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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]

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[1]Department of Social Science, UiT The Arctic University of Norway, Tromso, Troms og Finnmark, Norway
[2]Department of Pharmacy, UiT The Arctic University of Norway, Tromso, Troms og Finnmark, Norway
[3]Department of Community Medicine, UiT The Arctic University of Norway, Tromso, Troms og Finnmark, Norway

Correspondence to
Sigbjørn Svalestuen; sigbjorn.svalestuen@uit.no

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 −0.053 (95% CI −0.066 to −0.039) prescriptions per 100 children. Each additional percentage point in population education contributed a further −0.0034 (95% CI −0.006 to −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 allow 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, 1-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 (eg, 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'

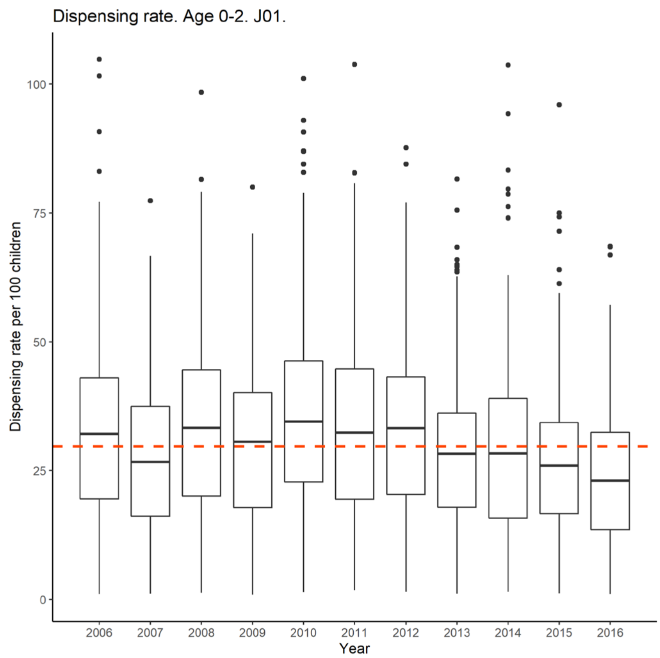

Figure 1 *Box-and-Whisker plot of dispensing rates by year. The dashed line is the grand mean dispensing rate throughout the period. The main takeaway from this figure is the notable variation between municipalities within a specific year. The intraclass correlation coefficient of the null model indicates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

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 versus 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. Online supplemental appendix figure A1 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. First, 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 second, 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 healthcare 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.

Finally, 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.

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 Biesanz *et al*[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 online supplemental appendix and demonstrate the consequences of simultaneous growth on trend estimation in online supplemental 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 online supplemental appendix figure A2 and A3, 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 online supplemental appendix figure A4–A7. 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 online supplemental 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 online supplemental table A2. Table 2 shows summary statistics for the types of antibacterial in the database, together with the total number of defined daily doses dispensed, summarised by year and subgroup. Table 3 presents summary statistics. Online supplemental table A3 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 −0.053 (SD=0.0927, p<0.001). A one percentage point increase in cluster mean education reduces the trend coefficient of the square root dispensing rate by −0.0034 (p=0.0051), *ceteris paribus*. There is, thus, a greater reduction in the dispensing rate in municipalities in which a larger proportion of the population has 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=0.892) in the model. The figure shows that the municipalities with low levels of population education have predicted reductions

Table 1 Multilevel linear growth curve model

Coefficient	$\sqrt{\text{Dispensed Rx per 100 children}}$	P values
Level 1		
Trend	−0.053 (−0.066 to −0.039)	<0.001
Poverty	−0.098 (−0.125 to −0.070)	<0.001
Population (ln)	1.265 (−0.061 to 2.592)	0.062
Level 2		
Education	−0.002 (−0.027 to 0.023)	0.892
Population (ln)	0.408 (0.290 to 0.525)	< 0.001
Poverty	−0.085 (−0.130 to −0.041)	< 0.001
Travel	−0.0003 (−0.0004 to −0.0003)	< 0.001
Trend×Education (L2)	−0.0034 (−0.006 to −0.001)	0.005
Intercept	5.459 (5.340 to 5.578)	< 0.001
Variance components		
Standard deviation. μ_1	.0927	
Standard deviation μ_0	.8647	
Misc.		
ρ Compound symmetry	.000	
Groups	426	
Observations	4503	
Log Likelihood	−6442.764	
Akaike information criterion	12 913.53	
Bayesian information criterion	13 003.3	

95% CI in parentheses.
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.

of approximately two prescriptions per 100 children, while municipalities with comparatively high levels of population education have predicted reductions approximately equal to 10 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.

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

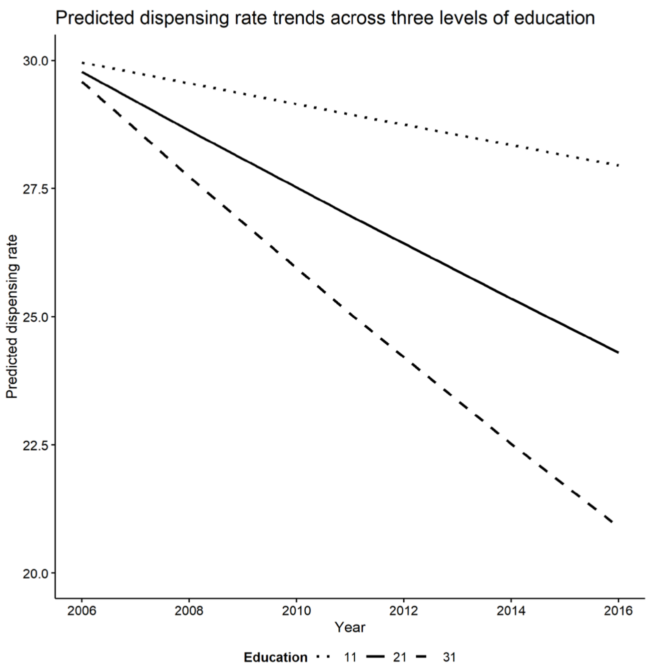

Figure 2 *Predicted cross-level interaction effect between trends and education. The Y-axis displays the dispensing rate on the original scale. The middle line represents the average cluster level of education, while the outer lines are predicted trends for±2 SD from the mean education levels. Predictions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

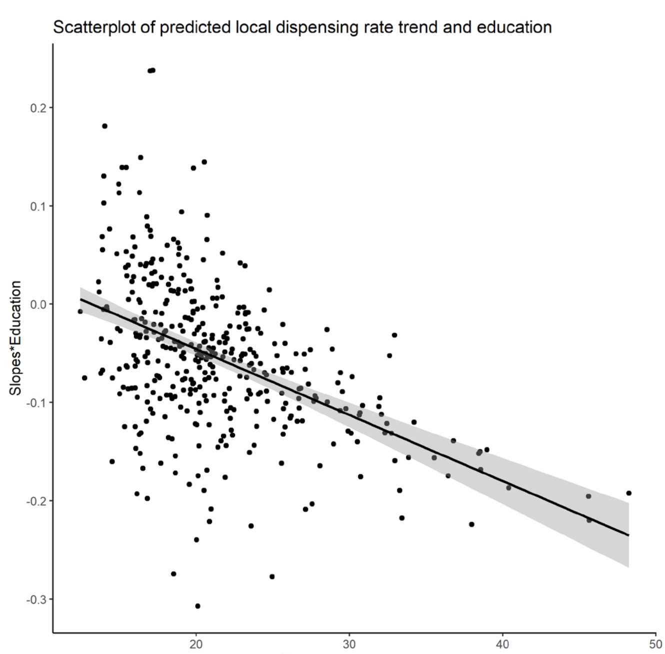

Figure 3 *Predicted slopes by population education. The points are the predicted square roots of the dispensing rate trends for each municipality. All 426 estimated trends are presented and plotted against education on the X-axis. The figure shows that the leaders in dispensing rate reductions also tend 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.*

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 on 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 healthcare system provides universal healthcare access, and health inequalities in care utilisation have diminished over time.[37] Need-adjusted socioeconomic differentiation in healthcare 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 healthcare usage in Norway, such as potential geographic variations, and, importantly, these studies do not include parental healthcare seeking. If parental healthcare seeking translates to paediatric healthcare seeking, healthcare usage may, hypothetically, not be socially determined in volume, but rather in kind. People from advantaged socioeconomic backgrounds may interact and use healthcare inputs more efficiently, thus achieving the same amount of health investment with less healthcare 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 healthcare provided to children is dependent on parental socioeconomic status and how they seek healthcare 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

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

DDD, defined daily dose; 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.

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 healthcare 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. First, we expect education to matter more in the context of primary healthcare, because parents are active participants in healthcare decision-making, and second, the primary healthcare 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

Table 3 Pooled statistics, including summary statistics for yearly observations for all municipalities, before centring

Statistic	N	Mean	Standard deviation	Minimum	Maximum
Dispensed Rx/100 children	4519	29.7	16.3	0.9	104.9
Education	4515	21.2	5.9	9.1	51.9
Population	4519	11 885	35 479	200	658 390
Poverty	4518	10.0	2.4	3.7	21.8
Trend	4519	5.01	3.16	0	10
Travel time (sec)	426	1674	1882	182	13 129

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 online supplemental appendix.

statistics. Further research is necessary to conclude an association between parental education, individual interactions with healthcare 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.

Contributors 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. SS acts as the guarantor. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but Regional Committees for Medical and Health Research Ethics Norway (2018/1021) exempted this study. Exempt from informed consent under the Norwegian Health Research Act. Data on prescriptions are retrospective and routinely collected through a national registry (making informed consent difficult), and the project was deemed valuable for the public. Individual prescription information was only used to calculate municipality dispensing rates and volume. The only information used relating to individual patients were their municipality of residence.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. 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) and are available from the corresponding author upon request.

ORCID iD

Sigbjørn Svalestuen http://orcid.org/0000-0002-4775-311X

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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

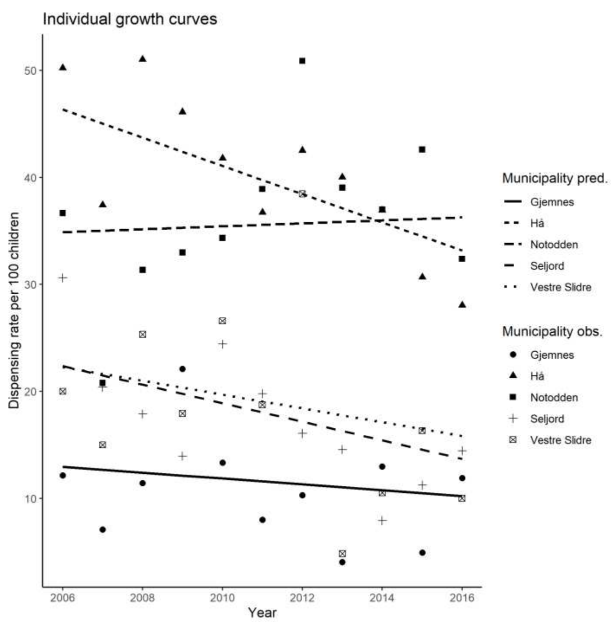

Figure A1: *Linear growth curve predictions and observations from a simple random trend null-model for five random municipalities. Municipalities were randomly sampled from a strata of slope quantiles to ensure that slope variance was represented in the figure. Note that the Y-axis is scaled by min-max 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

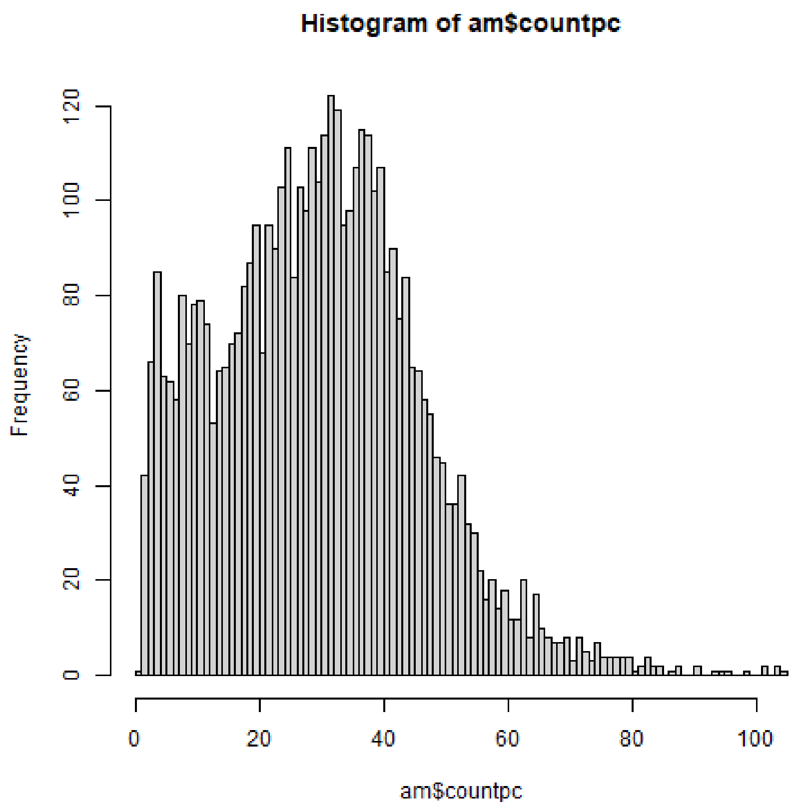

Figure A2: Dispense rate distribution before square root transformation. The distribution is closer to a Poisson distribution, due to the natural bounds of the data.

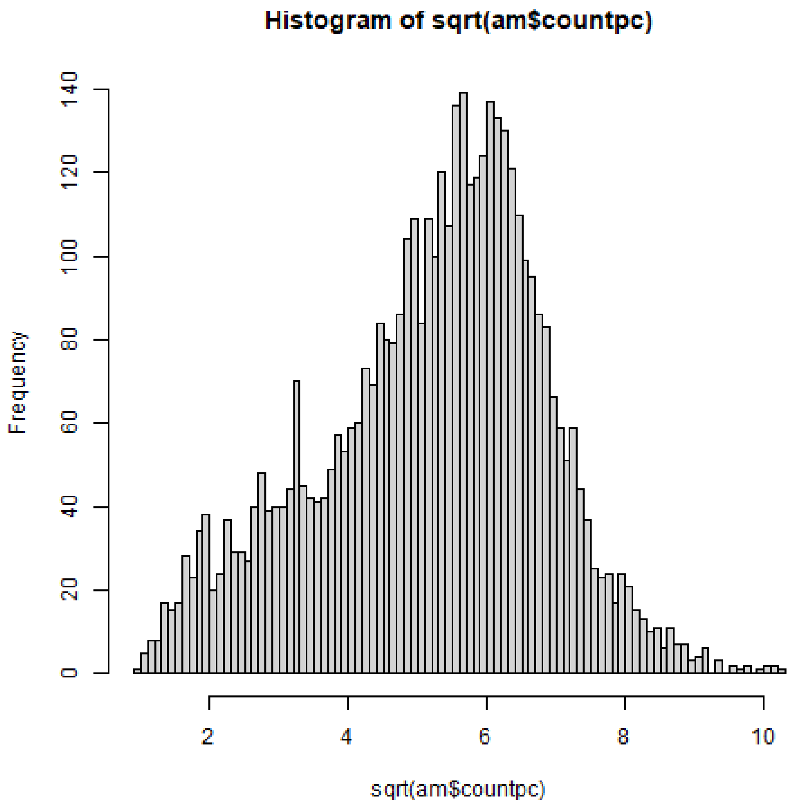

Figure A3: Dispense rate after square root transformation. Where the log-transformation (not shown) aggressively overcorrects the issue, leading to a worse fit than the untransformed version of the model, the square root transformation only moderately corrects the distribution, making residuals more 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.

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Residual plots main model

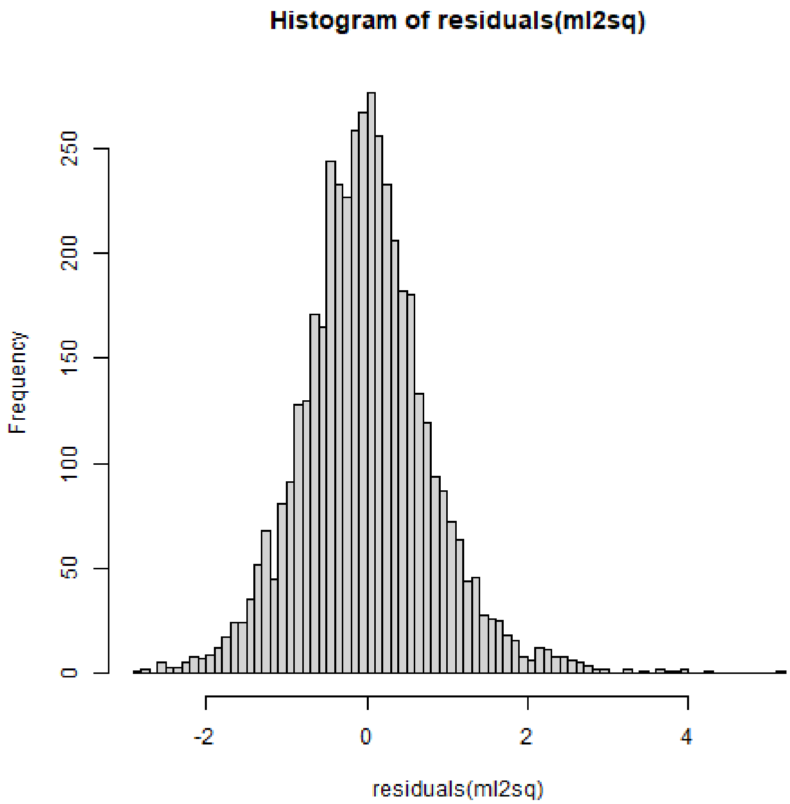

Figure A4: Level 1 Residual distribution after square root transformation of the dependent variable. While a marginally longer tail on positive residuals, we find no particular issues with this distribution.

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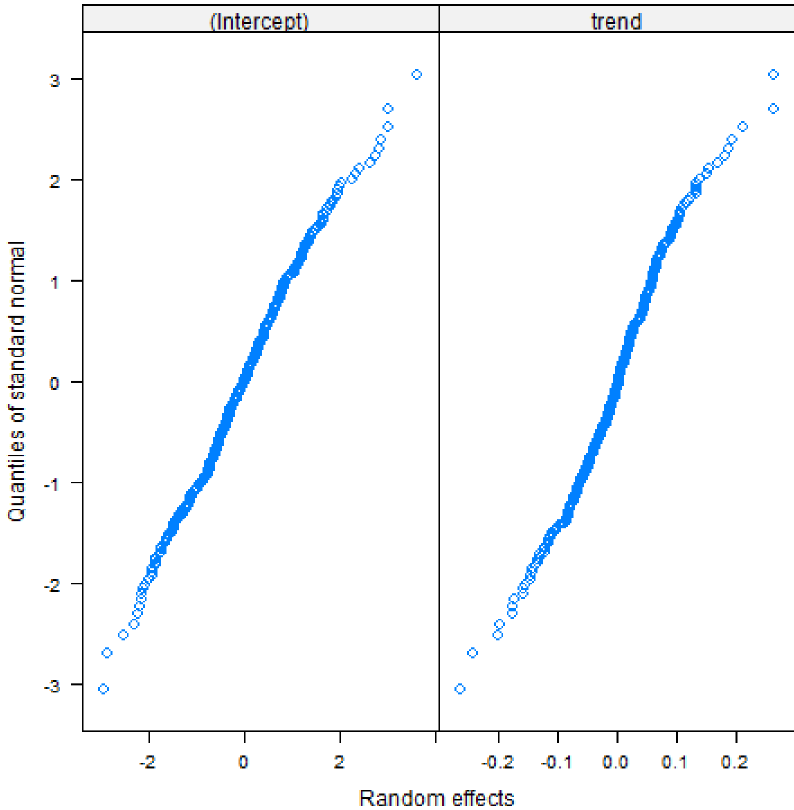

Figure A5: QQ-plot of the random terms in the model. We find that these are approximately normally distributed.

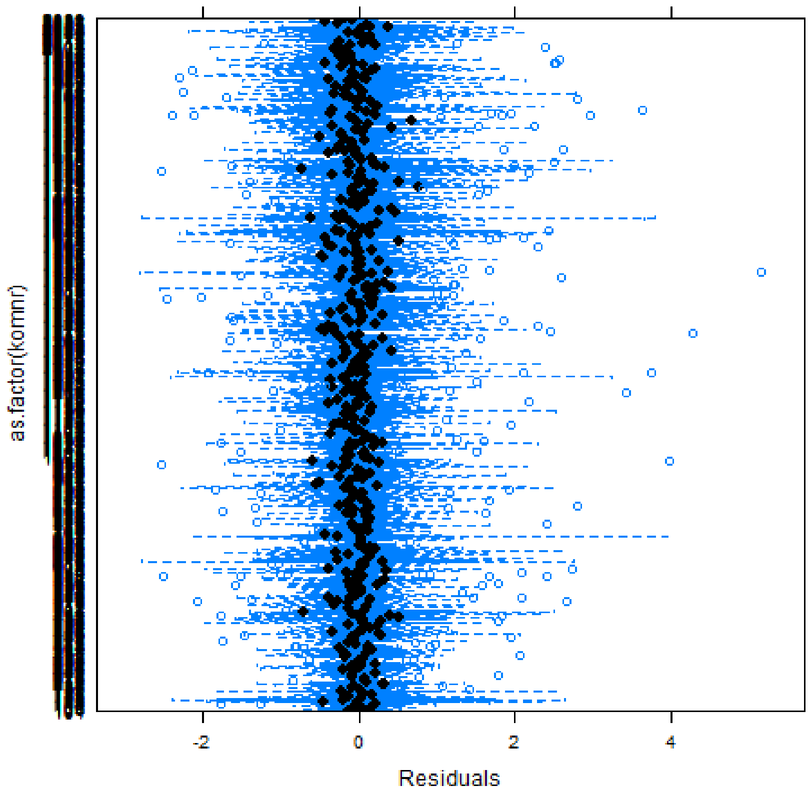

Figure A6: Level-1 residuals by municipality. Residuals seem overall to be centered at 0 with random deviation from this mean. Some differences in variance between municipalities is expected, as the number of repeat observations is relatively small (11).

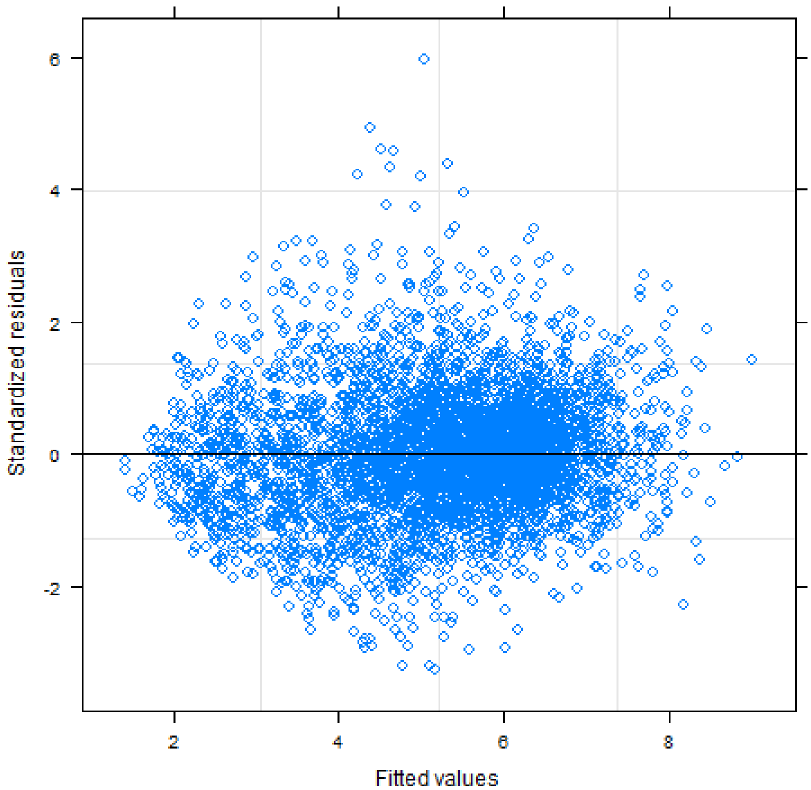

Figure A7: Standardized residuals vs. fitted values plot. We saw some problems with heteroskedasticity in the unadjusted model. While logarithmic transformation aggressively overcorrected the issue, the square root transformation adjusts for the moderate skewness and provides confidence to estimated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

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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.