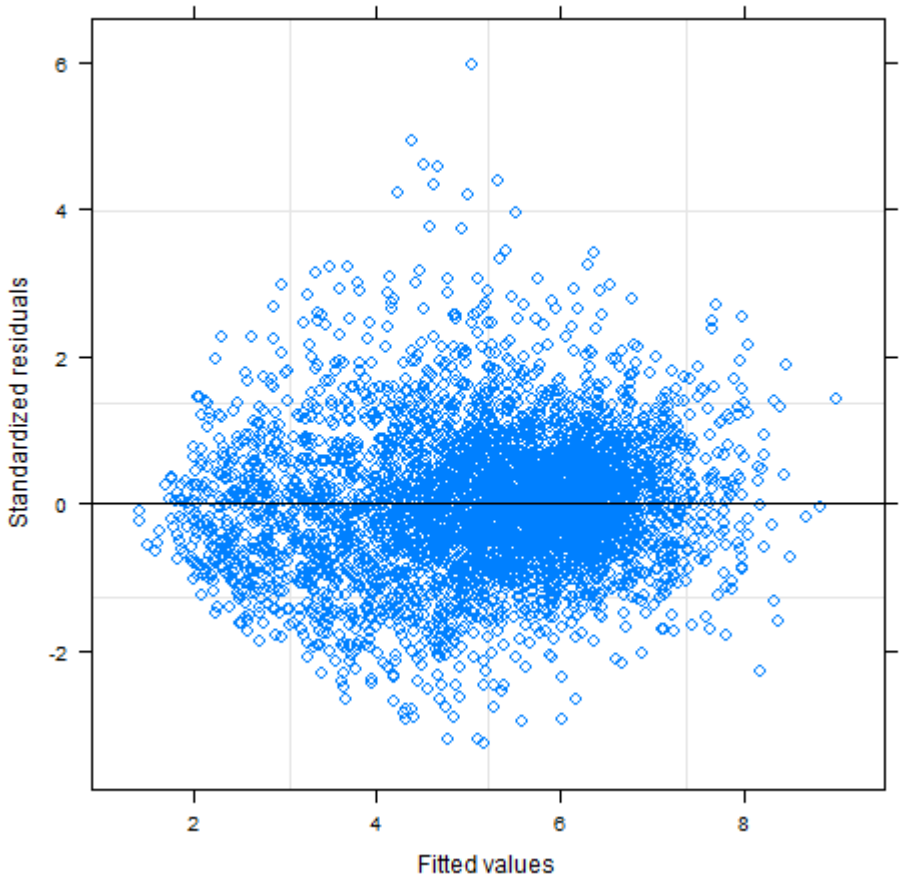


Figure A7: Standardized residuals vs. fitted values plot. We saw some problems with heteroskedasticity in the unadjusted model. While logarithmic transformation aggressively overcorrected the issue, the square root transformation adjusts for the moderate skewness and provides confidence to estimated standard errors.

Full version of summary statistics table

Statistics	N	Mean	St. Dev.	Min	Max
Pooled					
Dispensed Rx/100 chld.	4,519	29.7	16.3	0.9	104.9
Education	4,515	21.2	5.9	9.1	51.9
Population	4,519	11,885	35,479	200	658,390
Poverty	4,518	10.0	2.4	3.7	21.8
Within					
Dispensed Rx/100 child	4,519	0.00	9.58	−40.38	74.42
Education	4,515	0.00	1.87	−5.25	5.97
Population	4,519	0.00	2,180	−60,394	59,5842
Poverty	4,518	0.00	1.07	−3.46	5.76
Between					
Dispensed Rx/100 chld.	428	29.0	13.5	2.8	70.3
Education	428	21.0	5.6	11.2	48.2
Population	428	11,505	34,795	212	598,805
Poverty	428	10.0	2.2	5.1	18.6
Travel (sec.)	426	1,674	1,882	182.0	13,129

Table A3: Summary statistics grouped by levels. Pooled statistics include summary statistics for yearly observations for all municipalities before centering. The dependent variable. The within section shows descriptive statistics for all cluster-mean centered covariates, that is the level 1 parameters in the model. Note the mean 0 ensuring no correlation between level 1 and level 2 covariates. The between section represents the level 2 variables used in the model. These are 428 cluster-means for all covariates excluding travel times, due to municipality mergers before data collection.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1,3
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3-4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	3-4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	5/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3-4
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7/A
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.