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Are familial factors underlying the association between socio-economic position and prescription medicine? A register-based study on Danish twins

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Abstract:

Objectives: Although well-established, the association between socio-economic position and health and health behavior is not clearly understood and it has been speculated that familial factors may be underlying the association. The objective was to compare prescription fillings within twin pairs who are partly or fully genetically identical and share childhood exposures.

Design: Twin cohort study.

Setting: Denmark.

Participants: Data from the Danish Twin Registry was linked to registers in Statistics Denmark and the Danish Registry of Medicinal Product statistics. A total of 8582 monozygotic (MZ) and 15,788 dizygotic same sexed (DZSS) twins were included.

Outcome measures: Number of prescription fillings during follow-up (1995-2005) was analyzed according to education and income. Results of unpaired and intra-pair analyses were compared.

Results: An inverse social gradient in filling of prescriptions for all-purpose and system-specific drugs was observed in the unpaired analyses. In the intra-pair analyses, associations were attenuated some in DZSS and more in MZ twins. Filling of CNS-drugs was still strongly associated with income in the intra-pair analyses.

Conclusions: Familial factors seem to account for at least part of the observed social inequality in filling of prescription medicine.

ARTICLE SUMMARY

Article focus

- To investigate if the association between socio-economic factors and filling of drug prescriptions persists after controlling for genetic and childhood factors shared within twins.

Key messages

- The inverse association between socio-economic factors and filling of prescription medicine show substantial attenuation in intra-pair analyses of twins, except for drugs targeting the neurologic system.
- Greater attenuation within monozygotic than dizygotic same sex twins.
- Familial factors seem to account for at least part of the observed social inequality in fillings of prescription medicine.

Strengths and limitations

- This study is based on nation-wide register data covering more than a decade, and we present results from a largely unselected population of more than 8000 monozygotic and 15,000 dizygotic same sexed twins.
- This is the first twin study on health inequalities to report such clear-cut findings with sufficient power for meaningful interpretation of intra-pair analyses and for comparison of zygosity-specific results.
- Prescription fillings are not a perfect measure of health status, but we still argue that it is an inventive and fairly valid indicator in a Danish setting where prescription medicine has to be prescribed by a medical doctor and accounts for 96% of the total drug sale.
- The twin study is clearly a powerful approach, but when interpreting findings alternative explanations for the pattern of attenuation should be considered, including measurement error and unshared confounding. However, in this case we find it unlikely that these potential sources of bias could fully explain our findings.

INTRODUCTION

Social inequalities in health and health behaviour have been widely demonstrated in many societies, including the Scandinavian countries[1]. Often social disparities in health are not confined to the most marginalized groups of society but are expressed as a gradient over the entire spectrum of social stratification[2]. The inverse relationship between socio-economic position (SEP) and health has consistently been observed across different social indicators and for numerous types of health outcomes[3, 4]. Use of prescription medicine is one health-related outcome that has been found to be socially patterned, where Danish data have shown a greater use among people with low SEP compared to people with high SEP[5, 6]. Denmark has a tax financed decentralized health care system with a partly need-dependent reimbursement system for outpatient prescription drugs. All prescription-drugs have to be prescribed by a medical doctor and, compared to a number of other countries, prescription medicine constitute a fairly large proportion of the total drug sale in Denmark (96%)[7]. Many studies have shown substantially reduced social differences in drug use when health status have been taken into account[6, 8, 9], which may indicate that filling of prescription medicine to a large extent reflects health status. This is supported by the fact that comorbidity indices, based on prescription drug dispensings, have been established as strong predictors of mortality[10], and that drug use has proven to be a valid indicator of self-rated health[11, 12]. However, other factors such as health care seeking behaviour and access to health care[13, 14] may also influence drug use, but the social gradient in these factors would, theoretically, be expected to be opposite that of health status, i.e. greater drug use among people with high SEP compared to low SEP. Such a positive association is generally not supported by the existing Danish literature[5, 6, 15].

Although well-established, the inverse association between SEP and health and health behavior is not clearly understood but is likely to be driven via a number of different pathways, including material deprivation, behavioural factors, and psychological factors[16]. It has also been suggested that it is not SEP in adulthood per se that influences health, but underlying familial factors already at play in early life [17, 18].

With the discordant twin pair design, it is possible to investigate the effect of adult SEP on prescription fillings eliminating confounding from factors shared by a pair of twins, exploiting that twins are partly or fully genetically identical and have experienced a similar childhood environment due to their common upbringing. This approach has been applied in a number of previous twin studies investigating different health outcomes, including mortality[19], hospitalizations[20], breast cancer[21], and also softer endpoints such as depression

scores and self-rated health[22, 23]. However, the majority of these studies suffer from power limitations either due to small sample sizes and/or rare outcomes making interpretations difficult.

In this study we aimed to investigate if there was an effect of SEP in adulthood on the number of prescription fillings above and beyond the effect of shared familial factors. Filling of prescription medicine is a quantitative health measure rendering sufficient power for the intra-pair comparisons. Differences in genetic relatedness between monozygotic (MZ) (genetically identical) and dizygotic (DZ) twins (share on average 50% of segregating genes) may further give an indication of the possible types of confounding (i.e. genetic or environmental factors). In a theoretical situation of no measurement error and no confounding from unshared factors, genetic confounding would be indicated if an observed social gradient in prescription medicine was partly attenuated in DZ twins and fully attenuated in MZ twins, when shared familial factors had been taken into account. Likewise, an attenuation of similar size in DZ and MZ twins would be compatible with shared environmental confounding. Finally, to support a SEP-effect on prescription fillings not due to confounding from shared familial factors, the association would have to persist in both DZ and MZ twins.

To support the utility of prescription medicine as a health indicator we also analysed its association with mortality.

METHODS

Study population

Data from the Danish Twin Registry was linked with information in the Danish Registry of Medicinal Products and administrative registers in Statistics Denmark. The study population consisted of 24 370 twins, including 8582 monozygotic and 15 788 dizygotic same sex twins (DZSS), who were born during 1921-1965 and alive and resident in Denmark at the beginning of follow-up (January 1 1995), after exclusions due to triplets (n=384) unknown zygosity (UZ) (n=3731), and dizygotic opposite sex pairs (DZOS) (n=16 710), missing data on education or income (n=845), and non-intact twin pairs in which one twin was dead, emigrated, or had missing information (n=2847). To evaluate the representativeness of the results from the unpaired twin analyses, we also analysed a 5% population-based sample of the Danish population (n=137 300).

Social indicators

We used information on highest attained education in 1995 at age 30+ of the study population, categorized according to the International Standard Classification of Education of 1997[24] into: primary/lower secondary education (basic compulsory education), upper secondary education (secondary), and tertiary education (Bachelor's degree and above). Income was measured as an average of the equivalised gross household income (Danish currency) in 1994-1995, grouped into quartiles within each birth cohort. "Equivalised" income is adjusted to take into account that households can share resources. Inspired by the standard OECD equivalence scale[25], the household-denominator was constructed according to an equivalence scale that assigned a value of 1 to the first household member, of 0.7 to the second household member and of 0.5 to each additional household member.

Prescription medicine

The Danish Registry of Medicinal Products contains information on the total sale of prescription medicine in Denmark registered by the pharmacies via a computerized accounting system. The drug information is recorded according to the Anatomical Therapeutic Chemical classification system (ATC)[26] where the active substances in drugs are divided into different groups, primarily according to the organ system on which they act. Other information includes date of dispensing and *daily defined doses* (DDD), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults[26]. Outcomes of interest were

defined as the number of prescription fillings during follow-up for all-purpose medication (excluding the ATC-groups Q, which is for veterinary use, and G02B and G03A, which are for contraceptive use) and four groups of system-specific medication: ATC-C (circulatory system), ATC-N (nervous system), ATC-R (respiratory system) and ATC-A (alimentary tract/metabolism). If no ATC-code was assigned a prescription, it was excluded (1%). DDD was used as a supplementary outcome measure.

Other covariates

Sex and age were included in the analyses. Analyses were performed separately for MZ and DZSS twins. Zygosity had previously been determined by questionnaire[27], a method that has proven valid with an overall misclassification frequency of less than 5% validated against a classification based on genetic markers [28].

Data analysis

Analyses were carried out using Cox regression for recurrent events (proportional means regression), thereby accommodating multiple events (prescription fillings) per individual[29]. Age was used as underlying time-variable and subjects were followed from age at baseline to the age at end of follow-up (Dec 31 2005) or death or emigration, and the timing of each prescription filling during this period was recorded. Both unpaired and intra-pair analyses were performed. In the unpaired analyses robust standard errors were used to account for the interdependence of observations within pairs and within each individual. Results of the unpaired analyses were compared to the intra-pair analyses, which were performed using a stratified Cox model: $EN_{ij}(t)=\mu_{0j}(t)e^{\beta' z\_ij}$. Here $EN_{ij}(t)$ denotes the mean number of prescription fillings at time *t* for an individual *i* belonging to twin pair *j*, $\mu_{0j}(t)$ is the pair-specific baseline mean, and e^{β} is the effect of the covariates adjusted for shared familial factors. Thus, in this analysis the mean number of prescription fillings were compared within twin pairs, thereby controlling for familial factors shared within a pair of twins. In the stratified model only SEP-discordant twin pairs contribute information to the beta-parameter for SEP, although concordant pairs may contribute information to other beta-parameters.

As counting process models do not allow simultaneous events, only one prescription of interest per day was included in the analysis.

Analyses were performed separately for zygosity and sex, and potential interactions between the social indicators and zygosity, sex, and age, respectively, were evaluated by including interaction terms in the models

and using Wald test-statistics. To analyse the association between prescriptions and mortality, we used a Cox regression model, continuously updating the number of prescription fillings over time.

Subanalyses

Since DDD may reflect the actual drug use more precisely than number of prescription fillings, mean DDD were also analysed by means of a fixed-effects linear regression model taking censoring into account[30]. This was treated as a subanalysis due to the highly right-skewed distribution of DDD, making linear regression a less optimal choice of model.

Permission for linkage and use of data for this study was obtained from the Danish Data Protection Board (2000-54-0047).

RESULTS

According to table 1, showing the distribution of education and income in the population, men were better educated than women. Generally, the education of the twin population was comparable to that of the population-based sample. Only UZ twins had a markedly lower educational status and a higher proportion of missing information. The table also shows the mean income within each quartile. Twins have a somewhat higher mean income compared to the population-based sample

Table 1: Descriptives on Educational Status and Income in a 5% Population Based Sample (n=144749) and a Population of Danish Twins (n=48887), Including Intact and Non-intact Twin Pairs, Stratified on Sex and Zygosity.

	5% population sample				All twins (n=48887)				DZSS (n=18426)		MZ (n=9636)		DZOS (n=16710)		UZ (n=3731)	
Sex	N	%[a]	Mean	SD	n	%[a]	Mean	SD	n	%[a]	n	%[a]	n	%[a]	n	%[a]
Educational status[b]																
Men																
Primary	23550	32			8909	35			3553	36	1517	31	2882	34	957	43
Secondary	31336	43			11237	44			4309	44	2292	47	3834	45	802	36
Tertiary	13722	19			4515	18			1685	17	963	20	1530	18	337	15
Missing	4072	6			800	3			310	3	128	3	208	2	154	7
Total	72680	100			25461	100			9857	100	4900	101	8454	99	2250	101
Women									3857	45	1903	40	3633	44	789	53
Primary	31215	43			10182	44			2868	34	1730	37	2807	34	400	27
Secondary	23809	33			7805	34			1696	20	1004	21	1705	21	208	14
Tertiary	14229	20			4613	20			148	2	99	2	111	1	84	6
Missing	2816	4			442	2			8569	101	4736	100	8256	100	1481	100
Total	72069	100			23042	100			3553	36	1517	31	2882	34	957	43
									4309	44	2292	47	3834	45	802	36
Income (DKK)																
Men																
1st quartile	17348	24	88537	28373	5931	24	92330	27563	2251	23	1061	22	1929	23	690	31
2nd quartile	17510	24	145676	25887	6523	24	149367	24179	2563	26	1208	25	2201	26	551	24
3rd quartile	17976	25	191360	34863	6769	25	196738	31365	2612	27	1375	28	2246	27	536	24
4th quartile	18228	25	311232	141784	5960	25	314180	225459	2340	24	1218	25	2006	24	396	18
Missing	1618	2			278	2			91	1	38	1	72	1	77	3
Total	72680	100			25461	100			9875	101	4900	101	8454	101	2250	100
Women									2174	25	1158	24	2200	27	538	36
1st quartile	18958	26	88201	26316	6070	26	91205	25698	2316	27	1222	26	2186	27	353	24
2nd quartile	18219	25	142746	27689	6077	25	146427	25562	2152	25	1224	26	2106	26	313	21
3rd quartile	17753	25	18942	36067	5795	25	194968	33291	1882	22	1097	23	1730	21	232	16
4th quartile	16126	22	308876	225888	4941	22	312063	173113	45	1	35	1	34	0	45	3
Missing	1013	1			159	1			8569	100	4736	100	8256	101	1481	100
Total	72069	99			23042	99			2251	23	1061	22	1929	23	690	31

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; DZOS=Dizygotic opposite sex twins; UZ=Unknown zygosity, [a]May not sum to 100 because of rounding, [b]International Standard Classification of Education, [c]Average of equvalized gross household income in 1994-1995 in quartiles. DKK=Danish Crowns.

The proportion of education-discordant twin pairs was 30% for MZ twins and 42% for DZSS twins, while 61% MZ twins and 68% DZSS twins were discordant on income (table 2).

Table 2: Descriptives on Intra-Pair Discordances on Educational Status and Income, Stratified on Zygosity in a Population of Danish Twins (n=24370).

	DZSS (n=15788)		MZ (n=8582)	
	n	%[a]	n	%[a]
Educational status				
Primary vs Secondary	3590	23	1460	17
Primary vs Tertiary	900	6	316	4
Secondary vs Tertiary	2194	14	820	10
Any discordance	6684	42	2596	30
Income				
1st quartile vs 2nd quartile	2048	13	1072	12
1st quartile vs 3rd quartile	1706	11	754	9
1st quartile vs 4th quartile	1158	7	490	6
2nd quartile vs 3rd quartile	2266	14	1194	14
2nd quartile vs 4th quartile	1574	10	682	8
3rd quartile vs 4th quartile	2000	13	1080	13
Any discordance	10 752	68	5272	61

DZSS=Dizygotic same sexed twins; MZ=Monozygotic twins; [a]May not sum to 100 because of rounding.

In the twin population, 1.9% did not redeem any drug prescriptions during the total follow-up period and 25% redeemed less than one prescription/year, on average (results not shown). Overall, women filled more prescriptions than men for all age groups and the number of prescription fillings increased with age in both sexes (table 3).

Table 3: The Mean Number of Prescription Fillings After 1 and 10 Years of Follow-up in a 5% Population Based Sample and a Population of Danish Twins, Stratified on Age and Sex.

Type of drugs	**Nelson Aalen Cumulative Hazard**			
Age				
Sex	5 % pop. (n= 137 300)		Twins (n=24 370)	
All purpose	*1 year*	*10 years*	*1 year*	*10 years*
30-44 years				
Men	2.5	28.7	2.2	25.9
Women	4.1	44.5	3.8	41.1
45-59 years				
Men	3.6	47.4	3.3	43.1
Women	6.0	71.9	5.7	68.4
60+ years				
Men	6.4	87.5	5.8	82.2
Women	8.3	105.4	7.2	95.7
Circulatory system (ATC-C)				
30-44 years				
Men	0.1	3.3	0.1	2.9
Women	0.2	4.2	0.2	3.6
45-59 years				
Men	0.7	12.6	0.6	10.6
Women	0.8	13.8	0.7	13.0
60+ years				
Men	1.9	29.6	1.7	27.4
Women	1.9	30.0	1.6	26.7
Nervous system (ATC-N)				
30-44 years				
Men	0.8	9.8	0.7	8.6
Women	1.1	14.5	1.0	13.3
45-59 years				
Men	1.2	14.6	1.2	13.9
Women	2.1	25.0	2.0	24.1
60+ years				
Men	1.8	24.4	1.6	22.2
Women	3.1	39.2	2.7	35.8
Respiratory system (ATC-R)				
30-44 years				
Men	0.3	3.9	0.3	3.6
Women	0.6	6.5	0.5	5.7
45-59 years				
Men	0.5	5.8	0.4	5.0
Women	0.8	9.8	0.7	9.1
60+ years				
Men	1.1	14.4	0.9	12.5
Women	1.2	14.8	1.0	12.8
Alimentary tract & metabolism (ATC-A)				
30-44 years				
Men	0.3	3.5	0.2	3.1
Women	0.4	5.0	0.4	4.1
45-59 years				
Men	0.5	7.6	0.5	6.6
Women	0.7	9.6	0.7	8.6
60+ years				
Men	1.1	15.4	1.1	15.0
Women	1.3	18.3	1.0	16.4

ATC-N drug prescriptions were the most frequently redeemed in the youngest age group. The mean number of prescription fillings in the twin population was similar to that in the population-based sample, although slightly higher in the population-based sample.

The results of an analysis of the association between SEP and prescription fillings for all-purpose and system-specific drugs are presented in table 4.

Table 4: The ratio (MR) of the mean number of prescription fillings (1995-2005) for all-purpose and system-specific drugs according to educational status and income in a 5% population-based sample (137 300) and a population of Danish twins (n=24 370), showing results from unpaired and intra-pair analyses stratified on zygosity.

Type of drug	**Unpaired analysis[a]**						**Intra-pair analysis[b]**			
Income Educational status	Pop % n=137300		DZSS n=15788		MZ n=8582		DZSS		MZ	
	MR	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*
All purpose										
Secondary	**0.90**	0.90-0.90	**0.90**	0.86-0.95	**0.87**	0.81-0.93	**0.88**	0.84-0.93	0.97	0.91-1.03
Tertiary	**0.82**	0.82-0.83	**0.85**	0.80-0.91	**0.83**	0.76-0.90	**0.86**	0.80-0.92	0.95	0.86-1.05
2nd quartile	**0.78**	0.78-0.78	**0.81**	0.76-0.85	**0.81**	0.75-0.88	**0.86**	0.82-0.91	**0.91**	0.85-0.97
3rd quartile	**0.72**	0.72-0.73	**0.72**	0.69-0.77	**0.74**	0.69-0.80	**0.79**	0.75-0.83	**0.87**	0.81-0.94
4th quartile	**0.70**	0.70-0.70	**0.71**	0.67-0.75	**0.70**	0.65-0.77	**0.76**	0.72-0.81	**0.87**	0.81-0.94
Circulatory system (ATC-C)										
Secondary	**0.95**	0.95-0.96	**0.92**	0.85-0.99	**0.87**	0.78-0.96	**0.85**	0.79-0.92	**0.89**	0.81-0.97
Tertiary	**0.79**	0.79-0.80	**0.78**	0.71-0.87	**0.70**	0.60-0.82	**0.80**	0.71-0.90	0.93	0.79-1.08
2nd quartile	**0.91**	0.90-0.91	**0.94**	0.87-1.03	0.94	0.84-1.06	1.08	0.99-1.17	0.95	0.87-1.05
3rd quartile	**0.83**	0.83-0.84	**0.86**	0.78-0.94	**0.86**	0.76-0.97	0.97	0.89-1.06	0.98	0.89-1.08
4th quartile	**0.79**	0.79-0.79	**0.82**	0.74-0.90	**0.85**	0.74-0.97	0.97	0.88-1.08	0.94	0.84-1.05
Nervous system (ATC-N)										
Secondary	**0.80**	0.80-0.80	**0.87**	0.79-0.96	**0.77**	0.67-0.88	**0.85**	0.77-0.94	1.00	0.86-1.17
Tertiary	**0.71**	0.71-0.71	**0.77**	0.67-0.88	**0.75**	0.61.0.92	**0.78**	0.67-0.90	0.91	0.73-1.16
2nd quartile	**0.61**	0.60-0.61	**0.61**	0.55-0.68	**0.60**	0.52-0.70	**0.68**	0.61-0.75	**0.75**	0.67-0.87
3rd quartile	**0.49**	0.49-0.50	**0.47**	0.43-0.53	**0.47**	0.39-0.56	**0.54**	0.48-0.61	**0.59**	0.50-0.70
4th quartile	**0.44**	0.44-0.44	**0.45**	0.40-0.51	**0.42**	0.35-0.50	**0.50**	0.45-0.57	**0.60**	0.50-0.71
Respiratory system (ATC-R)										
Secondary	**0.86**	0.85-0.86	**0.77**	0.67-0.87	**0.82**	0.69-0.98	**0.83**	0.72-0.94	1.00	0.84-1.21
Tertiary	**0.81**	0.80-0.81	**0.79**	0.68-0.92	**0.76**	0.61-0.95	**0.80**	0.66-0.97	0.77	0.58-1.03
2nd quartile	**0.76**	0.75-0.76	**0.76**	0.66-0.87	**0.79**	0.65-0.98	**0.86**	0.75-0.99	1.04	0.86-1.25

3rd quartile	**0.68**	0.68-0.69	**0.74**	0.64-0.86	**0.69**	0.57-0.85	**0.85**	0.73-0.98	1.02	0.84-1.24
4th quartile	**0.63**	0.63-0.63	**0.69**	0.59-0.81	**0.64**	0.52-0.79	**0.83**	0.71-0.96	1.25	1.04-1.51
Alimentary tract & metabolism (ATC-A)										
Secondary	**0.84**	0.84-0.84	**0.85**	0.77-0.94	**0.81**	0.71-0.93	**0.84**	0.75-0.94	0.98	0.85-1.14
Tertiary	**0.68**	0.67-0.68	**0.71**	0.62-0.82	**0.64**	0.53-0.77	**0.81**	0.68-0.96	0.94	0.76-1.17
2nd quartile	**0.74**	0.74-0.75	**0.73**	0.65-0.81	**0.83**	0.72-0.96	**0.85**	0.76-0.96	0.88	0.77-1.01
3rd quartile	**0.64**	0.64-0.65	**0.63**	0.56-0.71	**0.77**	0.66-0.90	**0.77**	0.68-0.87	0.87	0.75-1.02
4th quartile	**0.61**	0.61-0.61	**0.60**	0.53-0.68	**0.65**	0.55-0.77	**0.76**	0.67-0.88	0.86	0.72-1.02

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; [a]Unpaired analysis treating twins as individuals while taking interdependence of observations within each individual and within twin pairs into account. The interpretation of MR is the ratio of the mean number of prescriptions at a given time of e.g. an individual with a secondary or tertiary education compared to a random individual with a primary education. MRs are adjusted for age and sex. Income and education are mutually adjusted, [b]Intra-pair analysis of twins by inclusion of a strata statement. The interpretation of MR is the ratio of the mean number of prescriptions at a given time of a twin with a secondary or tertiary education compared to its co-twin with a primary education. Bold typography indicates statistical significance at 5% level.

For all-purpose drugs, MZ twins in the highest income quartile had a 30% lower mean number of prescription fillings than MZ twins in the lowest income quartile (MR=0.70 (CI 95%; 0.65,0.77). Similarly, MZ twins with a tertiary education had 17% lower mean number of prescription fillings than twins with a primary education (MR=0.82 (CI 95%: 0.75,0.89)). The association was slightly less strong for ATC-C drugs while stronger associations could be observed for the other system-specific drugs, particularly for ATC-N. In the unpaired analyses, no large differences could be observed between MZ and DZSS twins and there was no strong evidence for an interaction between SEP and zygosity in the unpaired analysis (education: *P*=0.81, income: *P*=0.95). In contrast, the effect of SEP was moderated by zygosity in the intra-pair analyses (education: *P*=0.02, income: *P*=0.05), suggesting a more attenuated effect of SEP in MZ twins than in DZSS twins: In MZ twins, generally no statistically significant effect of education could be observed, while income was still somewhat associated with all-purpose medication and quite strongly with ACT-N drugs. In DZSS twins, a minor or moderate attenuation could be observed, and all effect parameters were statistically significant, except for ATC-C drugs. In the population-based sample, the associations were similar to that in the overall twin population.

When using DDD (for all-purpose drugs) as outcome measure (table 5), results similar to the results based on number of prescription fillings were obtained, although the attenuation patterns in MZ twins were somewhat more clear in this analysis, showing no statistically significant associations with DDD of neither education nor income. In the analysis of number of prescriptions as a predictor of mortality we found a 60% increase in mortality rate during follow-up for a person who, on average, filled 1 prescription per month during the follow-up period compared to a person without any prescription fillings (HR=1.60 (95% CI: 1.25,2.05).

Table 5: Results from a Linear Regression Model Showing Number of Daily Defined Doses (DDD) for All-Purpose Drugs According to Educational Status and Income in a Population of Danish Twins (n=24370) Stratified on Zygosity. Results from Unpaired and Intra-Pair Analyses are Shown.

Educational status	**Unpaired analysis[a]**				**Intra-pair analysis[b]**			
Income	**DZSS n=15788**		**MZ n=8582**		DZSS		MZ	
	DDD	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*
Secondary	**-287**	-397;-177	**-289**	-440;-138	**-245**	-399;-90	-143	-346;59
Tertiary	**-404**	-531;-277	**-424**	-606;-243	**-344**	-557;-131	-152	-440;136
2nd quartile	**-401**	-541;-260	**-275**	-463;-88	**-219**	-383;-54	18	-177;214
3rd quartile	**-541**	-680;-402	**-451**	-638;-263	**-367**	-535;-198	-83	-287;121
4th quartile	**-505**	-648;-363	**-437**	-630;-243	**-327**	-512;-142	16	-209;242

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; [a]Unpaired analysis treating twins as individuals while taking interdependence of observations within each individual and within twin pairs into account. The interpretation of e.g. the education estimate is difference in the mean number of DDDs of an individual with a secondary or tertiary education compared to a random individual with a primary education. The estimates are adjusted for age and sex. Income and education are mutually adjusted [b]Intra-pair analysis of twins by inclusion of a fixed-effect statement. The interpretation of e.g. the education estimate is the difference in the mean number of DDDs of a twin with a secondary or tertiary education compared to its co-twin with a primary education. Bold typography indicates statistical significance at 5% level.

DISCUSSION

In this large Danish twin population we demonstrated an inverse social gradient in fillings of prescription medicine for all-purpose and system-specific drugs. That is, a greater use of prescription medicine among those with a low SEP, in spite of their limited financial means, thus suggesting a worse health status of this group. These marginal findings are in accordance with previous Danish studies reporting an inverse social gradient in drug use[5, 6]. In the intra-pair analyses, where shared familial factors were controlled for per design, the association attenuated to a wide extent within MZ twins and somewhat less in DZSS twins. For education, there was generally no association with prescription fillings in MZ twins, except for drugs targeting the neurologic system. For income, there was still some association with all purpose and most system-specific drugs. However, no effect of income was seen in the intra-pair analyses when DDD were used as outcome measure. In spite of some variations between system-specific drugs, the overall pattern was the same as for all-purpose drugs, except for ATC-N drugs and to a lesser degree ATC-A drugs, which still showed some effect of SEP in the intra-pair analyses.

The finding of greatest attenuation in MZ twins is compatible with the scenario of genetic confounding, since MZ twins are genetically identical in contrast to DZSS twins who share on average 50% of their segregating genes. However, a number of things should be kept in mind when interpreting these findings.

First of all, part of the observed attenuation is likely caused by measurement error. Measurement error is random and therefore not shared by twins. In the intra-pair analysis, variance due to shared factors is removed, and a relatively larger proportion of exposure variance is thus due to measurement error. This will result in increasing attenuation of parameter estimates in the intra-pair analyses with increasing correlation in exposure[31], thus being most pronounced in MZ twins. However, using data from official registers it can be expected that education and income have very limited measurement error. In addition, the intra-pair correlation of education and income is not that different between MZ and DZ twins in this population and seems insufficient to explain the greater attenuation observed in MZ twins.

Twin studies generally rely on the equal environment assumption. That is, MZ and DZ twins share their environment equally. If this is does not hold, i.e. if MZ twins not only share their genes but also their

environment more closely than DZ twins[32], shared environmental factors could also produce a greater attenuation of effect in MZ twins.

In addition, twins' behaviours could be affected in reaction to each other, i.e. social interaction either by imitation or differentiation. The implications of a potential imitation could be smaller within-pair differences, which could be misinterpreted as confounding from underlying background factors. This may be of some concern in this study since fillings of prescription medicine is likely to have a behavioural component.

Another implication of the discordant twin pair approach is that only twin pairs who are discordant on exposure contribute with statistical information to the estimation of SEP-effects in the intra-pair analysis. This could potentially induce bias in the comparison of the unpaired and intra-pair analysis, since the two analyses are based on essentially different populations. Since MZ twins are less likely to be discordant, the selection bias may be most severe in MZ twins[33]. We examined this concern by restricting the unpaired analysis only to include groups with exposure-discordant twins. Results were similar in both MZ and DZ twins.

A further issue relates to the fact that twins who are discordant on exposure are special in the sense that they, in spite of overlapping genes and rearing environment, differ in their SEP. Thus, unshared factors are likely to explain these differences. This implies that the intra-pair analysis may still be confounded by unshared confounding factors, and that this confounding may be enforced in the intra-pair analysis[31]. Generally, confounding from unshared factors is thought to be more severe when confounders are less correlated than exposure[31]. This may or may not be true in our case, since we can only hypothesize on the correlation of unmeasured confounders. Nevertheless, education and income are less correlated than phenotypes like cognitive ability[34] and BMI[35] which have previously been investigated using similar designs. In any case, as shown by Frisell et al. (2012) in order for *increased* confounding to explain the *attenuation* of the association observed in this study, the potential non-shared confounders would have to create a positive association between education and prescription fillings. In most cases, however, we would expect a negative association, although filling of prescription medicine is indeed a complex health outcome and it is theoretically possible for a confounder to have a dual effect on prescription fillings by increasing the capability of getting the relevant prescriptions, while at the same time reducing the need for prescription fillings. Nevertheless, health status does seem to be the main

determinant of prescription medicine[10, 36, 37] and was clearly associated with mortality in this data. Thus, in the presence of non-shared confounding we would expect the net effect of any confounding to produce a negative association between education and prescription fillings resulting in bias away from the null[31]. This could not explain the observed attenuation of effect in the intra-pair analyses observed in this study.

As mentioned earlier, fillings of prescription medicine is not a perfect measure for health status, but we argue that the observed inverse relationship with education and income likely reflects a greater need for medicine among people of lower SEP. In case that access to health care also plays a role, presumably favouring people of high SEP, the social gradient in health status in this study could be underestimated. Although data did not contain information on over-the-counter (OTC) medication, it only constitutes a small part of the total drug consumption in Denmark, and since we were interested in drugs as an indicator of health status, it could be argued that the most valid approach is to focus on drugs that require a formal medical indication (i.e. prescription).

The finding of a persistent association with fillings of prescriptions for ATC-N drugs clearly stood out from the general results. The possible explanation for this could be reverse causation, i.e. that poor health status affects ones income and not the other way around. Income is much more sensitive to reverse causation than education, which is usually obtained early in life and remains constant once it is obtained. It is likely that health conditions requiring prescriptions for ATC-N drugs may affect the work ability and income of a person.

As models for counting processes only allow one event at a time, the number of prescription fillings was defined as the main outcome of interest. Therefore, it was reassuring that the subanalysis on DDD led to similar results.

Although the distribution of SEP-indicators and prescription fillings were not entirely identical in twins and the population-based sample, the associations between SEP and prescription fillings were indeed, which supports generalizability to the general population in line with previous studies that show that health and mortality in twins are similar to the background population[38, 39]. Furthermore, the fact that the analysis based only on discordant twin pairs show marginal results similar to those based on the total twin sample was reassuring.

In this study based on a comprehensive twin cohort we observed a social inequality in fillings of prescription medicine, showing fewer prescription fillings among people with high SEP. This association attenuated within twin pairs for most types of prescription-fillings, except those targeting the neurologic system. The attenuation was most pronounced in MZ twins. Several explanations may account for these findings. Measurement error can contribute to the observed attenuation of association, but it is likely to account only for a small fraction, considering the exposure and outcome measures in this study. As for potential non-shared confounding we would, if anything, expect it to bias the estimates away from the null. We therefore interpret the findings of this study as an indication that at least a part of the observed social inequality in prescription fillings is explained by shared familial factors. Previous studies have investigated the association between various SEP-indicators and health outcomes. However, most studies suffered from severe power limitations in the intra-pair analyses due to a small number of events[19, 21, 23, 40, 41]. This is not a concern in this study, where almost all of the 24 370 twins contributed with information to the intra-pair analyses, thus providing some of the most powerful twin results on social inequality in health to date.

COMPETING INTERESTS

None.

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CONTRIBUTORSHIP

KC and MO formulated the original study idea and provided funding. MM, KC, MO and A-MNA further developed the study idea and design of the study. MM carried out the data analyses in collaboration with PKA and MG. All authors participated in interpretation and discussion of the findings. MM drafted the first version of the manuscript, but all authors have contributed to the revisions and have approved the final version of the paper.

DATA SHARING

There are no additional data.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

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Are familial factors underlying the association between socio-economic position and prescription medicine? A register-based study on Danish twins

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Are familial factors underlying the association between socio-economic position and prescription medicine? A register-based study on Danish twins

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ABSTRACT

Objectives: Although well-established, the association between socio-economic position and health and health behavior is not clearly understood, and it has been speculated that familial factors, e.g. dispositional factors or exposures in the rearing environment, may be underlying the association. The objective was to compare prescription fillings within twin pairs who are partly or fully genetically identical and share childhood exposures.

Design: Twin cohort study.

Setting: Denmark.

Participants: Data from the Danish Twin Registry was linked to registers in Statistics Denmark and the Danish Registry of Medicinal Product statistics. A total of 8582 monozygotic (MZ) and 15,788 dizygotic same sexed (DZSS) twins were included.

Outcome measures: Number of prescription fillings during follow-up (1995-2005) was analyzed according to education and income. Results of unpaired and intra-pair analyses were compared.

Results: An inverse social gradient in filling of prescriptions for all-purpose and system-specific drugs was observed in the unpaired analyses. In the intra-pair analyses, associations were attenuated some in DZSS and more in MZ twins. Filling of drugs targeting the nervous system was still strongly associated with income in the intra-pair analyses.

Conclusions: Familial factors seem to account for part of the observed social inequality in filling of prescription medicine.

ARTICLE SUMMARY

Article focus

- To investigate if the association between socio-economic factors and filling of drug prescriptions persists after controlling for genetic and childhood factors shared within twins.

Key messages

- The inverse association between socio-economic factors and filling of prescription medicine show substantial attenuation in intra-pair analyses of twins, except for drugs targeting the nervous system.
- Greater attenuation within monozygotic than dizygotic same sex twins.
- Shared familial factors seem to account for at least part of the observed social inequality in fillings of prescription medicine.

Strengths and limitations

- This study is based on nation-wide register data covering more than a decade, and we present results from a largely unselected population of more than 8000 monozygotic and 15,000 dizygotic same sexed twins.
- This is the first twin study on health inequalities to report such clear-cut findings with sufficient power for meaningful interpretation of intra-pair analyses and for comparison of zygosity-specific results.
- Prescription fillings are not a perfect measure of health status, but we still argue that it is an inventive and fairly valid indicator in a Danish setting where prescription medicine has to be prescribed by a medical doctor and accounts for 96% of the total drug sale.
- The twin study is clearly a powerful approach, but when interpreting findings, alternative explanations for the pattern of attenuation should be considered, including measurement error and unshared confounding. However, in this case we find it unlikely that these potential sources of bias could fully explain our findings.

INTRODUCTION

Social inequalities in health and health behaviour have been widely demonstrated in many societies, including the Scandinavian countries[1]. Often social disparities in health are not confined to the most marginalized groups of society but are expressed as a gradient over the entire spectrum of social stratification[2]. The inverse relationship between socio-economic position (SEP) and health has consistently been observed across different social indicators and for numerous types of health outcomes[3, 4]. Use of prescription medicine is one health-related outcome that has been found to be socially patterned, where Danish data have shown a greater use among people with low SEP compared to people with high SEP[5, 6]. Denmark has a tax financed decentralized health care system with a partly need-dependent reimbursement system for outpatient prescription drugs. All prescription-drugs have to be prescribed by a medical doctor and, compared to a number of other countries, prescription medicine constitute the majority of the total drug sale in Denmark (app. 90%)[7]. Many studies have shown substantially reduced social differences in drug use when health status have been taken into account[6, 8, 9], which may indicate that filling of prescription medicine to a large extent reflects health status. This is supported by the fact that comorbidity indices, based on prescription drug dispensings, have been established as strong predictors of mortality[10], and that drug use has proven to be a valid indicator of self-rated health[11, 12]. However, other factors such as health care seeking behaviour and access to health care[13, 14] may also influence drug use, but the social gradient in these factors would, theoretically, be expected to be opposite that of health status, i.e. greater drug use among people with high SEP compared to low SEP. Such a positive association is generally not supported by the existing Danish literature[5, 6, 15].

Although well-established, the inverse association between SEP and health and health behaviour is not clearly understood, but many factors during the life course may play a role in the production of these social health differences. Suggested pathways include: Material deprivation, behavioural factors, and psychological factors[16]. It has also been suggested that it is not SEP in adulthood per se that influences health, but underlying familial factors already at play in early life [17, 18], e.g. rearing environment or genetic make-up are associated both with the obtainment of adult SEP and health status later in life .

In a recent commentary, Gilman & Loucks (2012) discuss why childhood environment may be such an important underlying factor in the production of social health differences. They argue that because childhood encompasses developmentally sensitive periods for the acquisition of cognitive-, psychologic-, and social skills that have a

profound impact on an individual's capacity for long term health and provide opportunities (and constraints) for adult socioeconomic conditions, it can potentially influence the association between any adult risk factor and later life health[19].The potential role of genetic setup in explaining health inequalities is reviewed by Mackenbach (2005), who suggests that the most plausible set of hypotheses relates to genetic influences of personal attributes such as cognitive ability, personality, and bodily and mental fitness that may influence both SEP and adult health status[20].

With the discordant twin pair design, it is possible to investigate the effect of adult SEP on prescription fillings eliminating confounding from factors shared by a pair of twins, exploiting that twins are partly or fully genetically identical and have experienced a similar childhood environment due to their common upbringing. This approach has been applied in a number of previous twin studies investigating different health outcomes, including mortality[21], hospitalizations[22], breast cancer[23], and also softer endpoints such as depression scores and self-rated health[24, 25]. However, the majority of these studies suffer from power limitations either due to small sample sizes and/or rare outcomes making interpretations difficult.

In this study we aimed to investigate if there was an effect of SEP in adulthood on the number of prescription fillings above and beyond the effect of shared familial factors. Filling of prescription medicine is a quantitative health measure rendering sufficient power for the intra-pair comparisons. Differences in genetic relatedness between monozygotic (MZ) (genetically identical) and dizygotic (DZ) twins (share on average 50% of segregating genes) may further give an indication of the possible types of confounding (i.e. genetic or environmental factors). In a theoretical situation of no measurement error and no confounding from unshared factors, genetic confounding would be indicated if an observed social gradient in prescription medicine was partly attenuated in DZ twins and fully attenuated in MZ twins, when shared familial factors had been taken into account. Likewise, an attenuation of similar size in DZ and MZ twins would be compatible with shared environmental confounding. Finally, to support a SEP-effect on prescription fillings not due to confounding from shared familial factors, the association would have to persist in both DZ and MZ twins.

To support the utility of prescription medicine as a health indicator we also analysed its association with mortality.

METHODS

Study population

Data from the Danish Twin Registry was linked with information in the Danish Registry of Medicinal Products and administrative registers in Statistics Denmark. The study population consisted of 24 370 twins, including 8582 monozygotic and 15 788 dizygotic same sex twins (DZSS), who were born during 1921-1965 and alive and resident in Denmark at the beginning of follow-up (January 1 1995), after exclusions due to triplets (n=384) unknown zygosity (UZ) (n=3731), and dizygotic opposite sex pairs (DZOS) (n=16 710), missing data on education or income (n=845), and non-intact twin pairs in which one twin was dead, emigrated, or had missing information (n=2847). To evaluate the representativeness of the results from the unpaired twin analyses, we also analysed a 5% population-based sample of the Danish population (n=137 300).

Social indicators

We used information on highest attained education in 1995 at age 30+ of the study population, categorized according to the International Standard Classification of Education of 1997[26] into: primary/lower secondary education (basic compulsory education), upper secondary education (secondary), and tertiary education (Bachelor's degree and above). Income was measured as an average of the equivalised gross household income (Danish currency) in 1994-1995, grouped into quartiles within each birth cohort. "Equivalised" income is adjusted to take into account that households can share resources. Inspired by the standard OECD equivalence scale[27], the household-denominator was constructed according to an equivalence scale that assigned a value of 1 to the first household member, of 0.7 to the second household member and of 0.5 to each additional household member. Calculating quartiles by birth cohort is aiming at taking into account that income is not fully comparable at different ages during the life course. An implication of this is that the income measure reflects a relative rather than absolute income level.

Prescription medicine

The Danish Registry of Medicinal Products was established in 1995 and contains information on the total sale of prescription medicine in Denmark registered by the pharmacies via a computerized accounting system. The drug information is recorded according to the Anatomical Therapeutic Chemical classification system (ATC)[28] where the active substances in drugs are divided into different groups, primarily according to the organ system

on which they act. Other information includes date of dispensing and *daily defined doses* (DDD), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults[28]. Outcomes of interest were defined as the number of prescription fillings during follow-up for all-purpose medication (ATC-groups: A,B,C,D,G,H,J,L,M,N,P,Q,R,S,V, excluding Q which is for veterinary use, and G02B and G03A, which are for contraceptive use) and four groups of system-specific medication: ATC-C (heart/circulatory system), ATC-N (nervous system), ATC-R (respiratory system) and ATC-A (alimentary tract/metabolism). If no ATC-code was assigned a prescription, it was excluded (1%). DDD was used as a supplementary outcome measure.

Other covariates

Sex and age were included in the analyses. Analyses were performed separately for MZ and DZSS twins. Zygosity had previously been determined by questionnaire[29], a method that has proven valid with an overall misclassification frequency of less than 5% validated against a classification based on genetic markers [30].

Data analysis

Analyses were carried out using Cox regression for recurrent events (proportional means regression), thereby accommodating multiple events (prescription fillings) per individual[31]. Age was used as underlying time-variable and subjects were followed from age at baseline to the age at end of follow-up (Dec 31 2005) or death or emigration, and the timing of each prescription filling during this period was recorded. Both unpaired and intra-pair analyses were performed. In the unpaired analyses robust standard errors were used to account for the interdependence of observations within pairs and within each individual. Results of the unpaired analyses were compared to the intra-pair analyses, which were performed using a stratified Cox model: $EN_{ij}(t)=\mu_{0j}(t)e^{\beta' z_{ij}}$. Here $EN_{ij}(t)$ denotes the mean number of prescription fillings at time *t* for an individual *i* belonging to twin pair *j*, $\mu_{0j}(t)$ is the pair-specific baseline mean, and e^{β} is the effect of the covariates adjusted for shared familial factors. Thus, in this analysis the mean number of prescription fillings were compared within twin pairs, thereby controlling for familial factors shared within a pair of twins. In the stratified model only SEP-discordant twin pairs contribute information to the beta-parameter for SEP, although concordant pairs may contribute information to other beta-parameters.

As counting process models do not allow simultaneous events, only one prescription of interest per day was included in the analysis.

Analyses were performed separately for zygosity and sex, and potential interactions between the social indicators and zygosity, sex, and age, respectively, were evaluated by including interaction terms in the models and using Wald test-statistics. To analyse the association between prescriptions and mortality, we used a Cox regression model, continuously updating the number of prescription fillings over time. Descriptive intra-pair correlations were calculated as polychoric correlation coefficients.

Subanalyses

Since DDD may reflect the actual drug use more precisely than number of prescription fillings, mean DDD were also analysed by means of a fixed-effects linear regression model taking censoring into account[32]. This was treated as a subanalysis due to the highly right-skewed distribution of DDD, making linear regression a less optimal choice of model.

Permission for linkage and use of data for this study was obtained from the Danish Data Protection Board (2000-54-0047).

RESULTS

According to table 1, showing the distribution of education and income in the population, men were better educated than women. Generally, the education of the twin population was comparable to that of the population-based sample. Only UZ twins had a markedly lower educational status and a higher proportion of missing information. The table also shows the mean income within each quartile. Twins have a somewhat higher mean income compared to the population-based sample.

Table 1: Descriptives on Educational Status and Income in a 5% Population Based Sample (n=144749) and a Population of Danish Twins (n=48887), Including Intact and Non-intact Twin Pairs, Stratified on Sex and Zygosity.

	5% population sample				All twins (n=48887)				DZSS (n=18426)		MZ (n=9636)		DZOS (n=16710)		UZ (n=3731)	
Sex	N	%[a]	Mean	SD	n	%[a]	Mean	SD	N	%[a]	N	%[a]	n	%[a]	n	%[a]
Educational status[b]																
Men																
Primary	23550	32			8909	35			3553	36	1517	31	2882	34	957	43
Secondary	31336	43			11237	44			4309	44	2292	47	3834	45	802	36
Tertiary	13722	19			4515	18			1685	17	963	20	1530	18	337	15
Missing	4072	6			800	3			310	3	128	3	208	2	154	7
Total	72680	100			25461	100			9857	100	4900	101	8454	99	2250	101
Women																
Primary	31215	43			10182	44			3857	45	1903	40	3633	44	789	53
Secondary	23809	33			7805	34			2868	34	1730	37	2807	34	400	27
Tertiary	14229	20			4613	20			1696	20	1004	21	1705	21	208	14
Missing	2816	4			442	2			148	2	99	2	111	1	84	6
Total	72069	100			23042	100			8569	101	4736	100	8256	100	1481	100
Income (DKK)																
Men																
1st quartile	17348	24	88537	28373	5931	24	92330	27563	2251	23	1061	22	1929	23	690	31
2nd quartile	17510	24	145676	25887	6523	24	149367	24179	2563	26	1208	25	2201	26	551	24
3rd quartile	17976	25	191360	34863	6769	25	196738	31365	2612	27	1375	28	2246	27	536	24
4th quartile	18228	25	311232	141784	5960	25	314180	225459	2340	24	1218	25	2006	24	396	18
Missing	1618	2			278	2			91	1	38	1	72	1	77	3
Total	72680	100			25461	100			9875	101	4900	101	8454	101	2250	100
Women									2174	25	1158	24	2200	27	538	36
1st quartile	18958	26	88201	26316	6070	26	91205	25698	2316	27	1222	26	2186	27	353	24
2nd quartile	18219	25	142746	27689	6077	25	146427	25562	2152	25	1224	26	2106	26	313	21
3rd quartile	17753	25	18942	36067	5795	25	194968	33291	1882	22	1097	23	1730	21	232	16
4th quartile	16126	22	308876	225888	4941	22	312063	173113	45	1	35	1	34	0	45	3
Missing	1013	1			159	1			8569	100	4736	100	8256	101	1481	100
Total	72069	99			23042	99			2251	23	1061	22	1929	23	690	31

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; DZOS=Dizygotic opposite sex twins; UZ=Unknown zygosity, [a]May not sum to 100 because of rounding, [b]International Standard Classification of Education, [c]Average of equvalized gross household income in 1994-1995 in quartiles. DKK=Danish Crowns.

The proportion of education-discordant twin pairs was 30% for MZ twins and 42% for DZSS twins, while 61% MZ twins and 68% DZSS twins were discordant on income (table 2).

Table 2: Descriptives on Intra-Pair Discordances on Educational Status and Income, Stratified on Zygosity in a Population of Danish Twins (n=24370).

	DZSS (n=15788)		MZ (n=8582)	
	N	%[a]	n	%[a]
Educational status				
Primary vs Secondary	3590	23	1460	17
Primary vs Tertiary	900	6	316	4
Secondary vs Tertiary	2194	14	820	10
Any discordance	6684	42	2596	30
Income				
1st quartile vs 2nd quartile	2048	13	1072	12
1st quartile vs 3rd quartile	1706	11	754	9
1st quartile vs 4th quartile	1158	7	490	6
2nd quartile vs 3rd quartile	2266	14	1194	14
2nd quartile vs 4th quartile	1574	10	682	8
3rd quartile vs 4th quartile	2000	13	1080	13
Any discordance	10 752	68	5272	61

DZSS=Dizygotic same sexed twins; MZ=Monozygotic twins; [a]May not sum to 100 because of rounding.

In the twin population, 1.9% did not redeem any drug prescriptions during the total follow-up period and 25% redeemed less than one prescription/year, on average (results not shown). Overall, women filled more prescriptions than men for all age groups and the number of prescription fillings increased with age in both sexes (table 3).

Table 3: The Mean Number of Prescription Fillings After 1 and 10 Years of Follow-up in a 5% Population Based Sample and a Population of Danish Twins, Stratified on Age and Sex.

Type of drugs	**Nelson Aalen Cumulative Hazard**			
Age				
Sex	5 % pop. (n= 137 300)		Twins (n=24 370)	
All purpose	*1 year*	*10 years*	*1 year*	*10 years*
30-44 years				
Men	2.5	28.7	2.2	25.9
Women	4.1	44.5	3.8	41.1
45-59 years				
Men	3.6	47.4	3.3	43.1
Women	6.0	71.9	5.7	68.4
60+ years				
Men	6.4	87.5	5.8	82.2
Women	8.3	105.4	7.2	95.7
Circulatory system (ATC-C)				
30-44 years				
Men	0.1	3.3	0.1	2.9
Women	0.2	4.2	0.2	3.6
45-59 years				
Men	0.7	12.6	0.6	10.6
Women	0.8	13.8	0.7	13.0
60+ years				
Men	1.9	29.6	1.7	27.4
Women	1.9	30.0	1.6	26.7
Nervous system (ATC-N)				
30-44 years				
Men	0.8	9.8	0.7	8.6
Women	1.1	14.5	1.0	13.3
45-59 years				
Men	1.2	14.6	1.2	13.9
Women	2.1	25.0	2.0	24.1
60+ years				
Men	1.8	24.4	1.6	22.2
Women	3.1	39.2	2.7	35.8
Respiratory system (ATC-R)				
30-44 years				
Men	0.3	3.9	0.3	3.6
Women	0.6	6.5	0.5	5.7
45-59 years				
Men	0.5	5.8	0.4	5.0
Women	0.8	9.8	0.7	9.1
60+ years				
Men	1.1	14.4	0.9	12.5
Women	1.2	14.8	1.0	12.8
Alimentary tract & metabolism (ATC-A)				
30-44 years				
Men	0.3	3.5	0.2	3.1
Women	0.4	5.0	0.4	4.1
45-59 years				
Men	0.5	7.6	0.5	6.6
Women	0.7	9.6	0.7	8.6
60+ years				
Men	1.1	15.4	1.1	15.0
Women	1.3	18.3	1.0	16.4

ATC-N drug prescriptions were the most frequently redeemed in the youngest age group. The mean number of prescription fillings in the twin population was similar to that in the population-based sample, although slightly higher in the population-based sample.

In order to get a better idea of the clinical outcomes underlying the observed prescription patterns, we have included a more detailed description of the most incident types of drugs at the 3-and 4-digit ATC level (Supplementary table 1). From the table it appears that the ATC-C category primarily comprises drugs indicated for hypertension and ischaemic heart disease, while the ATC-N category mainly includes drugs indicated for a wide range of different diagnoses, including chronic pain disorders, insomnia, anxiety, psychoses, depression etc.[28] In the ATC-R category the main types of drugs are drugs for obstructive airway disease such as asthma and Chronic Obstructive Lung Disorder (COPD)[28]. Finally, drugs for acid-related disorders and diabetes are the main constituents of the ATC-A category. The results of an analysis of the association between SEP and prescription fillings for all-purpose and system-specific drugs are presented in table 4.

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For all-purpose drugs, MZ twins in the highest income quartile had a 30% lower mean number of prescription fillings than MZ twins in the lowest income quartile (MR=0.70 (CI 95%; 0.65,0.77). Similarly, MZ twins with a tertiary education had 17% lower mean number of prescription fillings than twins with a primary education (MR=0.82 (CI 95%: 0.75,0.89)). The association was slightly less strong for ATC-C drugs while stronger associations could be observed for the other system-specific drugs, particularly for ATC-N. In the unpaired analyses, no large differences could be observed between MZ and DZSS twins and there was no strong evidence for an interaction between SEP and zygosity in the unpaired analysis (education: *P*=0.81, income: *P*=0.95). In contrast, the effect of SEP was moderated by zygosity in the intra-pair analyses (education: *P*=0.02, income: *P*=0.05), suggesting a more attenuated effect of SEP in MZ twins than in DZSS twins: In MZ twins, generally no statistically significant effect of education could be observed, while income was still somewhat associated with all-purpose medication and quite strongly with ACT-N drugs. In DZSS twins, a minor or moderate attenuation could be observed, and all effect parameters were statistically significant, except for ATC-C drugs. In the population-based sample, the associations were similar to that in the overall twin population.

When using DDD (for all-purpose drugs) as outcome measure (table 5), results similar to the results based on number of prescription fillings were obtained, although the attenuation patterns in MZ twins were somewhat more clear in this analysis, showing no statistically significant associations with DDD of neither education nor income. In the analysis of number of prescriptions as a predictor of mortality we found a 60% increase in mortality rate during follow-up for a person who, on average, filled 1 prescription per month during the follow-up period compared to a person without any prescription fillings (HR=1.60 (95% CI: 1.25,2.05).

Table 5: Results from a Linear Regression Model Showing Number of Daily Defined Doses (DDD) for All-Purpose Drugs According to Educational Status and Income in a Population of Danish Twins (n=24370) Stratified on Zygosity. Results from Unpaired and Intra-Pair Analyses are Shown.

Educational status	**Unpaired analysis[a]**				**Intra-pair analysis[b]**			
Income	**DZSS n=15788**		**MZ n=8582**		DZSS		MZ	
	DDD	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*
Secondary	**-287**	-397;-177	**-289**	-440;-138	**-245**	-399;-90	-143	-346;59
Tertiary	**-404**	-531;-277	**-424**	-606;-243	**-344**	-557;-131	-152	-440;136
2nd quartile	**-401**	-541;-260	**-275**	-463;-88	**-219**	-383;-54	18	-177;214
3rd quartile	**-541**	-680;-402	**-451**	-638;-263	**-367**	-535;-198	-83	-287;121
4th quartile	**-505**	-648;-363	**-437**	-630;-243	**-327**	-512;-142	16	-209;242

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; [a]Unpaired analysis treating twins as individuals while taking interdependence of observations within each individual and within twin pairs into account. The interpretation of e.g. the education estimate is difference in the mean number of DDDs of an individual with a secondary or tertiary education compared to a random individual with a primary education. The estimates are adjusted for age and sex. Income and education are mutually adjusted [b]Intra-pair analysis of twins by inclusion of a fixed-effect statement. The interpretation of e.g. the education estimate is the difference in the mean number of DDDs of a twin with a secondary or tertiary education compared to its co-twin with a primary education. Bold typography indicates statistical significance at 5% level.

DISCUSSION

Summary of findings

In this large Danish twin population we demonstrated an inverse social gradient in fillings of prescription medicine for all-purpose and system-specific drugs. That is, a greater use of prescription medicine among those with a low SEP thus suggesting a worse health status of this group. Furthermore, the number of prescription fillings was shown to be associated with a greater risk of mortality. In the intra-pair analyses, where shared familial factors were controlled per design, the association between SEP and prescription fillings attenuated to a wide extent within MZ twins and statistically significantly less in DZSS twins. For education, there was generally no association with prescription fillings in the intra-pair analyses of MZ twins, except for drugs targeting the nervous system, while there was still some association of income with all-purpose medication and most system-specific drugs. However, no effect of income was seen in the intra-pair analyses when DDD were used as outcome measure. In spite of some variations between system-specific drugs, the overall pattern was the same as for all-purpose drugs, except for ATC-N drugs and to a lesser degree ATC-A drugs, which still showed some effect of SEP in the intra-pair analyses.

Interpretation

The fact that the association was attenuated in the intra-pair analyses suggests that underlying factors shared by a pair of twins account for some of the observed association between SEP and prescription fillings. However, there may be a number of alternative or complementary explanations for this finding: Firstly, part of it is likely caused by measurement error. Measurement error is random and therefore not shared by twins. In the intra-pair analysis, variance due to shared factors is removed, and a relatively larger proportion of exposure variance is thus due to measurement error. This will result in increasing attenuation of parameter estimates in the intra-pair analyses[33]. However, since data come from official registers it can be expected that education and income have limited measurement error. Secondly, the behaviour of one twin could be affected by the behaviour of the other twin, i.e. 'social interaction' either by 'imitation' or 'differentiation'. The implications of a potential imitation could be smaller within-pair differences, which could be misinterpreted as confounding from underlying familial factors. This may be of some concern in this study since fillings of prescription medicine is likely to have a behavioural component. Another implication of the discordant twin pair approach is that only twin pairs who are discordant on exposure contribute with statistical information to the estimation of SEP-

effects in the intra-pair analysis. This could potentially induce bias in the comparison of the unpaired and intra-pair analysis, since the two analyses are based only partly overlapping populations. Since MZ twins are less likely to be discordant, the selection bias may be most severe in MZ twins[34]. We examined this concern by restricting the unpaired analysis only to include groups with exposure-discordant twins. Results were similar to those of the main analysis in both MZ and DZ twins. A further issue relates to the fact that twins who are discordant on exposure are special in the sense that they, in spite of overlapping genes and rearing environment, differ in their SEP. Thus, unshared factors may explain these differences. This implies that the intra-pair analysis may still be confounded by unshared confounding factors, and that this confounding may be enforced in the intra-pair analysis[33]. Generally, confounding from unshared factors is thought to be more severe when confounders are less correlated than exposure[33]. This may or may not be true in our case, since we can only hypothesize on the correlation of unmeasured confounders. Nevertheless, the correlation of education and income (MZ=0.79, DZ=0.58 and MZ=0.49, DZ=0.33) are more or less of the same magnitude as phenotypes like cognitive ability[35] and BMI[36] which have previously been investigated using similar designs. In any case, as shown by Frisell et al. (2012) in order for *increased* confounding to explain the *attenuation* of the association observed in this study, the potential non-shared confounders would have to create a positive association between education and prescription fillings. In most cases, however, we would expect a negative association, although filling of prescription medicine is indeed a complex health outcome and it is theoretically possible for a confounder to have a dual effect on prescription fillings by 1) increasing the capability of getting the relevant prescriptions, e.g. due to more regular heath checks or better understanding of symptoms 2) at the same time reducing the need for prescription fillings due to better health status. Nevertheless, in a Danish context health status does seem to be the main determinant of prescription medicine[10, 37, 38] and was clearly associated with mortality in this data. Thus, in the presence of non-shared confounding we would expect the net effect of any confounding to produce a negative association between education and prescription fillings resulting in bias away from the null[33], and therefore it could not explain the observed attenuation of effect in the intra-pair analyses observed in this study.

The finding of greatest attenuation in MZ twins is compatible with the scenario of genetic confounding described in the introduction. Since the genetic overlap is greater in MZ twins than DZSS twins, one would expect a larger attenuation in MZ twins, if genetic factors gave rise to the confounding. However, a number of other factors could

produce a greater attenuation in MZ twins: First of all, the aforementioned measurement error may be most pronounced in MZ twins, due to the fact that increasing correlation in exposure will result in a greater attenuation of intra-pair parameter estimates[33]. In addition, the comparison of strength of association between MZ and DZ twins to indicate the source of familial confounding relies on the equal environment assumption: That is, MZ and DZ twins share their environment equally. However, this assumption may be challenged, and if it does not hold, i.e. if MZ twins not only share their genes but also their environment more closely than DZ twins[39], shared environmental factors could also produce a greater attenuation of effect in MZ twins. However, the interplay between environment and genes is complex, and it is conceivable that the environment to a certain extent is shaped in response to the genetic dispositions of an individual. If, for instance, a genetically determined similar appearance of MZ twins also elicits a more similar treatment from their peers, then these similar environmental stimuli can also be ascribed to genetic factors[40].

Thus, although several factors may contribute to the observed attenuation of association between SEP and filling of prescription drugs in the intra-pair analyses and to the differences in strength of association between MZ and DZ twins, the findings suggest that a part of the observed social inequality in prescription fillings is explained by either genetic or environmental factors shared by twins.

The finding of a persistent association of particularly income with fillings of prescriptions for ATC-N drugs clearly stood out from the general results. We therefore carried out a post hoc subanalysis of specific categories of ATC-N drugs to test whether it were certain types of drugs driving the association. The analysis revealed that it was mainly for analgesics and psycholeptics that the association persisted, while the association was somewhat attenuated for psychoanaleptics (primarily antidepressants). This finding may support the notion of reverse causation, i.e. that health status influences SEP rather than the other way around, since it is likely that diagnoses such as chronic pain disorders, psychoses, anxiety and bipolar disorders associated with these types of drugs may affect the work ability and thus the income of a person. Income is much more sensitive to reverse causation than education, which is usually obtained early in life and remains constant once it is obtained.

Existing literature

In this study we argue that fillings of all-purpose and system-specific drug prescriptions to some extent serve as an indicator of general health status and of conditions like ischaemic heart disease, hypertension, COPD, and diabetes. The finding of weaker effects of SEP, when underlying familial factors were taken into account, accords with a large part of the life course literature that supports the importance of early life factors in the aetiology of chronic disease in adulthood[41, 42].

In addition, a number of previous twin and sibling studies have investigated the association between various SEP-indicators and health outcomes. While some studies have shown strong or some evidence of a causal effect of adult SEP[43-47] other suggest no or little effect of SEP, when familial factors have been adjusted for [48-52]. Other studies show mixed results[21, 23-25, 47, 53-55]. However, the studies vary with respect to a number of important parameters hampering overall comparisons. Most importantly, investigated health outcomes differ and may have different aetiologies and show different social gradients and patterns of familial confounding, but even for specific health outcomes there is no clear picture of evidence. E.g. for mortality, two sibling-[45, 46] and two twin studies[21, 44] have investigated the association with education. Although all studies support some effect of education after controlling for shared family factors, important differences exist: The twin study by Madsen et al.(2010) demonstrated an effect of education within twins only in older cohorts of men, but not in younger men and not in women. The influence of shared family factors was thus suggested in the latter, but not in the first subgroup of this study. The two sibling studies also suggested some effect of shared family factors, while the twin study by Lundborg (2008) did not support any such effect. For self-rated health, the majority of the existing twin studies [24, 25, 54] have shown mixed results, although Osler et al. [47] and Lundborg[43] did find a statistically significant association between social class respective education and self-rated health in the intra-pair analyses. One important reason for the inconsistencies may be that many studies have suffered from power limitations in the intra-pair analyses due to a small number of events[21, 23, 25, 47, 54]. This is not a concern in this study, where almost all of the exposure discordant twins contributed with information to the intra-pair analyses, thus providing some of the most powerful twin results on social inequality in health to date.

Strengths and limitations

The twin approach is clearly a strength of this study, since it makes it possible to adjust for unmeasured background factors shared by twins that may be underlying the association between SEP and health. Furthermore, the large sample size and the long follow-up allow a great number of events to be analysed. In

addition, the use of population-based registers has the advantage of relatively little selection and measurement error in the study population. Finally, this study not only focuses on prescription medicine in general, but also on drugs targeting specific organ systems which may give us a better idea of potential mechanisms.

Among study limitations is the fact that filling of prescription medicine is not a perfect measure of health status. We do, however, argue that the observed association with mortality and the inverse relationship with education and income likely reflect a greater need for medicine among people of lower SEP. In case that access to health care also plays a role, presumably favouring people of high SEP, the social gradient in health status in this study could be underestimated. Although data did not contain information on over-the-counter (OTC) medication, it only constitutes a minor part of the total drug consumption in Denmark[7], and since we were interested in drugs as an indicator of health status, it could be argued that the most valid approach is to focus on drugs that require a formal medical indication (i.e. prescription).

As models for counting processes only allow one event at a time, the number of prescription fillings was defined as the main outcome of interest. Therefore, it was reassuring that the subanalysis on DDD led to similar results.

Although the distribution of SEP-indicators and prescription fillings were not entirely identical in twins and the population-based sample, the associations between SEP and prescription fillings were indeed, which supports generalizability to the general population in line with previous studies that show that health and mortality in twins are similar to the background population[56, 57]. Furthermore, the fact that the analysis based only on discordant twin pairs show marginal results similar to those based on the total twin sample was reassuring.

Conclusion and perspectives

In this study, based on a comprehensive twin cohort, we observed a social inequality in fillings of prescription medicine, showing fewer prescription fillings among people with high SEP. This association attenuated within twin pairs for most types of prescription-fillings, except those targeting the nervous system. The attenuation was most pronounced in MZ twins. Measurement error can contribute to the observed attenuation of association, but it is likely to account only for a minor fraction, considering the exposure and outcome measures in this study. As for potential non-shared confounding we would, if anything, expect it to bias the estimates away from the null.

We therefore interpret the findings as an indication that at least a part of the observed social inequality in prescription fillings is explained by shared familial factors. The implications of these findings are by no means a disqualification of SEP as a determinant of health, but rather an indication that family matters in the production of social health inequalities; most likely through early environment, and possibly also genetic factors. Recognizing biological components and early life exposures as important explanatory factors may improve our understanding of the multifaceted aetiology of health inequalities over the life course and increase the potential for effective and targeted interventions.

COMPETING INTERESTS

None.

FUNDING

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CONTRIBUTORSHIP

KC and MO formulated the original study idea and provided funding. MM, KC, MO and A-MNA further developed the study idea and design of the study. MM carried out the data analyses in collaboration with PKA and MG. All authors participated in interpretation and discussion of the findings. MM drafted the first version of the manuscript, but all authors have contributed to the revisions and have approved the final version of the paper.

DATA SHARING

There are no additional data.

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Supplementary table 1: Description of the largest groups (≥2% of the total number of prescription fillings) of drugs at the 3-digit and 4-digit level of ATC-codes within each of the analysed main drug categories.

Organ system	ATC-codes		Type of drugs	% of total number of prescription fillings
	3-digit level	4-digit level		
Circulatory system	**C03**		**Diuretics**	**4.40**
		C03A	Low-ceiling diuretics, thiazides	1.93
		C03B	Low-ceiling diuretics, excl. thiazides	0.09
		C03C	High-ceiling diuretics	1.60
		C03D	Potassium-sparing agents	0.32
		C03E	Diuretics and potassium-sparing agents in combination	0.47
	C07		**Beta blocking agents**	**2.94**
		C07A	Beta blocking agents	2.83
		C07B	Beta blocking agents and thiazides	0.03
		C07C	Beta blocking agents and other diuretics	0.06
		C07F	Beta blocking agents and other hypertensives	0.02
	C08		**Calcium channel blockers**	**2.68**
		C08C	Selective calcium channel blockers with mainly Vascular effects	1.81
		C08D	Selective calcium channel blockers with direct cardiac effects	0.87
	C09		**Agents acting on the renin-angiotensin system**	**3.83**
		C09A	ACE inhibitors, plain	2.22
		C09B	ACE inhibitors, combinations	0.21
		C09C	Angiotensin ii antagonists, plain	0.93
		C09D	Angiotensin ii antagonists, combinations	0.46
	C10		**Lipid modifying agents**	**2.00**
		C10A	Lipid modifying agents, plain	2.00
Nervous system	**N02**		**Analgesics**	**10.09**
		N02A	Opiods	4.88
		N02B	Other analgesics and antipyretics	3.98
		N02C	Antimigraine preparations	1.22
	N05		**Psycholeptics**	**10.71**
		N05A	Antipsychotics	1.97
		N05B	Anxiolytics	4.93
		N05C	Hypnotics and sedatives	3.81
	N06		**Psychoanaleptics**	**4.16**
		N06A	Antidepressants	4.07
		N06B	Psychostimulants, agents used for adhd and Nootropics	0.02
		N06D	Antidementia drugs	0.07
Respiratory system	**R03**		**Drugs for obstructive airway diseases**	**7.11**
		R03A	Adrenergics, inhalants	4.14
		R03B	Other drugs for obstructive airway diseases, inhalants	2.12
		R03C	Adrenergics for systemic use	0.43
		R03D	Other systemic drugs for obstructive airway diseases	0.42
Alimentary tract and metabolism	**A02**		**Drugs for acid related disorders**	**3.67**
		A02A	Antiacids	0.3
		A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease	3.4
	A10		**Drugs used in diabetes**	**2.68**
		A10A	Insulins and analouges	1.1
		A10B	Blood glucose lowering drugs, excl. insulins	1.6
				54.3

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

ARTICLE SUMMARY

Article focus

- To investigate if the association between socio-economic factors and filling of drug prescriptions persists after controlling for genetic and childhood factors shared within twins.

Key messages

- The inverse association between socio-economic factors and filling of prescription medicine show substantial attenuation in intra-pair analyses of twins, except for drugs targeting the ~~neurologic~~nervous system.
- Greater attenuation within monozygotic than dizygotic same sex twins.
- Shared ~~F~~familial factors seem to account for at least part of the observed social inequality in fillings of prescription medicine.

Strengths and limitations

- This study is based on nation-wide register data covering more than a decade, and we present results from a largely unselected population of more than 8000 monozygotic and 15,000 dizygotic same sexed twins.
- This is the first twin study on health inequalities to report such clear-cut findings with sufficient power for meaningful interpretation of intra-pair analyses and for comparison of zygosity-specific results.
- Prescription fillings are not a perfect measure of health status, but we still argue that it is an inventive and fairly valid indicator in a Danish setting where prescription medicine has to be prescribed by a medical doctor and accounts for 96% of the total drug sale.
- The twin study is clearly a powerful approach, but when interpreting findings, alternative explanations for the pattern of attenuation should be considered, including measurement error and unshared confounding. However, in this case we find it unlikely that these potential sources of bias could fully explain our findings.

INTRODUCTION

Social inequalities in health and health behaviour have been widely demonstrated in many societies, including the Scandinavian countries[1]. Often social disparities in health are not confined to the most marginalized groups of society but are expressed as a gradient over the entire spectrum of social stratification[2]. The inverse relationship between socio-economic position (SEP) and health has consistently been observed across different social indicators and for numerous types of health outcomes[3, 4]. Use of prescription medicine is one health-related outcome that has been found to be socially patterned, where Danish data have shown a greater use among people with low SEP compared to people with high SEP[5, 6]. Denmark has a tax financed decentralized health care system with a partly need-dependent reimbursement system for outpatient prescription drugs. All prescription-drugs have to be prescribed by a medical doctor and, compared to a number of other countries, prescription medicine constitute the majority~~a fairly large proportion~~ of the total drug sale in Denmark (app. 9~~0~~6%)[7]. Many studies have shown substantially reduced social differences in drug use when health status have been taken into account[6, 8, 9], which may indicate that filling of prescription medicine to a large extent reflects health status. This is supported by the fact that comorbidity indices, based on prescription drug dispensings, have been established as strong predictors of mortality[10], and that drug use has proven to be a valid indicator of self-rated health[11, 12]. However, other factors such as health care seeking behaviour and access to health care[13, 14] may also influence drug use, but the social gradient in these factors would, theoretically, be expected to be opposite that of health status, i.e. greater drug use among people with high SEP compared to low SEP. Such a positive association is generally not supported by the existing Danish literature[5, 6, 15].

Although well-established, the inverse association between SEP and health and health behaviour is not clearly understood, but many factors during the life course may play a role in the production of these social health differences. Suggested ~~Possible~~ pathways ~~but is likely to be driven via a number of different pathways,~~ include:~~ing~~ M~~m~~aterial deprivation, behavioural factors, and psychological factors[16]. It has also been suggested that it is not SEP in adulthood per se that influences health, but underlying familial factors already at play in early life [17, 18], e.g. rearing environment or genetic make-up are associated both with the obtainment of adult SEP and health status later in life ~~already at play in early life [17, 18]~~.

In a recent commentary, Gilman & Loucks (2012) discuss why childhood environment may be such an important underlying factor in the production of social health differences. They argue that because childhood encompasses

developmentally sensitive periods for the acquisition of cognitive-, psychologic-, and social skills that have a profound impact on an individual's capacity for long term health and provide opportunities (and constraints) for adult socioeconomic conditions, it can potentially influence the association between any adult risk factor and later life health[19].The potential role of genetic setup in explaining health inequalities is reviewed by Mackenbach (2005), who suggests that the most plausible set of hypotheses relates to genetic influences of personal attributes such as cognitive ability, personality, and bodily and mental fitness that may influence both SEP and adult health status[20].

With the discordant twin pair design, it is possible to investigate the effect of adult SEP on prescription fillings eliminating confounding from factors shared by a pair of twins, exploiting that twins are partly or fully genetically identical and have experienced a similar childhood environment due to their common upbringing. This approach has been applied in a number of previous twin studies investigating different health outcomes, including mortality[21]~~[19]~~, hospitalizations[22]~~[20]~~, breast cancer[23]~~[21]~~, and also softer endpoints such as depression scores and self-rated health[24, 25]~~[22, 23]~~. However, the majority of these studies suffer from power limitations either due to small sample sizes and/or rare outcomes making interpretations difficult.

In this study we aimed to investigate if there was an effect of SEP in adulthood on the number of prescription fillings above and beyond the effect of shared familial factors. Filling of prescription medicine is a quantitative health measure rendering sufficient power for the intra-pair comparisons. Differences in genetic relatedness between monozygotic (MZ) (genetically identical) and dizygotic (DZ) twins (share on average 50% of segregating genes) may further give an indication of the possible types of confounding (i.e. genetic or environmental factors). In a theoretical situation of no measurement error and no confounding from unshared factors, genetic confounding would be indicated if an observed social gradient in prescription medicine was partly attenuated in DZ twins and fully attenuated in MZ twins, when shared familial factors had been taken into account. Likewise, an attenuation of similar size in DZ and MZ twins would be compatible with shared environmental confounding. Finally, to support a SEP-effect on prescription fillings not due to confounding from shared familial factors, the association would have to persist in both DZ and MZ twins.

To support the utility of prescription medicine as a health indicator we also analysed its association with mortality.

METHODS

Study population

Data from the Danish Twin Registry was linked with information in the Danish Registry of Medicinal Products and administrative registers in Statistics Denmark. The study population consisted of 24 370 twins, including 8582 monozygotic and 15 788 dizygotic same sex twins (DZSS), who were born during 1921-1965 and alive and resident in Denmark at the beginning of follow-up (January 1 1995), after exclusions due to triplets (n=384) unknown zygosity (UZ) (n=3731), and dizygotic opposite sex pairs (DZOS) (n=16 710), missing data on education or income (n=845), and non-intact twin pairs in which one twin was dead, emigrated, or had missing information (n=2847). To evaluate the representativeness of the results from the unpaired twin analyses, we also analysed a 5% population-based sample of the Danish population (n=137 300).

Social indicators

We used information on highest attained education in 1995 at age 30+ of the study population, categorized according to the International Standard Classification of Education of 1997[26][~~24~~] into: primary/lower secondary education (basic compulsory education), upper secondary education (secondary), and tertiary education (Bachelor's degree and above). Income was measured as an average of the equivalised gross household income (Danish currency) in 1994-1995, grouped into quartiles within each birth cohort. "Equivalised" income is adjusted to take into account that households can share resources. Inspired by the standard OECD equivalence scale[27][~~25~~], the household-denominator was constructed according to an equivalence scale that assigned a value of 1 to the first household member, of 0.7 to the second household member and of 0.5 to each additional household member. Calculating quartiles by birth cohort is aiming at taking into account that income is not fully comparable at different ages during the life course. An implication of this is that the income measure reflects a relative rather than absolute income level.

Field Code Changed

Prescription medicine

The Danish Registry of Medicinal Products was established in 1995 and contains information on the total sale of prescription medicine in Denmark registered by the pharmacies via a computerized accounting system. The drug information is recorded according to the Anatomical Therapeutic Chemical classification system (ATC)[28][~~26~~] where the active substances in drugs are divided into different groups, primarily according to the organ system

on which they act. Other information includes date of dispensing and *daily defined doses* (DDD), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults[28][26]. Outcomes of interest were defined as the number of prescription fillings during follow-up for all-purpose medication (ACT-groups: A,B,C,D,G,H,J,L,M,N,P,Q,R,S,V, excluding the ATC-groups Q, which is for veterinary use, and G02B and G03A, which are for contraceptive use) and four groups of system-specific medication: ATC-C (heart/-circulatory system), ATC-N (nervous system), ATC-R (respiratory system) and ATC-A (alimentary tract/metabolism). If no ATC-code was assigned a prescription, it was excluded (1%). DDD was used as a supplementary outcome measure.

Other covariates

Sex and age were included in the analyses. Analyses were performed separately for MZ and DZSS twins. Zygosity had previously been determined by questionnaire[29][27], a method that has proven valid with an overall misclassification frequency of less than 5% validated against a classification based on genetic markers [30][28].

Data analysis

Analyses were carried out using Cox regression for recurrent events (proportional means regression), thereby accommodating multiple events (prescription fillings) per individual[31][29]. Age was used as underlying time-variable and subjects were followed from age at baseline to the age at end of follow-up (Dec 31 2005) or death or emigration, and the timing of each prescription filling during this period was recorded. Both unpaired and intra-pair analyses were performed. In the unpaired analyses robust standard errors were used to account for the interdependence of observations within pairs and within each individual. Results of the unpaired analyses were compared to the intra-pair analyses, which were performed using a stratified Cox model: $EN_{ij}(t)=\mu_{0j}(t)e^{\beta' z_{ij}}$. Here $EN_{ij}(t)$ denotes the mean number of prescription fillings at time *t* for an individual *i* belonging to twin pair *j*, $\mu_{0j}(t)$ is the pair-specific baseline mean, and e^{β} is the effect of the covariates adjusted for shared familial factors. Thus, in this analysis the mean number of prescription fillings were compared within twin pairs, thereby controlling for familial factors shared within a pair of twins. In the stratified model only SEP-discordant twin pairs contribute information to the beta-parameter for SEP, although concordant pairs may contribute information to other beta-parameters.

As counting process models do not allow simultaneous events, only one prescription of interest per day was included in the analysis.

Analyses were performed separately for zygosity and sex, and potential interactions between the social indicators and zygosity, sex, and age, respectively, were evaluated by including interaction terms in the models and using Wald test-statistics. To analyse the association between prescriptions and mortality, we used a Cox regression model, continuously updating the number of prescription fillings over time. Descriptive intra-pair correlations were calculated as polychoric correlation coefficients.

Subanalyses

Since DDD may reflect the actual drug use more precisely than number of prescription fillings, mean DDD were also analysed by means of a fixed-effects linear regression model taking censoring into account[32] ~~[30]~~. This was treated as a subanalysis due to the highly right-skewed distribution of DDD, making linear regression a less optimal choice of model.

Permission for linkage and use of data for this study was obtained from the Danish Data Protection Board (2000-54-0047).

RESULTS

According to table 1, showing the distribution of education and income in the population, men were better educated than women. Generally, the education of the twin population was comparable to that of the population-based sample. Only UZ twins had a markedly lower educational status and a higher proportion of missing information. The table also shows the mean income within each quartile. Twins have a somewhat higher mean income compared to the population-based sample.

Table 1: Descriptives on Educational Status and Income in a 5% Population Based Sample (n=144749) and a Population of Danish Twins (n=48887), Including Intact and Non-intact Twin Pairs, Stratified on Sex and Zygosity.

	5% population sample				All twins (n=48887)				DZSS (n=18426)		MZ (n=9636)		DZOS (n=16710)		UZ (n=3731)	
Sex	N	%[a]	Mean	SD	n	%[a]	Mean	SD	N	%[a]	N	%[a]	n	%[a]	n	%[a]
Educational status[b]																
Men																
Primary	23550	32			8909	35			3553	36	1517	31	2882	34	957	43
Secondary	31336	43			11237	44			4309	44	2292	47	3834	45	802	36
Tertiary	13722	19			4515	18			1685	17	963	20	1530	18	337	15
Missing	4072	6			800	3			310	3	128	3	208	2	154	7
Total	72680	100			25461	100			9857	100	4900	101	8454	99	2250	101
Women									3857	45	1903	40	3633	44	789	53
Primary	31215	43			10182	44			2868	34	1730	37	2807	34	400	27
Secondary	23809	33			7805	34			1696	20	1004	21	1705	21	208	14
Tertiary	14229	20			4613	20			148	2	99	2	111	1	84	6
Missing	2816	4			442	2			8569	101	4736	100	8256	100	1481	100
Total	72069	100			23042	100			3553	36	1517	31	2882	34	957	43
									4309	44	2292	47	3834	45	802	36
Income (DKK)																
Men																
1st quartile	17348	24	88537	28373	5931	24	92330	27563	2251	23	1061	22	1929	23	690	31
2nd quartile	17510	24	145676	25887	6523	24	149367	24179	2563	26	1208	25	2201	26	551	24
3rd quartile	17976	25	191360	34863	6769	25	196738	31365	2612	27	1375	28	2246	27	536	24
4th quartile	18228	25	311232	141784	5960	25	314180	225459	2340	24	1218	25	2006	24	396	18
Missing	1618	2			278	2			91	1	38	1	72	1	77	3
Total	72680	100			25461	100			9875	101	4900	101	8454	101	2250	100
Women									2174	25	1158	24	2200	27	538	36
1st quartile	18958	26	88201	26316	6070	26	91205	25698	2316	27	1222	26	2186	27	353	24
2nd quartile	18219	25	142746	27689	6077	25	146427	25562	2152	25	1224	26	2106	26	313	21
3rd quartile	17753	25	18942	36067	5795	25	194968	33291	1882	22	1097	23	1730	21	232	16
4th quartile	16126	22	308876	225888	4941	22	312063	173113	45	1	35	1	34	0	45	3
Missing	1013	1			159	1			8569	100	4736	100	8256	101	1481	100
Total	72069	99			23042	99			2251	23	1061	22	1929	23	690	31

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; DZOS=Dizygotic opposite sex twins; UZ=Unknown zygosity, [a]May not sum to 100 because of rounding, [b]International Standard Classification of Education, [c]Average of equvalized gross household income in 1994-1995 in quartiles. DKK=Danish Crowns.

The proportion of education-discordant twin pairs was 30% for MZ twins and 42% for DZSS twins, while 61% MZ twins and 68% DZSS twins were discordant on income (table 2).

Table 2: Descriptives on Intra-Pair Discordances on Educational Status and Income, Stratified on Zygosity in a Population of Danish Twins (n=24370).

	DZSS (n=15788)		**MZ (n=8582)**	
	N	%[a]	n	%[a]
Educational status				
Primary vs Secondary	3590	23	1460	17
Primary vs Tertiary	900	6	316	4
Secondary vs Tertiary	2194	14	820	10
Any discordance	6684	42	2596	30
Income				
1st quartile vs 2nd quartile	2048	13	1072	12
1st quartile vs 3rd quartile	1706	11	754	9
1st quartile vs 4th quartile	1158	7	490	6
2nd quartile vs 3rd quartile	2266	14	1194	14
2nd quartile vs 4th quartile	1574	10	682	8
3rd quartile vs 4th quartile	2000	13	1080	13
Any discordance	10 752	68	5272	61

DZSS=Dizygotic same sexed twins; MZ=Monozygotic twins; [a]May not sum to 100 because of rounding.

In the twin population, 1.9% did not redeem any drug prescriptions during the total follow-up period and 25% redeemed less than one prescription/year, on average (results not shown). Overall, women filled more prescriptions than men for all age groups and the number of prescription fillings increased with age in both sexes (table 3).

Table 3: The Mean Number of Prescription Fillings After 1 and 10 Years of Follow-up in a 5% Population Based Sample and a Population of Danish Twins, Stratified on Age and Sex.

Type of drugs	**Nelson Aalen Cumulative Hazard**			
Age				
Sex	5 % pop. (n= 137 300)		Twins (n=24 370)	
All purpose	*1 year*	*10 years*	*1 year*	*10 years*
30-44 years				
Men	2.5	28.7	2.2	25.9
Women	4.1	44.5	3.8	41.1
45-59 years				
Men	3.6	47.4	3.3	43.1
Women	6.0	71.9	5.7	68.4
60+ years				
Men	6.4	87.5	5.8	82.2
Women	8.3	105.4	7.2	95.7
Circulatory system (ATC-C)				
30-44 years				
Men	0.1	3.3	0.1	2.9
Women	0.2	4.2	0.2	3.6
45-59 years				
Men	0.7	12.6	0.6	10.6
Women	0.8	13.8	0.7	13.0
60+ years				
Men	1.9	29.6	1.7	27.4
Women	1.9	30.0	1.6	26.7
Nervous system (ATC-N)				
30-44 years				
Men	0.8	9.8	0.7	8.6
Women	1.1	14.5	1.0	13.3
45-59 years				
Men	1.2	14.6	1.2	13.9
Women	2.1	25.0	2.0	24.1
60+ years				
Men	1.8	24.4	1.6	22.2
Women	3.1	39.2	2.7	35.8
Respiratory system (ATC-R)				
30-44 years				
Men	0.3	3.9	0.3	3.6
Women	0.6	6.5	0.5	5.7
45-59 years				
Men	0.5	5.8	0.4	5.0
Women	0.8	9.8	0.7	9.1
60+ years				
Men	1.1	14.4	0.9	12.5
Women	1.2	14.8	1.0	12.8
Alimentary tract & metabolism (ATC-A)				
30-44 years				
Men	0.3	3.5	0.2	3.1
Women	0.4	5.0	0.4	4.1
45-59 years				
Men	0.5	7.6	0.5	6.6
Women	0.7	9.6	0.7	8.6
60+ years				
Men	1.1	15.4	1.1	15.0
Women	1.3	18.3	1.0	16.4

ATC-N drug prescriptions were the most frequently redeemed in the youngest age group. The mean number of prescription fillings in the twin population was similar to that in the population-based sample, although slightly higher in the population-based sample.

In order to get a better idea of the clinical outcomes underlying the observed prescription patterns, we have included a more detailed description of the most incident types of drugs at the 3-and 4-digit ATC level (Supplementary table 1). From the table it appears that the ATC-C category primarily comprises drugs indicated for hypertension and ischaemic heart disease, while the ATC-N category mainly includes drugs indicated for a wide range of different diagnoses, including chronic pain disorders, insomnia, anxiety, psychoses, depression etc.[28] In the ATC-R category the main types of drugs are drugs for obstructive airway disease such as asthma and Chronic Obstructive Lung Disorder (COPD)[28]. Finally, drugs for acid-related disorders and diabetes are the main constituents of the ATC-A category.

The results of an analysis of the association between SEP and prescription fillings for all-purpose and system-specific drugs are presented in table 4.

Table 4: The ratio (MR) of the mean number of prescription fillings (1995-2005) for all-purpose and system-specific drugs according to educational status and income in a 5% population-based sample (137 300) and a population of Danish twins (n=24 370), showing results from unpaired and intra-pair analyses stratified on zygosity.

Type of drug		**Unpaired analysis[a]**						**Intra-pair analysis[b]**			
		Pop % n=137300		DZSS n=15788		MZ n=8582		DZSS		MZ	
		MR	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*	*MR*	*CI 95%*
All purpose											
Education	Secondary	**0.90**	0.90-0.90	**0.90**	0.86-0.95	**0.87**	0.81-0.93	**0.88**	0.84-0.93	0.97	0.91-1.03
	Tertiary	**0.82**	0.82-0.83	**0.85**	0.80-0.91	**0.83**	0.76-0.90	**0.86**	0.80-0.92	0.95	0.86-1.05
Income	2nd quartile	**0.78**	0.78-0.78	**0.81**	0.76-0.85	**0.81**	0.75-0.88	**0.86**	0.82-0.91	**0.91**	0.85-0.97
	3rd quartile	**0.72**	0.72-0.73	**0.72**	0.69-0.77	**0.74**	0.69-0.80	**0.79**	0.75-0.83	**0.87**	0.81-0.94
	4th quartile	**0.70**	0.70-0.70	**0.71**	0.67-0.75	**0.70**	0.65-0.77	**0.76**	0.72-0.81	**0.87**	0.81-0.94
Circulatory system (ATC-C)											
Education	Secondary	**0.95**	0.95-0.96	**0.92**	0.85-0.99	**0.87**	0.78-0.96	**0.85**	0.79-0.92	**0.89**	0.81-0.97
	Tertiary	**0.79**	0.79-0.80	**0.78**	0.71-0.87	**0.70**	0.60-0.82	**0.80**	0.71-0.90	0.93	0.79-1.08
Income	2nd quartile	**0.91**	0.90-0.91	**0.94**	0.87-1.03	0.94	0.84-1.06	1.08	0.99-1.17	0.95	0.87-1.05
	3rd quartile	**0.83**	0.83-0.84	**0.86**	0.78-0.94	**0.86**	0.76-0.97	0.97	0.89-1.06	0.98	0.89-1.08
	4th quartile	**0.79**	0.79-0.79	**0.82**	0.74-0.90	**0.85**	0.74-0.97	0.97	0.88-1.08	0.94	0.84-1.05
Nervous system (ATC-N)											
Education	Secondary	**0.80**	0.80-0.80	**0.87**	0.79-0.96	**0.77**	0.67-0.88	**0.85**	0.77-0.94	1.00	0.86-1.17
	Tertiary	**0.71**	0.71-0.71	**0.77**	0.67-0.88	**0.75**	0.61.0.92	**0.78**	0.67-0.90	0.91	0.73-1.16
Income	2nd quartile	**0.61**	0.60-0.61	**0.61**	0.55-0.68	**0.60**	0.52-0.70	**0.68**	0.61-0.75	**0.75**	0.67-0.87
	3rd quartile	**0.49**	0.49-0.50	**0.47**	0.43-0.53	**0.47**	0.39-0.56	**0.54**	0.48-0.61	**0.59**	0.50-0.70
	4th quartile	**0.44**	0.44-0.44	**0.45**	0.40-0.51	**0.42**	0.35-0.50	**0.50**	0.45-0.57	**0.60**	0.50-0.71
Respiratory system (ATC-R)											
Education	Secondary	**0.86**	0.85-0.86	**0.77**	0.67-0.87	**0.82**	0.69-0.98	**0.83**	0.72-0.94	1.00	0.84-1.21
	Tertiary	**0.81**	0.80-0.81	**0.79**	0.68-0.92	**0.76**	0.61-0.95	**0.80**	0.66-0.97	0.77	0.58-1.03
Income	2nd quartile	**0.76**	0.75-0.76	**0.76**	0.66-0.87	**0.79**	0.65-0.98	**0.86**	0.75-0.99	1.04	0.86-1.25
	3rd quartile	**0.68**	0.68-0.69	**0.74**	0.64-0.86	**0.69**	0.57-0.85	**0.85**	0.73-0.98	1.02	0.84-1.24
	4th quartile	**0.63**	0.63-0.63	**0.69**	0.59-0.81	**0.64**	0.52-0.79	**0.83**	0.71-0.96	1.25	1.04-1.51
Alimentary tract & metabolism (ATC-A)											
Education	Secondary	**0.84**	0.84-0.84	**0.85**	0.77-0.94	**0.81**	0.71-0.93	**0.84**	0.75-0.94	0.98	0.85-1.14
	Tertiary	**0.68**	0.67-0.68	**0.72**	0.62-0.83	**0.64**	0.53-0.77	**0.81**	0.68-0.96	0.94	0.76-1.17
Income	2nd quartile	**0.74**	0.74-0.75	**0.73**	0.65-0.81	**0.83**	0.72-0.96	**0.85**	0.76-0.96	0.88	0.77-1.01
	3rd quartile	**0.64**	0.64-0.65	**0.63**	0.56-0.71	**0.77**	0.66-0.90	**0.77**	0.68-0.87	0.87	0.75-1.02
	4th quartile	**0.61**	0.61-0.61	**0.60**	0.53-0.68	**0.65**	0.55-0.77	**0.76**	0.67-0.88	0.86	0.72-1.02

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; [a]Unpaired analysis treating twins as individuals while taking interdependence of observations within each individual and within twin pairs into account. The interpretation of MR is the ratio of the mean number of prescriptions at a given time of e.g. an individual with a secondary or tertiary education compared to a random individual with a primary education. MRs are adjusted for age and sex. Income and education are mutually adjusted, [b]Intra-pair analysis of twins by inclusion of a strata statement. The interpretation of MR is the ratio of the mean number of prescriptions at a given time of a twin with a secondary or tertiary education compared to its co-twin with a primary education. Bold typography indicates statistical significance at 5% level.

For all-purpose drugs, MZ twins in the highest income quartile had a 30% lower mean number of prescription fillings than MZ twins in the lowest income quartile (MR=0.70 (CI 95%; 0.65,0.77). Similarly, MZ twins with a tertiary education had 17% lower mean number of prescription fillings than twins with a primary education (MR=0.82 (CI 95%: 0.75,0.89)). The association was slightly less strong for ATC-C drugs while stronger associations could be observed for the other system-specific drugs, particularly for ATC-N. In the unpaired analyses, no large differences could be observed between MZ and DZSS twins and there was no strong evidence for an interaction between SEP and zygosity in the unpaired analysis (education: *P*=0.81, income: *P*=0.95). In contrast, the effect of SEP was moderated by zygosity in the intra-pair analyses (education: *P*=0.02, income: *P*=0.05), suggesting a more attenuated effect of SEP in MZ twins than in DZSS twins: In MZ twins, generally no statistically significant effect of education could be observed, while income was still somewhat associated with all-purpose medication and quite strongly with ACT-N drugs. In DZSS twins, a minor or moderate attenuation could be observed, and all effect parameters were statistically significant, except for ATC-C drugs. In the population-based sample, the associations were similar to that in the overall twin population.

When using DDD (for all-purpose drugs) as outcome measure (table 5), results similar to the results based on number of prescription fillings were obtained, although the attenuation patterns in MZ twins were somewhat more clear in this analysis, showing no statistically significant associations with DDD of neither education nor income. In the analysis of number of prescriptions as a predictor of mortality we found a 60% increase in mortality rate during follow-up for a person who, on average, filled 1 prescription per month during the follow-up period compared to a person without any prescription fillings (HR=1.60 (95% CI: 1.25,2.05).

Table 5: Results from a Linear Regression Model Showing Number of Daily Defined Doses (DDD) for All-Purpose Drugs According to Educational Status and Income in a Population of Danish Twins (n=24370) Stratified on Zygosity. Results from Unpaired and Intra-Pair Analyses are Shown.

Educational status	**Unpaired analysis[a]**				**Intra-pair analysis[b]**			
Income	**DZSS n=15788**		**MZ n=8582**		DZSS		MZ	
	DDD	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*	*DDD*	*CI 95%*
Secondary	**-287**	-397;-177	**-289**	-440;-138	**-245**	-399;-90	-143	-346;59
Tertiary	**-404**	-531;-277	**-424**	-606;-243	**-344**	-557;-131	-152	-440;136
2nd quartile	**-401**	-541;-260	**-275**	-463;-88	**-219**	-383;-54	18	-177;214
3rd quartile	**-541**	-680;-402	**-451**	-638;-263	**-367**	-535;-198	-83	-287;121
4th quartile	**-505**	-648;-363	**-437**	-630;-243	**-327**	-512;-142	16	-209;242

DZSS=Dizygotic same sex twins; MZ=Monozygotic twins; [a]Unpaired analysis treating twins as individuals while taking interdependence of observations within each individual and within twin pairs into account. The interpretation of e.g. the education estimate is difference in the mean number of DDDs of an individual with a secondary or tertiary education compared to a random individual with a primary education. The estimates are adjusted for age and sex. Income and education are mutually adjusted [b]Intra-pair analysis of twins by inclusion of a fixed-effect statement. The interpretation of e.g. the education estimate is the difference in the mean number of DDDs of a twin with a secondary or tertiary education compared to its co-twin with a primary education. Bold typography indicates statistical significance at 5% level.

DISCUSSION

Summary of findings

In this large Danish twin population we demonstrated an inverse social gradient in fillings of prescription medicine for all-purpose and system-specific drugs. That is, a greater use of prescription medicine among those with a low SEP thus suggesting a worse health status of this group. Furthermore, the number of prescription fillings was shown to be associated with a greater risk of mortality. In the intra-pair analyses, where shared familial factors were controlled per design, the association between SEP and prescription fillings attenuated to a wide extent within MZ twins and statistically significantly less in DZSS twins. For education, there was generally no association with prescription fillings in the intra-pair analyses of MZ twins, except for drugs targeting the nervous system, while there was still some association of income with all-purpose medication and most system-specific drugs. However, no effect of income was seen in the intra-pair analyses when DDD were used as outcome measure. In spite of some variations between system-specific drugs, the overall pattern was the same as for all-purpose drugs, except for ATC-N drugs and to a lesser degree ATC-A drugs, which still showed some effect of SEP in the intra-pair analyses.

Interpretation

The fact that the association was attenuated in the intra-pair analyses suggests that underlying factors shared by a pair of twins account for some of the observed association between SEP and prescription fillings. However, there may be a number of alternative or complementary explanations for this finding: Firstly, part of it is likely caused by measurement error. Measurement error is random and therefore not shared by twins. In the intra-pair analysis, variance due to shared factors is removed, and a relatively larger proportion of exposure variance is thus due to measurement error. This will result in increasing attenuation of parameter estimates in the intra-pair analyses[33]. However, since data come from official registers it can be expected that education and income have limited measurement error. Secondly, the behaviour of one twin could be affected by the behaviour of the other twin, i.e. 'social interaction' either by 'imitation' or 'differentiation'. The implications of a potential imitation could be smaller within-pair differences, which could be misinterpreted as confounding from underlying familial factors. This may be of some concern in this study since fillings of prescription medicine is likely to have a behavioural component. Another implication of the discordant twin pair approach is that only twin pairs who are discordant on exposure contribute with statistical information to the estimation of SEP-

effects in the intra-pair analysis. This could potentially induce bias in the comparison of the unpaired and intra-pair analysis, since the two analyses are based only partly overlapping populations. Since MZ twins are less likely to be discordant, the selection bias may be most severe in MZ twins[34]. We examined this concern by restricting the unpaired analysis only to include groups with exposure-discordant twins. Results were similar to those of the main analysis in both MZ and DZ twins. A further issue relates to the fact that twins who are discordant on exposure are special in the sense that they, in spite of overlapping genes and rearing environment, differ in their SEP. Thus, unshared factors may explain these differences. This implies that the intra-pair analysis may still be confounded by unshared confounding factors, and that this confounding may be enforced in the intra-pair analysis[33]. Generally, confounding from unshared factors is thought to be more severe when confounders are less correlated than exposure[33]. This may or may not be true in our case, since we can only hypothesize on the correlation of unmeasured confounders. Nevertheless, the correlation of education and income (MZ=0.79, DZ=0.58 and MZ=0.49, DZ=0.33) are more or less of the same magnitude as phenotypes like cognitive ability[35] and BMI[36] which have previously been investigated using similar designs. In any case, as shown by Frisell et al. (2012) in order for *increased* confounding to explain the *attenuation* of the association observed in this study, the potential non-shared confounders would have to create a positive association between education and prescription fillings. In most cases, however, we would expect a negative association, although filling of prescription medicine is indeed a complex health outcome and it is theoretically possible for a confounder to have a dual effect on prescription fillings by 1) increasing the capability of getting the relevant prescriptions, e.g. due to more regular heath checks or better understanding of symptoms 2) at the same time reducing the need for prescription fillings due to better health status. Nevertheless, in a Danish context health status does seem to be the main determinant of prescription medicine[10, 37, 38] and was clearly associated with mortality in this data. Thus, in the presence of non-shared confounding we would expect the net effect of any confounding to produce a negative association between education and prescription fillings resulting in bias away from the null[33], and therefore it could not explain the observed attenuation of effect in the intra-pair analyses observed in this study.

The finding of greatest attenuation in MZ twins is compatible with the scenario of genetic confounding described in the introduction. Since the genetic overlap is greater in MZ twins than DZSS twins, one would expect a larger attenuation in MZ twins, if genetic factors gave rise to the confounding. However, a number of other factors could

produce a greater attenuation in MZ twins: First of all, the aforementioned measurement error may be most pronounced in MZ twins, due to the fact that increasing correlation in exposure will result in a greater attenuation of intra-pair parameter estimates[33]. In addition, the comparison of strength of association between MZ and DZ twins to indicate the source of familial confounding relies on the equal environment assumption: That is, MZ and DZ twins share their environment equally. However, this assumption may be challenged, and if it does not hold, i.e. if MZ twins not only share their genes but also their environment more closely than DZ twins[39], shared environmental factors could also produce a greater attenuation of effect in MZ twins. However, the interplay between environment and genes is complex, and it is conceivable that the environment to a certain extent is shaped in response to the genetic dispositions of an individual. If, for instance, a genetically determined similar appearance of MZ twins also elicits a more similar treatment from their peers, then these similar environmental stimuli can also be ascribed to genetic factors[40].

Thus, although several factors may contribute to the observed attenuation of association between SEP and filling of prescription drugs in the intra-pair analyses and to the differences in strength of association between MZ and DZ twins, the findings suggest that a part of the observed social inequality in prescription fillings is explained by either genetic or environmental factors shared by twins.

The finding of a persistent association of particularly income with fillings of prescriptions for ATC-N drugs clearly stood out from the general results. We therefore carried out a post hoc subanalysis of specific categories of ATC-N drugs to test whether it were certain types of drugs driving the association. The analysis revealed that it was mainly for analgesics and psycholeptics that the association persisted, while the association was somewhat attenuated for psychoanaleptics (primarily antidepressants). This finding may support the notion of reverse causation, i.e. that health status influences SEP rather than the other way around, since it is likely that diagnoses such as chronic pain disorders, psychoses, anxiety and bipolar disorders associated with these types of drugs may affect the work ability and thus the income of a person. Income is much more sensitive to reverse causation than education, which is usually obtained early in life and remains constant once it is obtained.

Existing literature

In this study we argue that fillings of all-purpose and system-specific drug prescriptions to some extent serve as an indicator of general health status and of conditions like ischaemic heart disease, hypertension, COPD, and diabetes. The finding of weaker effects of SEP, when underlying familial factors were taken into account, accords with a large part of the life course literature that supports the importance of early life factors in the aetiology of chronic disease in adulthood[41, 42].

In addition, a number of previous twin and sibling studies have investigated the association between various SEP-indicators and health outcomes. While some studies have shown strong or some evidence of a causal effect of adult SEP[43-47] other suggest no or little effect of SEP, when familial factors have been adjusted for [48-52]. Other studies show mixed results[21, 23-25, 47, 53-55]. However, the studies vary with respect to a number of important parameters hampering overall comparisons. Most importantly, investigated health outcomes differ and may have different aetiologies and show different social gradients and patterns of familial confounding, but even for specific health outcomes there is no clear picture of evidence. E.g. for mortality, two sibling-[45, 46] and two twin studies[21, 44] have investigated the association with education. Although all studies support some effect of education after controlling for shared family factors, important differences exist: The twin study by Madsen et al.(2010) demonstrated an effect of education within twins only in older cohorts of men, but not in younger men and not in women. The influence of shared family factors was thus suggested in the latter, but not in the first subgroup of this study. The two sibling studies also suggested some effect of shared family factors, while the twin study by Lundborg (2008) did not support any such effect. For self-rated health, the majority of the existing twin studies [24, 25, 54] have shown mixed results, although Osler et al. [47] and Lundborg[43] did find a statistically significant association between social class respective education and self-rated health in the intra-pair analyses. One important reason for the inconsistencies may be that many studies have suffered from power limitations in the intra-pair analyses due to a small number of events[21, 23, 25, 47, 54]. This is not a concern in this study, where almost all of the exposure discordant twins contributed with information to the intra-pair analyses, thus providing some of the most powerful twin results on social inequality in health to date.

Strengths and limitations

The twin approach is clearly a strength of this study, since it makes it possible to adjust for unmeasured background factors shared by twins that may be underlying the association between SEP and health. Furthermore, the large sample size and the long follow-up allow a great number of events to be analysed. In

addition, the use of population-based registers has the advantage of relatively little selection and measurement error in the study population. Finally, this study not only focuses on prescription medicine in general, but also on drugs targeting specific organ systems which may give us a better idea of potential mechanisms.

Among study limitations is the fact that filling of prescription medicine is not a perfect measure of health status. We do, however, argue that the observed association with mortality and the inverse relationship with education and income likely reflect a greater need for medicine among people of lower SEP. In case that access to health care also plays a role, presumably favouring people of high SEP, the social gradient in health status in this study could be underestimated. Although data did not contain information on over-the-counter (OTC) medication, it only constitutes a minor part of the total drug consumption in Denmark[7], and since we were interested in drugs as an indicator of health status, it could be argued that the most valid approach is to focus on drugs that require a formal medical indication (i.e. prescription).

As models for counting processes only allow one event at a time, the number of prescription fillings was defined as the main outcome of interest. Therefore, it was reassuring that the subanalysis on DDD led to similar results.

Although the distribution of SEP-indicators and prescription fillings were not entirely identical in twins and the population-based sample, the associations between SEP and prescription fillings were indeed, which supports generalizability to the general population in line with previous studies that show that health and mortality in twins are similar to the background population[56, 57]. Furthermore, the fact that the analysis based only on discordant twin pairs show marginal results similar to those based on the total twin sample was reassuring.

Conclusion and perspectives

In this study, based on a comprehensive twin cohort, we observed a social inequality in fillings of prescription medicine, showing fewer prescription fillings among people with high SEP. This association attenuated within twin pairs for most types of prescription-fillings, except those targeting the nervous system. The attenuation was most pronounced in MZ twins. Measurement error can contribute to the observed attenuation of association, but it is likely to account only for a minor fraction, considering the exposure and outcome measures in this study. As for potential non-shared confounding we would, if anything, expect it to bias the estimates away from the null.

We therefore interpret the findings as an indication that at least a part of the observed social inequality in prescription fillings is explained by shared familial factors. The implications of these findings are by no means a disqualification of SEP as a determinant of health, but rather an indication that family matters in the production of social health inequalities; most likely through early environment, and possibly also genetic factors. Recognizing biological components and early life exposures as important explanatory factors may improve our understanding of the multifaceted aetiology of health inequalities over the life course and increase the potential for effective and targeted interventions.

DISCUSSION

In this large Danish twin population we demonstrated an inverse social gradient in fillings of prescription medicine for all-purpose and system-specific drugs. That is, a greater use of prescription medicine among those with a low SEP, in spite of their limited financial means, thus suggesting a worse health status of this group. These marginal findings are in accordance with previous Danish studies reporting an inverse social gradient in drug use[5, 6]. In the intra-pair analyses, where shared familial factors were controlled for per design, the association attenuated to a wide extent within MZ twins and somewhat less in DZSS twins. For education, there was generally no association with prescription fillings in MZ twins, except for drugs targeting the neurologic system. For income, there was still some association with all purpose and most system-specific drugs. However, no effect of income was seen in the intra-pair analyses when DDD were used as outcome measure. In spite of some variations between system-specific drugs, the overall pattern was the same as for all-purpose drugs, except for ATC-N drugs and to a lesser degree ATC-A drugs, which still showed some effect of SEP in the intra-pair analyses.

The finding of greatest attenuation in MZ twins is compatible with the scenario of genetic confounding, since MZ twins are genetically identical in contrast to DZSS twins who share on average 50% of their segregating genes. However, a number of things should be kept in mind when interpreting these findings.

First of all, part of the observed attenuation is likely caused by measurement error. Measurement error is random and therefore not shared by twins. In the intra-pair analysis, variance due to shared factors is removed, and a relatively larger proportion of exposure variance is thus due to measurement error. This will result in increasing attenuation of parameter estimates in the intra-pair analyses with increasing correlation in

exposure[31], thus being most pronounced in MZ twins. However, using data from official registers it can be expected that education and income have very limited measurement error. In addition, the intra-pair correlation of education and income is not that different between MZ and DZ twins in this population and seems insufficient to explain the greater attenuation observed in MZ twins.

Twin studies generally rely on the equal environment assumption. That is, MZ and DZ twins share their environment equally. If this is does not hold, i.e. if MZ twins not only share their genes but also their environment more closely than DZ twins[32], shared environmental factors could also produce a greater attenuation of effect in MZ twins.

In addition, twins' behaviours could be affected in reaction to each other, i.e. social interaction either by imitation or differentiation. The implications of a potential imitation could be smaller within-pair differences, which could be misinterpreted as confounding from underlying background factors. This may be of some concern in this study since fillings of prescription medicine is likely to have a behavioural component.

Another implication of the discordant twin pair approach is that only twin pairs who are discordant on exposure contribute with statistical information to the estimation of SEP-effects in the intra-pair analysis. This could potentially induce bias in the comparison of the unpaired and intra-pair analysis, since the two analyses are based on essentially different populations. Since MZ twins are less likely to be discordant, the selection bias may be most severe in MZ twins[33]. We examined this concern by restricting the unpaired analysis only to include groups with exposure-discordant twins. Results were similar in both MZ and DZ twins.

A further issue relates to the fact that twins who are discordant on exposure are special in the sense that they, in spite of overlapping genes and rearing environment, differ in their SEP. Thus, unshared factors are likely to explain these differences. This implies that the intra-pair analysis may still be confounded by unshared confounding factors, and that this confounding may be enforced in the intra-pair analysis[31]. Generally, confounding from unshared factors is thought to be more severe when confounders are less correlated than exposure[31]. This may or may not be true in our case, since we can only hypothesize on the correlation of unmeasured confounders. Nevertheless, education and income are less correlated than phenotypes like cognitive

ability[34] and BMI[35] which have previously been investigated using similar designs. In any case, as shown by Frisell et al. (2012) in order for *increased* confounding to explain the *attenuation* of the association observed in this study, the potential non-shared confounders would have to create a positive association between education and prescription fillings. In most cases, however, we would expect a negative association, although filling of prescription medicine is indeed a complex health outcome and it is theoretically possible for a confounder to have a dual effect on prescription fillings by increasing the capability of getting the relevant prescriptions, while at the same time reducing the need for prescription fillings. Nevertheless, health status does seem to be the main determinant of prescription medicine[10, 36, 37] and was clearly associated with mortality in this data. Thus, in the presence of non-shared confounding we would expect the net effect of any confounding to produce a negative association between education and prescription fillings resulting in bias away from the null[31]. This could not explain the observed attenuation of effect in the intra-pair analyses observed in this study.

As mentioned earlier, fillings of prescription medicine is not a perfect measure for health status, but we argue that the observed inverse relationship with education and income likely reflects a greater need for medicine among people of lower SEP. In case that access to health care also plays a role, presumably favouring people of high SEP, the social gradient in health status in this study could be underestimated. Although data did not contain information on over-the-counter (OTC) medication, it only constitutes a small part of the total drug consumption in Denmark, and since we were interested in drugs as an indicator of health status, it could be argued that the most valid approach is to focus on drugs that require a formal medical indication (i.e. prescription).

The finding of a persistent association with fillings of prescriptions for ATC-N drugs clearly stood out from the general results. The possible explanation for this could be reverse causation, i.e. that poor health status affects ones income and not the other way around. Income is much more sensitive to reverse causation than education, which is usually obtained early in life and remains constant once it is obtained. It is likely that health conditions requiring prescriptions for ATC-N drugs may affect the work-ability and income of a person.

As models for counting processes only allow one event at a time, the number of prescription fillings was defined as the main outcome of interest. Therefore, it was reassuring that the subanalysis on DDD led to similar results.

~~Although the distribution of SEP-indicators and prescription fillings were not entirely identical in twins and the population-based sample, the associations between SEP and prescription fillings were indeed, which supports generalizability to the general population in line with previous studies that show that health and mortality in twins are similar to the background population[38, 39]. Furthermore, the fact that the analysis based only on discordant twin pairs show marginal results similar to those based on the total twin sample was reassuring.~~

~~In this study based on a comprehensive twin cohort we observed a social inequality in fillings of prescription medicine, showing fewer prescription fillings among people with high SEP. This association attenuated within twin pairs for most types of prescription-fillings, except those targeting the neurologic system. The attenuation was most pronounced in MZ twins. Several explanations may account for these findings. Measurement error can contribute to the observed attenuation of association, but it is likely to account only for a small fraction, considering the exposure and outcome measures in this study. As for potential non-shared confounding we would, if anything, expect it to bias the estimates away from the null. We therefore interpret the findings of this study as an indication that at least a part of the observed social inequality in prescription fillings is explained by shared familial factors. Previous studies have investigated the association between various SEP-indicators and health outcomes. However, most studies suffered from severe power limitations in the intra-pair analyses due to a small number of events[19, 21, 23, 40, 41]. This is not a concern in this study, where almost all of the 24 370 twins contributed with information to the intra-pair analyses, thus providing some of the most powerful twin results on social inequality in health to date.~~

COMPETING INTERESTS

None.

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