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Preterm birth and prescriptions for cardiovascular, anti-seizure, antibiotics and anti-asthmatic medication in children up to ten years of age: A population-based data linkage cohort study across six European regions

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Abstract

Objectives: Preterm children are exposed to many medications in neonatal intensive care units, but little is known about the effect of prematurity on medication use throughout infancy and childhood. We examined prescriptions of cardiovascular medication (CVM), anti-seizure medication (ASM), anti-asthmatic medication and antibiotics issued/dispensed in the first 10 years of life for very and moderately preterm children compared to term.

Design: Population-based data linkage cohort study linking information from birth records to prescription records.

Setting: Six registries from five countries in the EUROlinkCAT study.

Participants: The study population included 1,722,912 children, of whom 10,820 (0.6%) were very preterm (<32 weeks gestational age (GA)), 92,814 (5.4%) were moderately preterm (32-36 weeks GA), 1,606,643 (93.3%) were born at term (≥37 weeks GA) and 0.7% had missing GA. Children with major or minor congenital anomalies were excluded (including patent arterial duct).

Main outcome measures: Relative risk (RR) of receiving a prescription for CVM, ASM, anti-asthmatic and antibiotics.

Results: Very preterm children had a higher RR of receiving a prescription for CVM and ASM than preterm children. For all preterm children, the RR of having a CVM prescription was 3.58 (95% Confidence interval (CI); 2.06-6.23); 2.06 (CI: 1.73-2.41) for ASM; 1.13 (CI: 0.99-1.29) for anti-asthmatics; and 0.96 (CI: 0.93-0.99) for antibiotics in the first year of life. Increased prescription of CVM, ASM and anti-asthmatics persisted for all 10-years of follow-up. Although the RR was highest for CVM and ASM, in absolute numbers more children received prescriptions for antibiotics (42.34%

(CI: 38.81-45.91) and anti-asthmatics (28.40% (CI: 16.07-42.649) than for CVM (0.18% (CI: 0.12-0.25)) and ASM (0.16% (CI: 0.13-0.20)) in the first year of life.

Conclusion: Preterm children had a higher risk of being prescribed/dispensed CVM, ASM and anti-asthmatics up to age 10. This study highlights a need for further research into morbidity beyond age 10.

Strengths and limitations of this study

- This is a population-based study including data on more than 100,000 children born preterm in six geographically different European regions.
- With the high number of children included in our study we are able to report data on relatively infrequently prescribed medications such as anti-seizure and cardiovascular medication.
- The study includes data for the first 10 years of life and we are thus able to detect impacts of preterm birth extending into childhood.
- An important limitation is that we do not have access to the medical files for included children and therefore we do not have information regarding the specific indication for which a medication was prescribed.

Introduction

Complications due to preterm birth, i.e. before 37 completed weeks of gestation, is the leading cause of death for children under 5 years of age(1). In high income countries close to 100% of babies born at a gestational age (GA) of 32 weeks are expected to survive infancy(2), but babies born extremely preterm (< 28 weeks GA) and with low birthweight still have a mortality rate of 33 – 50 % in developed countries(3). The increased survival of children born preterm raises the question "does the increased survival come with the price of an increased morbidity in childhood compared to term born children?". One such indicator of disease burden is prescription of medication, as this will reflect underlying disease. Although a number of studies have addressed prescriptions and use of medications in the neonatal intensive care unit (NICU), little is known about prescriptions after discharge. The few available studies have focused on prescriptions in the first year or two of life (4,

5), but long-term follow-up is lacking. Life in the first year after discharge from the NICU is characterized by frequent paediatric visits and an average of 5.5 prescriptions per year(4). One study from the United States (US) found that the most frequently prescribed medication in the first two years of life were palivizumab, ranitidine, albuterol, lansoprazole, budesonide and prednisolone(5). Of these medications only palivizumab has a specific indication in preterm infants, and concerns regarding safety and lack of efficacy have been raised for lansoprazole(6), ranitidine(7) and budesonide(8). Most research has centred on prescriptions of these medications while for instance cardiovascular medication (CVM) and anti-seizure medication (ASM) have received less research interest.

The aim of the present study was to evaluate the community prescription of CVM, ASM, anti-asthmatics and antibiotics to children born before 37 weeks GA compared with term children from birth up to 10 years of age, as an indicator of chronic disease burden. Furthermore, we aimed to look at differences in prescription of CVM between term (+37 weeks GA), moderately preterm (32-36 weeks GA) and very preterm (<32 weeks GA) children for their first 10 years of life in six different European regions.

Methods

This is a European, population-based linkage cohort study arising from the EUROlinkCAT project (9). The EUROlinkCAT project includes data on morbidity and medication use for children born with congenital anomalies and for reference children without congenital anomalies born in the same geographical area. In the present paper we focus on these reference children. Five regions provided data on all liveborn children in their region and one region (Tuscany) provided a random 10%

sample, matched on date of birth and sex, of their population of reference children. The minimum GA for inclusion was 23 weeks except for Wales where it was 24 weeks. Data were included for children born between 2000-2014, but three registries had a shorter study period as linked data in these regions were not available at the start of the study period (Table 1).

	First Year of birth	Source of prescriptions	Number of Children			
			Reference population	<32 GA	32 – 36 GA	+37 GA
Denmark: Funen*	2000	Dispensed by pharmacy	72,290	525	4045	66625
Finland	2000	Dispensed by pharmacy	755,923	4,245	33,860	715,620
Italy: Emilia Romagna	2008	Dispensed by pharmacy	250,829	1,902	16,350	232,507
Italy: Tuscany	2008	Dispensed by pharmacy	16,844	77	926	15,840
Spain: Valencian Region	2010	Dispensed by pharmacy	223,760	1,173	14,618	202,304
UK: Wales *	2000	Prescribed by GP	403,265	2,895	23,015	373,750
Total number of children			1,722,912	10,820	92,814	1,606,643

Information on medication was available by linking children identified in birth records to local electronic prescription databases in each of the six regions. All children in the six regions needed to have a valid identification (ID) number to be identified in the relevant prescription database. Four regions had valid IDs for >99% of children, one region had valid IDs for 95% of children (Emilia Romagna), and one had valid IDs for 85% of children (Wales). The proportion was lower for Wales as information on prescriptions were obtained only from General Practitioners (GPs) who contributed to the Secure Anonymised Information Linkage (SAIL) database. In total, 1,722,912

children aged up to 10 years of age had a valid ID that allowed them to be identified in a prescribing database, between the years 2000-2015 (Table 1).

Analyses were performed according to three age groups (<1 year, 1-4 years and 5-9 years). GA at birth was categorised as very preterm (<32 weeks GA), moderately preterm (32-36 weeks GA) and term births (37+ weeks GA).

Exclusions: Children with a code for a major or minor congenital anomaly in the hospital in-patient databases were excluded from the study population, i.e. any child with a WHO International Statistical Classification of Diseases and Related Health Problems (ICD) 9th revision (code with 74-75) or 10th Revision code (Q-chapter)(10). This criteria also excluded children with a patent arterial duct (PDA).

Minimum number of prescriptions: A child must have at least one prescription to be classified as exposed to a medication. In epidemiology, risk has been defined as "the probability of an event during a specified period of time"(11), and as such uses the term risk for the probability of receiving medication.

Small numbers: In two of the participating registries extraction of small numbers were not allowed, we therefore restricted the analysis to 4th level in the ATC system as outlined below.

Classification of medication:

CVM: As previously described in detail (12) antiarrhythmic medication is classified according to the Vaughan Williams classification (VWC)(13). Antihypertensive medication and diuretics were classified according to the Anatomical Therapeutic Classification (ATC) system codes reported in the electronic prescription databases. In brief, this gave us the categories outlined below:

- Any CVM: All ATC codes beginning with C01-C03 and C07-C09, excluding C01BA51, C01BA71, C01CA24
- VWC1 (Fast sodium-channel blockers) : ATC codes beginning with C01BA (excluding C01BA51 and C01BA71), C01BB and C01BC (i.e. procainamide, lidocaine and flecanide)
- VWC2 (Beta-blockers): ATC codes beginning with C07A (i.e. atenolol, propranolol)
- VWC3 (Potassium-channel blockers): ATC codes beginning with C01BD (i.e. nefidipine)
- VWC5 (Other mechanism of action): ATC codes C01AA05 (i.e. digoxin, adenosine)
- Antihypertensives: ATC codes beginning with C08 and C09
- Diuretics: ATC codes beginning with C03

ASM: Medication used for the treatment of epilepsy/seizures were stratified into four groups:

- Any ASM: all medication included in the ATC system beginning with N03.
- First generation ASM: ATC codes beginning with N03AA, N03AB, N03AE, N03AF (i.e. phenobarbital, phenytoin, clonazepam, carbamazepine).
- Second generation ASM: ATC codes beginning with N03AX (i.e. lamotrigine, gabapentin, topiramate, and levetiracetam).
- Fatty acid derivatives (FAD): ATC codes beginning with N03AG (i.e. valproic acid, valpromid, progabide etc.).

Anti-asthmatics: All medication used in the treatment of obstructive airway diseases as classified under ATC codes beginning with R03. These were divided into the following categories:

- Anti-asthmatic: ATC codes beginning with R03

- Beta-2-agonists: ATC codes beginning with R03AC, which comprises all inhaled selective beta-2-adrenoreceptor agonists (i.e. salbutamol, terbutaline, fenoterol etc.).
- Glucocorticoids: ATC codes beginning with R03BA which includes all inhaled glucocorticoids (i.e. beclometasone, budesonide, fluticasone etc.) except combinations with adrenergics and anticholinergics which are classified under R02AK and R03AL.

Antibiotics: In this study, the broad term "antibiotics" is used to cover all systemic antibacterials as defined by the ATC system using codes beginning with J01. All topical antibiotics (ointments/ creams) for skin infections, drops for eye or ear infections, antibiotics that are administered intravenously and antibiotics not classified under the ATC code J01 were not included. Medications were then stratified into three subgroups:

- Any antibiotic: ATC codes J01.
- Penicillins: ATC codes J01C (comprises both beta-lactamase sensitive and resistant penicillins plus combinations with beta-lactamase-inhibitors).
- Macrolides: ATC codes J01F (also includes lincosamides and streptogramins).

Statistical methods: Each registry standardised their data using the EUROlinkCAT common data model (14) which enabled them to run a centrally written analysis script on their individual case data. The number of children prescribed/dispensed at least one prescription and the number of child years observed during each year of age were calculated in children according to GA at birth categorised into very preterm (GA <32 weeks), moderately preterm (GA 32-36 weeks) and term (GA 37+ weeks) and submitted to the central results repository at Ulster University (only aggregate data;

no individual case data were provided to Ulster University). The aggregate results for all registries were then provided to the researchers. The risk of being prescribed/dispensed a medication at a particular year of age was calculated as the number of children prescribed/dispensed at least one prescription when they were that age divided by the number of child years observed during the same age year (to allow for children being censored during the year). The relative risks (RR) of being prescribed/dispensed a medication in preterm children (<37 weeks GA) compared to in term children (37+ weeks GA) were calculated for each year of age within each registry. The data were then combined and analysed by performing an inverse variance random effects meta-analysis of the RR and 95% confidence intervals (CI) of being prescribed/dispensed a medication at each year of age in preterm children (<37 weeks GA) group compared to the risk in term children (37+ weeks GA). In addition the RR for <32 weeks GA and 32-36 weeks GA compared to term children (37+ weeks GA) were calculated within three age groups (<1 year, 1-4 years, 5-9 years). Three registries had no information on children over 7 years of age, as their data started in 2008 (Emilia Romagna and Tuscany) and 2010 (Valencian Region), so they were excluded from the 5-9 years' analysis.

Ethics Approval: All registries that are part of the EUROCAT network have the required ethics permissions and procedures for routine surveillance, data collection and transmission of anonymised data to the EUROCAT central database. In accordance with national guidelines, the registries submitted evidence of these permissions to the EUROlinkCAT ethics portfolio. The central data repository Ulster University also obtained ethics approval (approval number FCNUR-21-060). Local registries follow national legislation as to whether parental consent is needed for registration of babies with anomalies. For details please refer to separate protocol paper (9).

Patient Public Involvement: Patients/parents were not involved in the study design, however as part of the project we have plans for dissemination and knowledge exchange with parents as described in detail on our webpage(15) and protocol paper(9).

Results

Population characteristics: The study population included 1,722,912 children, of whom 10,820 (0.6%) were very preterm (< 32 weeks GA), 92,814 (5.4%) were preterm (32-37 weeks GA), 1,606,643 (93.3%) were term (Table 1) and 0.7% had missing GA in the databases (these were evenly distributed among participating regions).

CVM:

Prescription of CVM at each year of age: The risk of receiving a CVM prescription for preterm children (<37 weeks GA) compared to term children was highest in the first year of life (RR 3.58, 95%CI: 2.06-6.23) and slowly decreased for each consecutive year up to age 9 years (Fig 1A). The percentages of preterm children receiving a CVM prescription were 0.18% (95% CI: 0.12-0.25) in the first year of life, 0.06% (95% CI: 0.03-0.09) for ages 1-4 years and 0.07% (95% CI: 0.02-0.14) for ages 5-9 years (Table 2).

	<1 year		1-4 years		5-9 years	
Medication	Percentage of preterm (<37 GA) children with a prescription (N = 10,3634)	RR for preterm (< 37 GA) vs term (+37 GA) children	Percentage of preterm (<37 GA) children with a prescription (N=102,309)	RR for preterm (< 37 GA) vs term (+37 GA) children	Percentage of preterm (<37 GA) children with a prescription (N = 60,489)	RR for preterm (< 37 GA) vs term (+37 GA) children
Any CVM	0.18 (0.12-0.25)	3.58 (2.06-6.23)	0.06 (0.03-0.09)	2.05 (1.71-2.46)	0.07 (0.02-0.14)	1.43 (1.04-1.97)
Diuretics	0.07 (0.01-0.16)	7.19 (2.29-22.60)	0.01 (0.01-0.02)	3.29 (2.09-5.17)	0.00 (0.00-0.00)	2.35 (1.34-4.10)
Antihypertensives	0.02 (0.00-0.03)	2.34 (0.94-5.82)	0.01 (0.01-0.03)	1.66 (1.12-2.48)	0.02 (0.01-0.03)	1.68 (1.22-2.32)
VWC2 (beta-blockers)	0.07 (0.05 – 0.09)	2.82 (2.24-3.55)	0.06 (0.03 – 0.09)	2.12 (1.68-2.67)	0.05 (0.01-0.18)	1.32 (1.07-1.63)
Any ASM	0.16 (0.13-0.20)	2.06 (1.76-2.41)	0.27 (0.22-0.32)	1.77 (1.50-2.08)	0.38 (0.31-0.46)	1.59 (1.48-1.70)

New ASM	0.02 (0.01-0.05)	2.03 (1.44-2.85)	0.08 (0.06-0.12)	1.87 (1.50-2.35)	0.13 (0.11-0.15)	1.70 (1.43-2.02)
Old ASM	0.08 (0.06-0.10)	2.09 (1.67-2.61)	0.07 (0.05-0.09)	1.84 (1.32-2.58)	0.11 (0.08-0.14)	1.80 (1.35-2.38)
FAD	0.07 (0.04-0.11)	2.21 (1.78-2.74)	0.17 (0.13-0.22)	1.75 (1.53-2.00)	0.22 (0.18-0.27)	1.63 (1.50-1.78)
Any anti-asthmatic	28.40 (16.07-42.64)	1.13 (0.99-1.29)	25.67 (18.35-33.75)	1.20 (1.04-1.37)	12.84 (11.44-14.31)	1.21 (1.07-1.36)
Beta-2-agonists	14.83 (8.45-22.63)	1.29 (1.06-1.56)	14.93 (12.13-17.96)	1.31 (1.14-1.51)	7.77 (6.55-9.09)	1.22 (1.10-1.36)
Glucocorticoids	10.47 (2.70-22.47)	1.41 (0.94-2.12)	12.91 (6.54-21.04)	1.34 (1.05-1.70)	7.80 (5.94-9.87)	1.28 (1.11-1.48)
Any antibacterial	42.34 (38.81-45.91)	0.96 (0.93-0.99)	51.05 (47.63-54.46)	1.02 (0.98-1.06)	29.41 (26.42-32.49)	1.02 (0.98-1.07)
Penicillins	37.19 (33.58-40.88)	0.95 (0.92-0.98)	43.44 (41.72-45.16)	1.03 (0.99-1.07)	22.79 (21.67-23.94)	1.03 (0.98-1.08)
Macrolides	8.43 (5.94-11.30)	0.95 (0.94-0.97)	13.62 (9.76-18.01)	1.07 (1.02-1.12)	6.90 (4.84-9.30)	1.06 (0.98-1.15)

Impact of preterm birth on CVM prescriptions: A dose dependent effect was observed i.e. the lower the gestational age at birth, the higher the RR of receiving a CVM prescription in their first year of life compared with term children. In very preterm children (<32 weeks GA), the RR was 12.06 (95% CI 3.28-44.35) and in moderately preterm (32-37 weeks GA) the RR was 2.44 (95% CI 2.00-2.98). The dose dependent effect of preterm birth on prescriptions of CVM was present across all age groups included in the study (Fig 2A).

Pharmacological types of CVM prescribed/dispensed:

*VWC2 (beta-blockers): T*he RR for receiving a VWC2 prescription in preterm vs term children, was 2.82 (95% CI: 2.24-3.55) in the first year of life, 2.12 (95% CI: 1.68-2.67) for ages 1-4 years and 1.32 (95% CI: 1.07-1.63) for ages 5-9 years. The percentage of preterm children receiving a beta-blocker in their first year of life was 0.07% (95% CI; 0.05-0.09).

Diuretics: The RR of having a diuretic prescribed/dispensed was highest in the first year of life (RR 7.19; 95% CI: 2.29-22.60), and then decreased for ages 1-4 years (RR 3.29; 95% CI: 2.09-5.17) and 5-9 years (RR 2.35; 95% CI: 1.34-4.10). The percentage of preterm children receiving a diuretic in their first year of life was 0.07% (95% CI; 0.01-0.16).

Antihypertensives: Prescriptions for antihypertensives remained stable at a RR of around 2 for all three age groups, i.e. 2.34 (95% CI: 0.94-5.82), 1.67 (95% CI: 1.12-2.48) and 1.68 (95% CI: 1.22-2.32) for ages <1, 1-4 and 5-9 years, respectively. The percentage of preterm children receiving antihypertensive prescriptions in their first year of life was 0.02% (95% CI: 0.00-0.03).

VWC1, VWC3, VWC5: numbers were too small to report.

Regional differences in prescription: Fig 3A displays the RR of receiving a CVM prescription in the first year of life for each of the regions included in the meta-analysis reported above. A significantly increased RR was observed for five of the six regions (range of RR 2.18 – 8.70) with the exception of Tuscany where there was no increased RR and the confidence intervals were extremely wide.

ASM

Prescriptions of ASM at each year of age: At each individual year of age during the 10-year follow-up period, prescriptions of ASM were higher for preterm (< 37 weeks GA) than for term children. The RR decreased with age, but prescriptions remained significantly higher for preterm than term children (Fig 1B). The percentages of pre-term children receiving a prescription in a year increased with age from 0.16% (95% CI: 0.13-0.20) for ages <1 year, 0.27% (95% CI: 0.22-0.32) for ages 1-4 years to 0.38% (95% CI: 0.31-0.46) for ages 5-9 years (Table 2).

Impact of preterm birth on ASM prescription: In the first year of life children born very preterm (<32 weeks GA) and moderately preterm (32-36 weeks GA) had a higher RR of being prescribed/dispensed an ASM compared to term children (RR 3.15, 95% CI: 1.68-5.90 and RR 1.91, 95% CI: 1.58 – 2.31). The effect of increased prescription with lower GA was seen across all age groups (Fig 2B).

Pharmacological types of ASM prescribed/dispensed (Table 2):

The same pattern of an increased RR at around 2 of being prescribed/dispensed an ASM was observed for all three pharmacological types of ASM (first/second generation and FAD) for the first 10 years of life. There was an increase in percentage of children receiving a prescription with age for all three age groups (for details please see Table 2).

Regional differences in prescription: An increased risk for preterm children compared to term children was observed across all six regions (RR range 1.41 – 2.43, Fig 3B), although for both Italian regions the increase was not statistically significant.

Anti-asthmatics

Prescription of anti-asthmatics at each year of age for all preterm born children (<37 weeks GA): For all preterm children, the RR of being prescribed/dispensed a prescription for anti-asthmatic medication was significantly higher than for term children for all 10 years of follow-up. The RR was relatively stable around 1.2 for all 10 years (Fig 1C).

Impact of prematurity on anti-asthmatic prescription: There was no discernible dose dependent effect of prematurity on prescription of anti-asthmatic medication, i.e. for both very preterm and moderately preterm children the RR for prescription of anti-asthmatics in the three different age categories remained around 1.3 (Fig 2C). In total 28% of all preterm born children received a prescription for any anti-asthmatic medication in the first year of life.

Pharmacological types of anti-asthmatics prescribed/dispensed (Table 2):

Beta-2-agonists: The RR for receiving or having a prescription for a beta-2-agonist was around 1.3 for all age categories, i.e. 1.29 (95% CI: 1.06-1.56) for ages <1 years, 1.31 (95% CI: 1.14-1.51) for ages 1-4 years and 1.22 (95% CI: 1.10-1.36) for ages 4-9 years.

Glucocorticoids: The RR for being prescribed/dispensed a prescription for a beta-2-agonist was around 1.3 for all age categories, i.e. 1.41 (95% CI: 0.94-2.12) for ages <1 years, 1.34 (95% CI: 1.05-1.70) for ages 1-4 years and 1.28 (95% CI: 1.11-1.48) for ages 4-9 years.

Regional differences in prescription: In three of six regions (United Kingdom: Wales, DK: Funen and Finland) there was a significantly increased RR of prescription for preterm children in the first year of life, whereas in the three other regions no significant difference between term and preterm children was observed (Fig 3C).

Antibiotics

Prescription of antibiotics at each year of age: The RR of preterm children having an antibiotic prescription issued /dispensed compared to term children was slightly lower in the first year of life. There were no significant differences in risk between preterm and term children during the next 9 years of follow-up (Fig 1D).

Impact of preterm birth on prescriptions for antibiotics: In the first year of life children born very preterm (<32 weeks GA) and moderately preterm (32-36 weeks GA) had a lower RR of receiving a prescription for antibiotics than term children (RR 0.86, 95% CI: 0.78-0.95 and RR 0.97, 95% CI: 0.95-1.00). For the age categories 1-4 years and 5-9 years, there was no difference in prescriptions compared to term children. Furthermore we did not observe a dose dependent effect of preterm birth on prescription, i.e. no effect of decreasing GA on RR for prescription (Fig 2D).

Pharmacological types of antibiotics prescribed/dispensed (Table 2):

Any antibiotics: 42.34% (95% CI; 38.81-45.91) received a prescription in their first year of life, 51.05% (95% CI; 47.63-54.46) were issued/dispensed a prescription each year for ages 1-4 years and 29.41% (95% CI; 26.42-32.49) each year for ages 5-9 years.

Penicillins: were prescribed/dispensed for 37.19% (95% CI; 33.58-40.88) of children < 1years, 43.44% (95% CI; 41.72-45.16) had a penicillin prescription each year for ages 1-4 years and 22.79% (95% CI; 21.67-23.94) each year for ages 5-9 years.

Macrolides: 8.43% (95% CI; 5.94-11.30) received a prescription in their first year of life, 13.62 (95% CI; 9.76-18.01) were issued/dispended a prescription for macrolides each year for ages 1-4 years and 6.90% (95% CI; 4.84-9.30) each year for ages 5-9 years.

Regional differences in prescription: A significantly decreased RR for prescription of antibiotics was observed in four of six regions (Fig. 3D).

Discussion

To our knowledge this is the first study to examine medications prescribed/dispensed for cardiovascular diseases, neurological seizures, asthma and infections in a paediatric cohort comparing preterm and term born children up to ten years of age. We show that children born preterm had an increased risk compared to term children of being prescribed/dispensed CVM, ASM and anti-asthmatic medication. For CVM and ASM risks were higher for earlier gestations. For CVM the increased relative risk was most pronounced in the first year of life, whereas for ASM the risk was at a constant level for the first 10 years of life. Although the RR was highest for CVM and ASM, in absolute numbers more children were receiving prescriptions for antibiotics and anti-asthmatics than for CVM and ASM. In the first year of life preterm children had a reduced RR for receiving antibiotics compared to term children.

An important limitation of our study is that all preterm children with a code for PDA are excluded as we excluded all children with congenital anomalies as defined in the method section. There is an inverse relationship between GA and PDA, such that the more preterm an infant is born the higher

the probability that arterial duct will not close spontaneously (16). Furthermore, it has been established that having a PDA is associated with prolonged mechanical ventilation, bronchopulmonary BPD, and necrotizing enterocolitis (16, 17). Therefore, the net effect of excluding infants with a PDA is that we may be underestimating the true burden of morbidity for the group of preterm born children. Also this study only assesses prescription patterns, and as such we are not able to assess whether or not medication are prescribed rationally in accordance with the current standards of evidence, further studies are need to address this question.

Cardiovascular medication: The highest RR in the present study was for diuretics in the first year of life. Although the RR was higher for preterm children with respect to all CVM, it is important to note that in absolute terms few children were prescribed these medications. In preterm born children, development of BPD is the most frequent chronic morbidity and strongly predicts both death and disability in childhood(18-20). The most regularly prescribed medication to infants admitted with an exacerbation in BPD is diuretics(21) and as much as 86% of infants admitted for BPD exacerbation will follow a treatment course for > 5 days with diuretics(22). It therefore seems plausible that the high RR for diuretics in the first year of life most likely reflects either chronic treatment for BPD or shorter periods given in relation to exacerbations in BPD. However, there is a lack of evidence on the efficacy of diuretics in preterm children. For example a Cochrane review examining the risks and benefits of administration of diuretics (furosemide) to preterm children in the NICU at a post menstrual age <40 weeks with ongoing or incipient chronic lung disease found that “furosemide administration has either inconsistent effects or no detectable effect”(23). There are no systematic reviews for long-term use of diuretics to infants/children after discharge from the NICU. In view of this, it is noteworthy that we in the present study find that there is an increased prescription of diuretics to preterm born children up to 10 years of age. The increased RR for prescription of

antihypertensives (which includes ACE-inhibitors) and beta-blockers could reflect chronic heart failure treatment as these are recommended first-line therapies for paediatric heart failure(24). As with diuretics for BPD heart failure treatment in adults with congenital heart defects are generally based on position statements rather than solid evidence(25), a problem that "is even more pertinent in children" (26). The few available studies on heart failure treatments in children have either failed to show an effect or have been underpowered (27-29). Future studies are needed to address whether or not these patterns of increased prescription of CVM can affect clinical course or outcome in preterm children.

Anti-seizure medication: Increased prescription of ASM probably reflects an increased risk for epilepsy among preterm born children. It has previously been shown that there is an inverse dose-response curve with decreasing gestational age increasing epilepsy risk later in life(30), a phenomenon we also observe in our data. A recent meta-analysis estimated that the increased odds ratio (OR) for epilepsy for children born preterm versus term was 2.14 which is consistent with our estimates of increased ASM prescription(31). It is noteworthy, in our data, that while the RR for ASM prescription was relatively stable over the age groups, in absolute terms the number of children receiving treatment roughly doubles from <1 years of age to the age group 5-9 years. The cumulative incidence of epilepsy increases through childhood(32), but it seems that the extra RR conferred by preterm birth is present for at least 10 years after birth. Randomized controlled trials on management of epilepsy in infants are lacking, and as pointed "There is no high-level evidence to support any particular current agents for use in infants with seizures"(33). Treatment strategies are thus based on expert opinion rather than solid evidence(34)., In the present study the RR for prescription of both first/second generation ASM and FAD are remarkably similar, suggesting that

no group is preferred specifically for the epilepsy forms associated with preterm birth. Again studies of medication efficacy are warranted in this patient group.

Anti-asthmatic medication: Preterm birth has been associated with an increased risk of childhood asthma or wheezing disorder with an increased odds ratio of 1.46(35), although considerable heterogeneity across studies have been noted(36). A Danish cohort study reported a strong inverse association with GA and purchase of anti-asthmatics (defined as purchasing both an inhaled beta-2-agonist and glucocorticoids) and found that OR decreased as the age of children increased (37). The waning effect of preterm birth with advancing age has later been shown to progress beyond 11 years of age (38). In the present study preterm birth is associated with an increased risk of being prescribed/dispensed anti-asthmatics at a RR around 1.2 which is similar to that reported in the Danish study, although we did not observe a waning effect with age for the 10 years follow-up after birth. In absolute numbers 28% of preterm children are prescribed anti-asthmatics in their first year of life which then declines to around 13% for ages 5-9 years, so although the RR is lower than for CVM and ASM in absolute numbers far more children were prescribed anti-asthmatics than CVM and ASM. Prescriptions of inhaled beta-2-agonist and glucocorticoids in our study were not substantially different and seems to suggest that children, if treated with anti-asthmatics, are treated with both.

Antibiotics: The present study did not find a dose dependent effect of preterm birth on RR for prescription of antibiotics. Lorch and colleagues looked at the effect of GA on antibiotic prescription in children born <32 weeks GA for the first year of life and did not find an effect of GA on prescription of antibiotics for very preterm born infants (39). In contrast, it has been reported for children from 2 years of age and older that lower GA resulted in higher prescription rates of antibiotics up until ages 10-11 years where an inverse pattern was observed with decreasing prescription(40). The

authors reported a similar pattern with respect to hospital admission for airway infections(40). Several studies have reported higher rates of admissions for respiratory infections both in infancy and childhood for preterm born children (41-43). The study by Lorch et al. did not include a control group, and their finding of lower prescription rates cannot be corroborated by other studies. The higher rates of hospitalizations due to infections for preterm born infants and children reported by other studies might provide some part of the explanation for our data. Our study included prescriptions for children outside hospitals only as we did not include medication given during hospital admissions. Further, preterm born infants stay in hospital for up to three months after birth and therefore they are less "exposed" to prescriptions (as defined in our study) in the first year of life. It is also possible that the lower RR in the first year of life reflects that preterm children are kept more at home and shielded from infections than term children. In teenagers it has been suggested that there is an *ex-preterm behavioral phenotype*(44) that may lead to a more socially isolated life-style with less exposure to infections(40). It can be speculated that there might be a similar behavioral pattern in parents during infancy.

Regional differences: Overall we observed similar trends across all six European regions included in the present study. As there is considerable overlap of confidence intervals between various European regions we cannot for certain identify clinically relevant differences in prescription between geographical regions. Due to a small sample from Tuscany, this sub-cohort failed to find any differences in prescription patterns for preterm vs. term born children.

Conclusion: Children born preterm are at a higher risk of being prescribed/dispensed prescriptions for CVM, anti-seizure medication and anti-asthmatic medication in their first 10 years of life. The higher risk was also present for the moderate preterm born children. While it is known that children

born preterm are vulnerable, this study demonstrates that these children have an excess risk of chronic diseases requiring medication up to age 10 years. Future studies should assess if the excess morbidity associated with preterm birth continues into adolescence/ young adulthood or if it levels off after ten years of age. Preterm born infants have a long life a head of them when they start out the PICU. Optimization of management though infancy and childhood can have profound consequence of quality of life for many years to come, in light of this it seems peculiar that so little of the current prescription practice for ex-preterm infants and children are based on solid scientific evidence.

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The views presented here are those of the authors only, and the European Commission is not responsible for any use that may be made of the information presented here.

Conflict of interest

None declared.

Data Availability Statement

All data from the local registries were sent to a central data repository at Ulster University. A condition for local approval for linking databases was that we are not allowed to share data.

Transparency declaration

The lead author (MD) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; no important aspects of the study have been omitted. Dissemination to patient and public communities: It is anticipated to disseminate the results of this research to wider community via press release, our webpage and social media platforms.

Contributorship statement

Mads Damkjær: wrote first draft of the paper and revised the paper after feedback

Maria Loane: Extraction and analysis of local registry data. Part of steering group and helped design of the study. Gave continuous input in the process of drafting the paper.

Stine Kjaer Urhoj: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Elisa Bellardini: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Clara Cavero-Carbonell: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Alessio Coi: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Laura Garcia-Villodre: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Joanne Given: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

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Aurora Puccini: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Ester Garne: : Extraction and analysis of local registry data. Part of steering group and helped design of the study. Gave continuous input in the process of drafting the paper.

Joan K Morris: Extraction and analysis of local registry data and meta-analysis of pooled data from each individual registry. Help revised paper. Part of steering group who designed the study.

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Legends:

Fig 1: Relative risk (RR) of receiving a prescription for all preterm (< 37 GA) versus term (+37 GA) children for their first 10 years of life. Data plotted are the RR and Error bars indicated 95% confidence intervals. Each point on the graph indicates a child year, i.e. from age 0 until the day before turning 1 year are termed <1 and from 1 till the day before turning 2 is termed <2 etc. The dotted line indicates a RR of 1 which is that of term children. Data are shown for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication; and D) antibiotics. The highest RR is observed for CVM in the first year of life. For CVM, ASM and anti-asthmatics the RR remains elevated compared to term children for all 10 years included in the analysis.

Centres with data on <1000 children <37 GA was excluded from the analysis; for the two first years of life data was included from all six regions, for ages 2 years to <6 years five regions, ages 6 years to <8 years 4 regions and 8 years to <10 years 3 regions.

Fig 2: Relative risk (RR) of receiving a prescription for very preterm (< 32 GA, blue line) and preterm (32-36 GA, red line) versus term children in their 10 years of life. Data are pooled into three age categories; <1 years; 1-4 years and 5-9 years. Error bars indicated 95% confidence intervals. The dotted line indicate a RR of 1 which is that of term children. Please note the logarithmic scale of the y-axis. Data are shown for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication; D) antibiotics. An increased relative risk of prescription is observed for CVM, ASM and anti-asthmatic medication for the three age groups, but not for antibiotics.

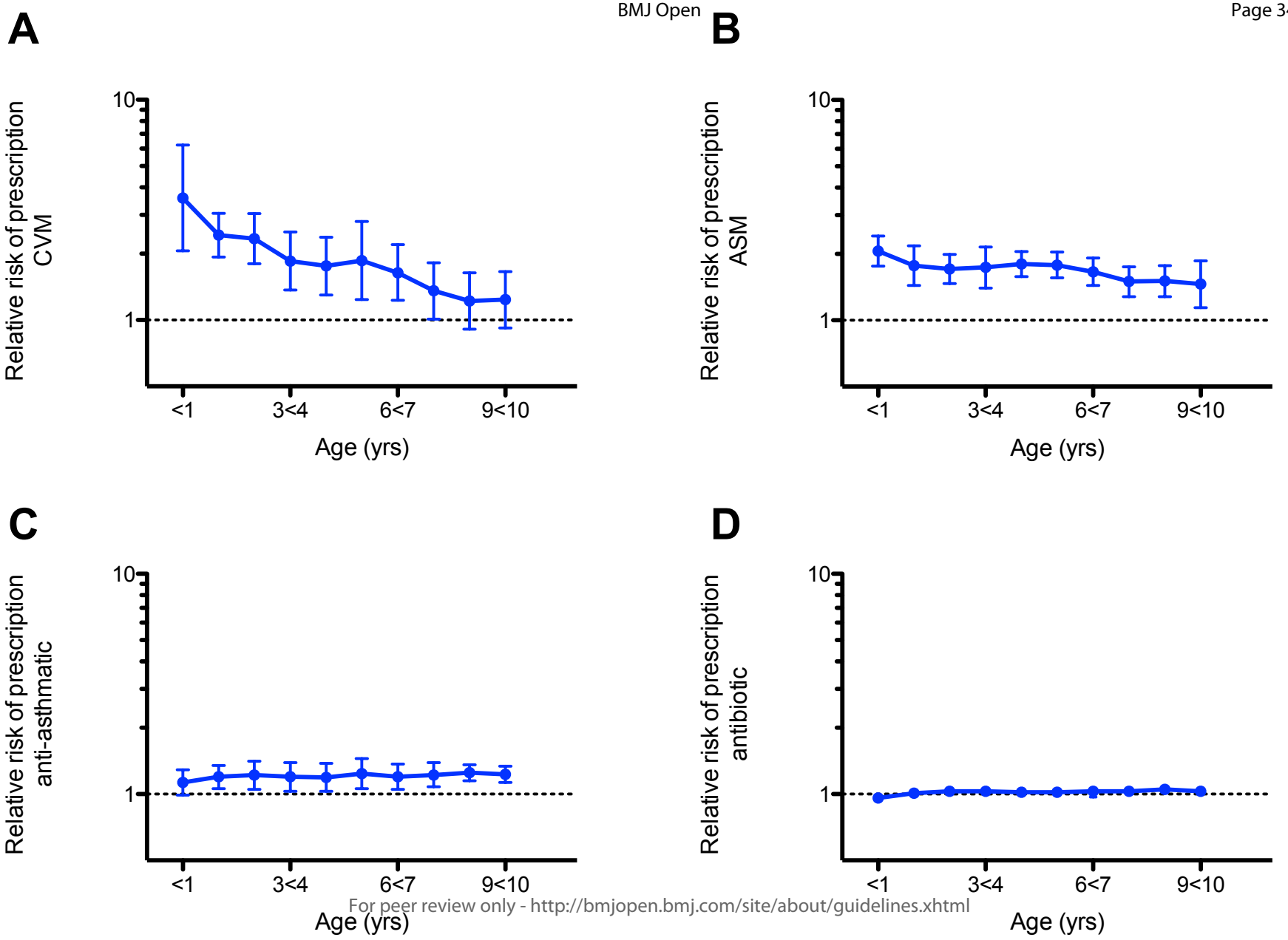
Centres with data on <1000 children <37 GA was excluded from the analysis; for the two first years of life data was included from all six regions, for ages 2 years to <6 years five regions, ages 6 years to <8 years 4 regions and 8 years to <10 years 3 regions.

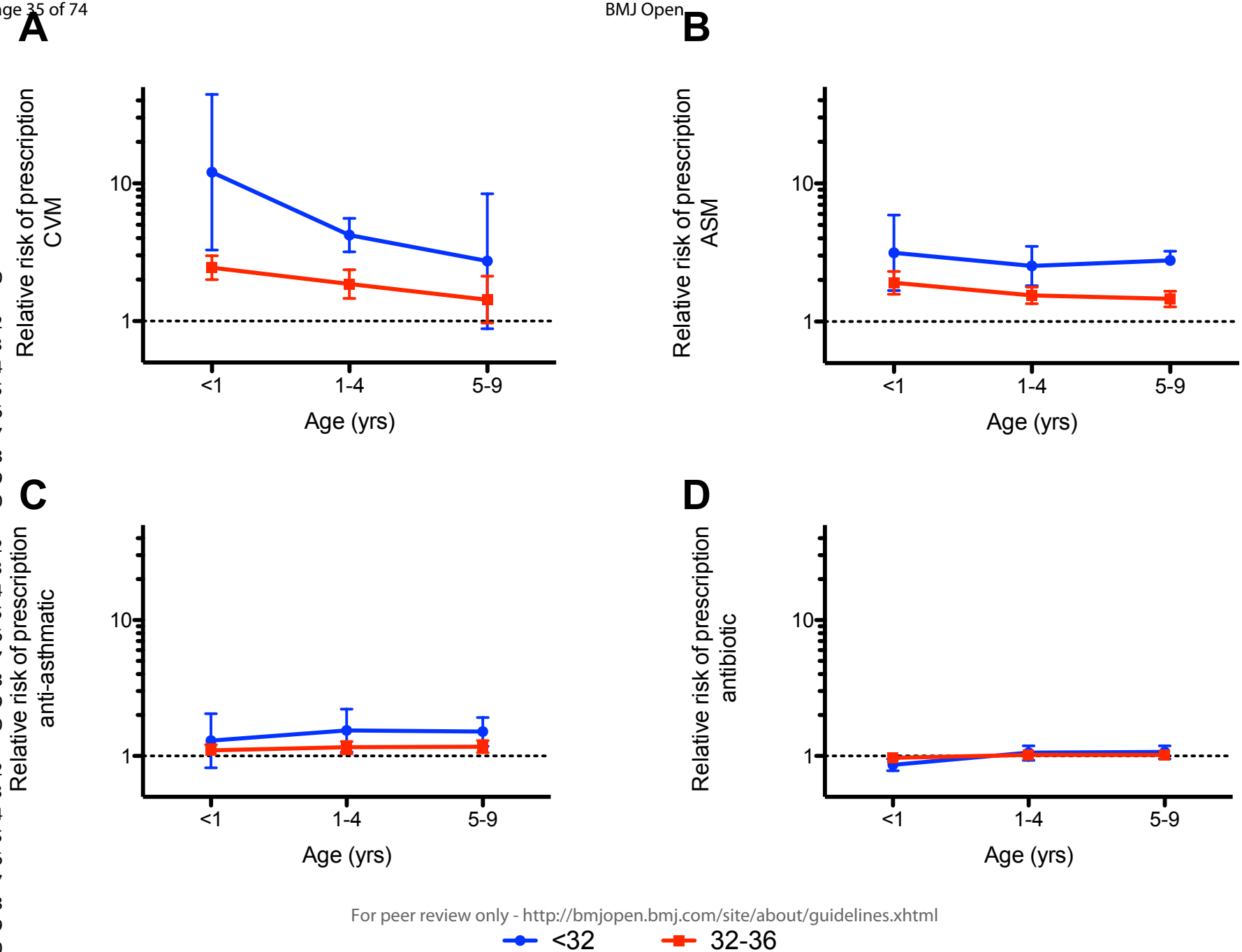
Fig 3: Relative risk (RR) of receiving a prescription for all preterm (< 37 GA) versus term (+37 GA) children in the first year of life. Error bars indicate 95% confidence intervals.Data are shown for all of the six regions individually (black) and the total (red) for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication and D) antibiotics. Please note the logarithmic scale of the x-axis in the upper panel, while in the lower panel the scale is linear but the x-axis values varies between graphs.

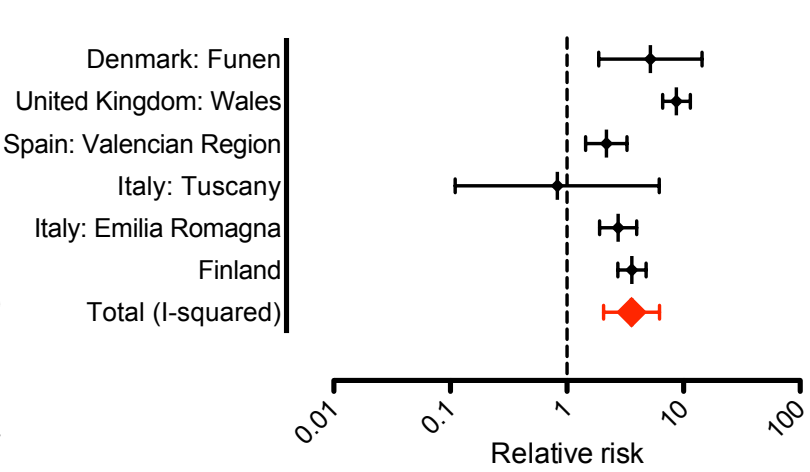
Table 1: Overview of the prescription databases from which data were extracted for the study and seize of the study population. Information includes the source of prescription data (either community pharmacy or General Practitioner) and the number of children in each group. The reference population are children without congenital anomalies who were born term. For some databases numbers have been rounded to nearest 5 to insure anonymity. Abbreviations; GA, weeks of gestation

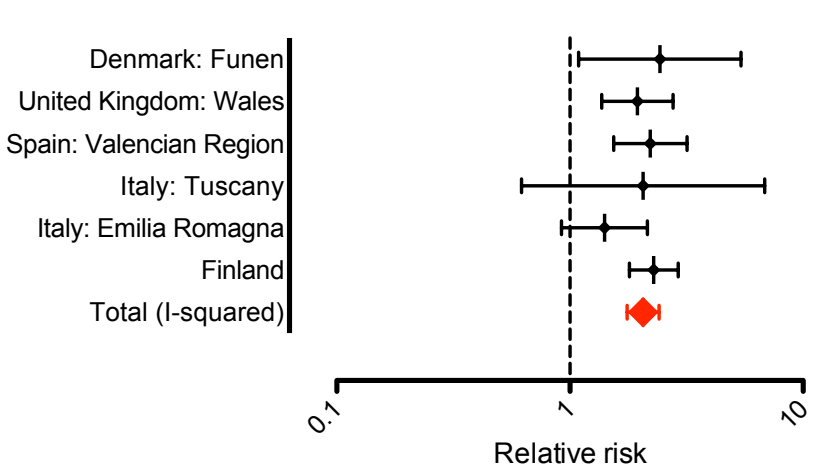
Table 2: Percentage of preterm (<37 GA) children with a prescription and relative risk for preterm (< 37 GA) vs term (+37 GA) children for receiving a prescription. Data are shown in three age groups and for each class of medication. The total number of children being prescribed/dispensed medication is indicated by the n number. Due to small numbers data on VWC1, VWC3, and VWC5

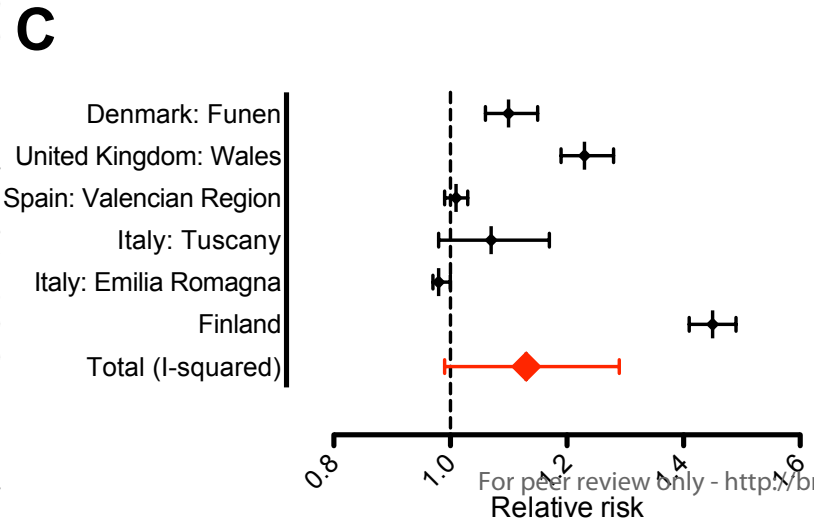
are not available. Abbreviations; GA, weeks of gestation; CVM, cardiovascular medication; ASM, anti-seizure medication; FAD, fatty acid derivatives; RR, relative risk; VW1, Vaughn Williams class 1; VW2, Vaughn Williams class 2; VW3, Vaughn Williams class 3; VW5, Vaughn Williams class 5.

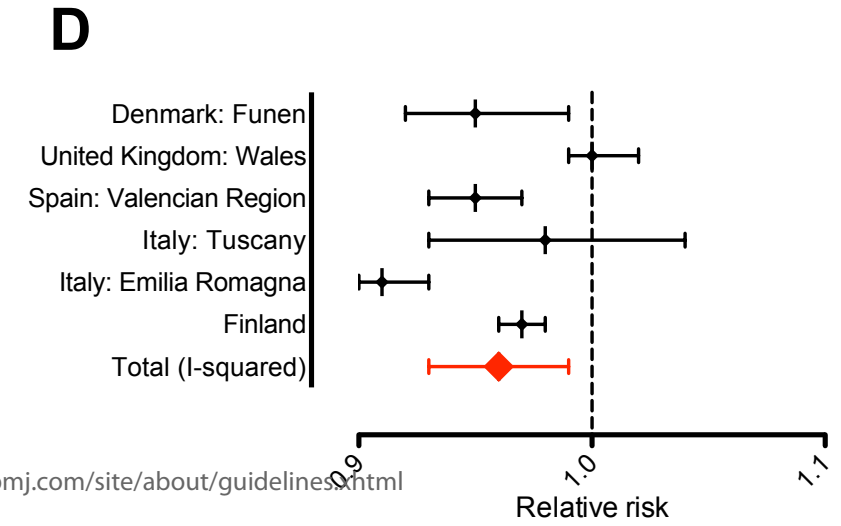












STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6-10	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8	
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	*6-10*	
Bias	9	Describe any efforts to address potential sources of bias	6	
Study size	10	Explain how the study size was arrived at	6	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	10
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11-15*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*11-15*
		Cross-sectional study—Report numbers of outcome events or summary measures	*11-15*
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	11-15
		(*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	11-15

Continued on next page

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	16-20
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	16-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-20
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	20

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

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

Preterm birth and prescriptions for cardiovascular, anti-seizure, antibiotics and anti-asthmatic medication in children up to ten years of age: A population-based data linkage cohort study across six European regions

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Abstract

Objectives: Preterm children are exposed to many medications in neonatal intensive care units, but little is known about the effect of prematurity on medication use throughout infancy and childhood. We examined prescriptions of cardiovascular medication (CVM), anti-seizure medication (ASM), anti-asthmatic medication and antibiotics issued/dispensed in the first 10 years of life for very and moderately preterm children compared to term.

Design: Population-based data linkage cohort study linking information from birth records to prescription records.

Setting: Six registries from five countries in the EUROlinkCAT study.

Participants: The study population included 1,722,912 children, of whom 10,820 (0.6%) were very preterm (<32 weeks gestational age (GA)), 92,814 (5.4%) were moderately preterm (32-36 weeks GA), 1,606,643 (93.3%) were born at term (≥37 weeks GA) and 0.7% had missing GA. Children with major or minor congenital anomalies were excluded (including patent arterial duct).

Main outcome measures: Relative risk (RR) of receiving a prescription for CVM, ASM, anti-asthmatic and antibiotics.

Results: Very preterm children had a higher RR of receiving a prescription for CVM and ASM than preterm children. For all preterm children, the RR of having a CVM prescription was 3.58 (95% Confidence interval (CI); 2.06-6.23); 2.06 (CI: 1.73-2.41) for ASM; 1.13 (CI: 0.99-1.29) for anti-asthmatics; and 0.96 (CI: 0.93-0.99) for antibiotics in the first year of life. Increased prescription of CVM, ASM and anti-asthmatics persisted for all 10-years of follow-up. Although the RR was highest for CVM and ASM, in absolute numbers more children received prescriptions for antibiotics (42.34%

(CI: 38.81-45.91) and anti-asthmatics (28.40% (CI: 16.07-42.649) than for CVM (0.18% (CI: 0.12-0.25)) and ASM (0.16% (CI: 0.13-0.20)) in the first year of life.

Conclusion: Preterm children had a higher risk of being prescribed/dispensed CVM, ASM and anti-asthmatics up to age 10. This study highlights a need for further research into morbidity beyond age 10.

Strengths and limitations of this study

- This is a population-based study including data on more than 100,000 children born preterm in six geographically different European regions.
- With the high number of children included in our study we are able to report data on relatively infrequently prescribed medications such as anti-seizure and cardiovascular medication.
- The study includes data for the first 10 years of life and we are thus able to detect impacts of preterm birth extending into childhood.
- An important limitation is that we do not have access to the medical files for included children and therefore we do not have information regarding the specific indication for which a medication was prescribed.

Introduction

Complications due to preterm birth, i.e. before 37 completed weeks of gestation, is the leading cause of death for children under 5 years of age(1). In high income countries close to 100% of babies born at a gestational age (GA) of 32 weeks are expected to survive infancy(2), but babies born extremely preterm (< 28 weeks GA) and with low birthweight still have a mortality rate of 33 – 50 % in developed countries(3). The increased survival of children born preterm raises the question "does the increased survival come with the price of an increased morbidity in childhood compared to term born children?". One such indicator of disease burden is prescription of medication, as this will reflect underlying disease. Although a number of studies have addressed prescriptions and use of medications in the neonatal intensive care unit (NICU), little is known about prescriptions after discharge. The few available studies have focused on prescriptions in the first year or two of life (4,

5), but long-term follow-up is lacking. Life in the first year after discharge from the NICU is characterized by frequent paediatric visits and an average of 5.5 prescriptions per year(4). One study from the United States (US) found that the most frequently prescribed medication in the first two years of life were palivizumab, ranitidine, albuterol, lansoprazole, budesonide and prednisolone(5). Of these medications only palivizumab has a specific indication in preterm infants, and concerns regarding safety and lack of efficacy have been raised for lansoprazole(6), ranitidine(7) and budesonide(8). Most research has centred on prescriptions of these medications while for instance cardiovascular medication (CVM) and anti-seizure medication (ASM) have received less research interest.

The aim of the present study was to evaluate the community prescription of CVM, ASM, anti-asthmatics and antibiotics to children born before 37 weeks GA compared with term children from birth up to 10 years of age, as an indicator of chronic disease burden. Furthermore, we aimed to look at differences in prescription of CVM between term (+37 weeks GA), moderately preterm (32-36 weeks GA) and very preterm (<32 weeks GA) children for their first 10 years of life in six different European regions.

Methods

This is a European, population-based linkage cohort study arising from the EUROlinkCAT project (9). The EUROlinkCAT project includes data on morbidity and medication use for children born with congenital anomalies and for reference children without congenital anomalies born in the same geographical area. In the present paper we focus on these reference children. Five regions provided data on all liveborn children in their region and one region (Tuscany) provided a random 10%

sample, matched on date of birth and sex, of their population of reference children. The minimum GA for inclusion was 23 weeks except for Wales where it was 24 weeks. Data were included for children born between 2000-2014, but three registries had a shorter study period as linked data in these regions were not available at the start of the study period (Table 1).

	First Year of birth	Source of prescriptions	Number of Children			
			Reference population	<32 GA	32 – 36 GA	+37 GA
Denmark: Funen*	2000	Dispensed by pharmacy	72,290	525	4045	66625
Finland	2000	Dispensed by pharmacy	755,923	4,245	33,860	715,620
Italy: Emilia Romagna	2008	Dispensed by pharmacy	250,829	1,902	16,350	232,507
Italy: Tuscany	2008	Dispensed by pharmacy	16,844	77	926	15,840
Spain: Valencian Region	2010	Dispensed by pharmacy	223,760	1,173	14,618	202,304
UK: Wales *	2000	Prescribed by GP	403,265	2,895	23,015	373,750
Total number of children			1,722,912	10,820	92,814	1,606,643

Information on medication was available by linking children identified in birth records to local electronic prescription databases in each of the six regions. All children in the six regions needed to have a valid identification (ID) number to be identified in the relevant prescription database. Four regions had valid IDs for >99% of children, one region had valid IDs for 95% of children (Emilia Romagna), and one had valid IDs for 85% of children (Wales). The proportion was lower for Wales as information on prescriptions were obtained only from General Practitioners (GPs) who contributed to the Secure Anonymised Information Linkage (SAIL) database. In total, 1,722,912

children aged up to 10 years of age had a valid ID that allowed them to be identified in a prescribing database, between the years 2000-2015 (Table 1).

Analyses were performed according to three age groups (<1 year, 1-4 years and 5-9 years). GA at birth was categorised as very preterm (<32 weeks GA), moderately preterm (32-36 weeks GA) and term births (37+ weeks GA).

Exclusions: Children with a code for a major or minor congenital anomaly in the hospital in-patient databases were excluded from the study population, i.e. any child with a WHO International Statistical Classification of Diseases and Related Health Problems (ICD) 9th revision (code with 74-75) or 10th Revision code (Q-chapter)(10). This criteria also excluded children with a patent arterial duct (PDA).

Minimum number of prescriptions: A child must have at least one prescription to be classified as exposed to a medication. In epidemiology, risk has been defined as "the probability of an event during a specified period of time"(11), and as such uses the term risk for the probability of receiving medication.

Small numbers: In two of the participating registries extraction of small numbers were not allowed, we therefore restricted the analysis to 4th level in the ATC system as outlined below.

Classification of medication:

CVM: As previously described in detail (12) antiarrhythmic medication is classified according to the Vaughan Williams classification (VWC)(13). Antihypertensive medication and diuretics were classified according to the Anatomical Therapeutic Classification (ATC) system codes reported in the electronic prescription databases. In brief, this gave us the categories outlined below:

- Any CVM: All ATC codes beginning with C01-C03 and C07-C09, excluding C01BA51, C01BA71, C01CA24
- VWC1 (Fast sodium-channel blockers) : ATC codes beginning with C01BA (excluding C01BA51 and C01BA71), C01BB and C01BC (i.e. procainamide, lidocaine and flecanide)
- VWC2 (Beta-blockers): ATC codes beginning with C07A (i.e. atenolol, propranolol)
- VWC3 (Potassium-channel blockers): ATC codes beginning with C01BD (i.e. nefidipine)
- VWC5 (Other mechanism of action): ATC codes C01AA05 (i.e. digoxin, adenosine)
- Antihypertensives: ATC codes beginning with C08 and C09
- Diuretics: ATC codes beginning with C03

ASM: Medication used for the treatment of epilepsy/seizures were stratified into four groups:

- Any ASM: all medication included in the ATC system beginning with N03.
- First generation ASM: ATC codes beginning with N03AA, N03AB, N03AE, N03AF (i.e. phenobarbital, phenytoin, clonazepam, carbamazepine).
- Second generation ASM: ATC codes beginning with N03AX (i.e. lamotrigine, gabapentin, topiramate, and levetiracetam).
- Fatty acid derivatives (FAD): ATC codes beginning with N03AG (i.e. valproic acid, valpromid, progabide etc.).

Anti-asthmatics: All medication used in the treatment of obstructive airway diseases as classified under ATC codes beginning with R03. These were divided into the following categories:

- Anti-asthmatic: ATC codes beginning with R03

- Beta-2-agonists: ATC codes beginning with R03AC, which comprises all inhaled selective beta-2-adrenoreceptor agonists (i.e. salbutamol, terbutaline, fenoterol etc.).
- Glucocorticoids: ATC codes beginning with R03BA which includes all inhaled glucocorticoids (i.e. beclometasone, budesonide, fluticasone etc.) except combinations with adrenergics and anticholinergics which are classified under R02AK and R03AL.

Antibiotics: In this study, the broad term "antibiotics" is used to cover all systemic antibacterials as defined by the ATC system using codes beginning with J01. All topical antibiotics (ointments/ creams) for skin infections, drops for eye or ear infections, antibiotics that are administered intravenously and antibiotics not classified under the ATC code J01 were not included. Medications were then stratified into three subgroups:

- Any antibiotic: ATC codes J01.
- Penicillins: ATC codes J01C (comprises both beta-lactamase sensitive and resistant penicillins plus combinations with beta-lactamase-inhibitors).
- Macrolides: ATC codes J01F (also includes lincosamides and streptogramins).

Statistical methods: Each registry standardised their data using the EUROlinkCAT common data model (14) which enabled them to run a centrally written analysis script on their individual case data. The number of children prescribed/dispensed at least one prescription and the number of child years observed during each year of age were calculated in children according to GA at birth categorised into very preterm (GA <32 weeks), moderately preterm (GA 32-36 weeks) and term (GA 37+ weeks) and submitted to the central results repository at Ulster University (only aggregate data;

no individual case data were provided to Ulster University). The aggregate results for all registries were then provided to the researchers. The risk of being prescribed/dispensed a medication at a particular year of age was calculated as the number of children prescribed/dispensed at least one prescription when they were that age divided by the number of child years observed during the same age year (to allow for children being censored during the year). The relative risks (RR) of being prescribed/dispensed a medication in preterm children (<37 weeks GA) compared to in term children (37+ weeks GA) were calculated for each year of age within each registry. The data were then combined and analysed by performing an inverse variance random effects meta-analysis of the RR and 95% confidence intervals (CI) of being prescribed/dispensed a medication at each year of age in preterm children (<37 weeks GA) group compared to the risk in term children (37+ weeks GA). In addition the RR for <32 weeks GA and 32-36 weeks GA compared to term children (37+ weeks GA) were calculated within three age groups (<1 year, 1-4 years, 5-9 years). Three registries had no information on children over 7 years of age, as their data started in 2008 (Emilia Romagna and Tuscany) and 2010 (Valencian Region), so they were excluded from the 5-9 years' analysis.

Ethics Approval: All registries that are part of the EUROCAT network have the required ethics permissions and procedures for routine surveillance, data collection and transmission of anonymised data to the EUROCAT central database. In accordance with national guidelines, the registries submitted evidence of these permissions to the EUROlinkCAT ethics portfolio. The central data repository Ulster University also obtained ethics approval (approval number FCNUR-21-060). Local registries follow national legislation as to whether parental consent is needed for registration of babies with anomalies. For details please refer to separate protocol paper (9).

Patient Public Involvement: Patients/parents were not involved in the study design, however as part of the project we have plans for dissemination and knowledge exchange with parents as described in detail on our webpage(15) and protocol paper(9).

Results

Population characteristics: The study population included 1,722,912 children, of whom 10,820 (0.6%) were very preterm (< 32 weeks GA), 92,814 (5.4%) were preterm (32-37 weeks GA), 1,606,643 (93.3%) were term (Table 1) and 0.7% had missing GA in the databases (these were evenly distributed among participating regions).

CVM:

Prescription of CVM at each year of age: The risk of receiving a CVM prescription for preterm children (<37 weeks GA) compared to term children was highest in the first year of life (RR 3.58, 95%CI: 2.06-6.23) and slowly decreased for each consecutive year up to age 9 years (Fig 1A). The percentages of preterm children receiving a CVM prescription were 0.18% (95% CI: 0.12-0.25) in the first year of life, 0.06% (95% CI: 0.03-0.09) for ages 1-4 years and 0.07% (95% CI: 0.02-0.14) for ages 5-9 years (Table 2).

	<1 year		1-4 years		5-9 years	
Medication	Percentage of preterm (<37 GA) children with a prescription (N = 10,3634)	RR for preterm (< 37 GA) vs term (+37 GA) children	Percentage of preterm (<37 GA) children with a prescription (N=102,309)	RR for preterm (< 37 GA) vs term (+37 GA) children	Percentage of preterm (<37 GA) children with a prescription (N = 60,489)	RR for preterm (< 37 GA) vs term (+37 GA) children
Any CVM	0.18 (0.12-0.25)	3.58 (2.06-6.23)	0.06 (0.03-0.09)	2.05 (1.71-2.46)	0.07 (0.02-0.14)	1.43 (1.04-1.97)
Diuretics	0.07 (0.01-0.16)	7.19 (2.29-22.60)	0.01 (0.01-0.02)	3.29 (2.09-5.17)	0.00 (0.00-0.00)	2.35 (1.34-4.10)
Antihypertensives	0.02 (0.00-0.03)	2.34 (0.94-5.82)	0.01 (0.01-0.03)	1.66 (1.12-2.48)	0.02 (0.01-0.03)	1.68 (1.22-2.32)
VWC2 (beta-blockers)	0.07 (0.05 – 0.09)	2.82 (2.24-3.55)	0.06 (0.03 – 0.09)	2.12 (1.68-2.67)	0.05 (0.01-0.18)	1.32 (1.07-1.63)
Any ASM	0.16 (0.13-0.20)	2.06 (1.76-2.41)	0.27 (0.22-0.32)	1.77 (1.50-2.08)	0.38 (0.31-0.46)	1.59 (1.48-1.70)

New ASM	0.02 (0.01-0.05)	2.03 (1.44-2.85)	0.08 (0.06-0.12)	1.87 (1.50-2.35)	0.13 (0.11-0.15)	1.70 (1.43-2.02)
Old ASM	0.08 (0.06-0.10)	2.09 (1.67-2.61)	0.07 (0.05-0.09)	1.84 (1.32-2.58)	0.11 (0.08-0.14)	1.80 (1.35-2.38)
FAD	0.07 (0.04-0.11)	2.21 (1.78-2.74)	0.17 (0.13-0.22)	1.75 (1.53-2.00)	0.22 (0.18-0.27)	1.63 (1.50-1.78)
Any anti-asthmatic	28.40 (16.07-42.64)	1.13 (0.99-1.29)	25.67 (18.35-33.75)	1.20 (1.04-1.37)	12.84 (11.44-14.31)	1.21 (1.07-1.36)
Beta-2-agonists	14.83 (8.45-22.63)	1.29 (1.06-1.56)	14.93 (12.13-17.96)	1.31 (1.14-1.51)	7.77 (6.55-9.09)	1.22 (1.10-1.36)
Glucocorticoids	10.47 (2.70-22.47)	1.41 (0.94-2.12)	12.91 (6.54-21.04)	1.34 (1.05-1.70)	7.80 (5.94-9.87)	1.28 (1.11-1.48)
Any antibacterial	42.34 (38.81-45.91)	0.96 (0.93-0.99)	51.05 (47.63-54.46)	1.02 (0.98-1.06)	29.41 (26.42-32.49)	1.02 (0.98-1.07)
Penicillins	37.19 (33.58-40.88)	0.95 (0.92-0.98)	43.44 (41.72-45.16)	1.03 (0.99-1.07)	22.79 (21.67-23.94)	1.03 (0.98-1.08)
Macrolides	8.43 (5.94-11.30)	0.95 (0.94-0.97)	13.62 (9.76-18.01)	1.07 (1.02-1.12)	6.90 (4.84-9.30)	1.06 (0.98-1.15)

Impact of preterm birth on CVM prescriptions: A dose dependent effect was observed i.e. the lower the gestational age at birth, the higher the RR of receiving a CVM prescription in their first year of life compared with term children. In very preterm children (<32 weeks GA), the RR was 12.06 (95% CI 3.28-44.35) and in moderately preterm (32-37 weeks GA) the RR was 2.44 (95% CI 2.00-2.98). The dose dependent effect of preterm birth on prescriptions of CVM was present across all age groups included in the study (Fig 2A).

Pharmacological types of CVM prescribed/dispensed:

*VWC2 (beta-blockers): T*he RR for receiving a VWC2 prescription in preterm vs term children, was 2.82 (95% CI: 2.24-3.55) in the first year of life, 2.12 (95% CI: 1.68-2.67) for ages 1-4 years and 1.32 (95% CI: 1.07-1.63) for ages 5-9 years. The percentage of preterm children receiving a beta-blocker in their first year of life was 0.07% (95% CI; 0.05-0.09).

Diuretics: The RR of having a diuretic prescribed/dispensed was highest in the first year of life (RR 7.19; 95% CI: 2.29-22.60), and then decreased for ages 1-4 years (RR 3.29; 95% CI: 2.09-5.17) and 5-9 years (RR 2.35; 95% CI: 1.34-4.10). The percentage of preterm children receiving a diuretic in their first year of life was 0.07% (95% CI; 0.01-0.16).

Antihypertensives: Prescriptions for antihypertensives remained stable at a RR of around 2 for all three age groups, i.e. 2.34 (95% CI: 0.94-5.82), 1.67 (95% CI: 1.12-2.48) and 1.68 (95% CI: 1.22-2.32) for ages <1, 1-4 and 5-9 years, respectively. The percentage of preterm children receiving antihypertensive prescriptions in their first year of life was 0.02% (95% CI: 0.00-0.03).

VWC1, VWC3, VWC5: numbers were too small to report.

Regional differences in prescription: Fig 3A displays the RR of receiving a CVM prescription in the first year of life for each of the regions included in the meta-analysis reported above. A significantly increased RR was observed for five of the six regions (range of RR 2.18 – 8.70) with the exception of Tuscany where there was no increased RR and the confidence intervals were extremely wide.

ASM

Prescriptions of ASM at each year of age: At each individual year of age during the 10-year follow-up period, prescriptions of ASM were higher for preterm (< 37 weeks GA) than for term children. The RR decreased with age, but prescriptions remained significantly higher for preterm than term children (Fig 1B). The percentages of pre-term children receiving a prescription in a year increased with age from 0.16% (95% CI: 0.13-0.20) for ages <1 year, 0.27% (95% CI: 0.22-0.32) for ages 1-4 years to 0.38% (95% CI: 0.31-0.46) for ages 5-9 years (Table 2).

Impact of preterm birth on ASM prescription: In the first year of life children born very preterm (<32 weeks GA) and moderately preterm (32-36 weeks GA) had a higher RR of being prescribed/dispensed an ASM compared to term children (RR 3.15, 95% CI: 1.68-5.90 and RR 1.91, 95% CI: 1.58 – 2.31). The effect of increased prescription with lower GA was seen across all age groups (Fig 2B).

Pharmacological types of ASM prescribed/dispensed (Table 2):

The same pattern of an increased RR at around 2 of being prescribed/dispensed an ASM was observed for all three pharmacological types of ASM (first/second generation and FAD) for the first 10 years of life. There was an increase in percentage of children receiving a prescription with age for all three age groups (for details please see Table 2).

Regional differences in prescription: An increased risk for preterm children compared to term children was observed across all six regions (RR range 1.41 – 2.43, Fig 3B), although for both Italian regions the increase was not statistically significant.

Anti-asthmatics

Prescription of anti-asthmatics at each year of age for all preterm born children (<37 weeks GA): For all preterm children, the RR of being prescribed/dispensed a prescription for anti-asthmatic medication was significantly higher than for term children for all 10 years of follow-up. The RR was relatively stable around 1.2 for all 10 years (Fig 1C).

Impact of prematurity on anti-asthmatic prescription: There was no discernible dose dependent effect of prematurity on prescription of anti-asthmatic medication, i.e. for both very preterm and moderately preterm children the RR for prescription of anti-asthmatics in the three different age categories remained around 1.3 (Fig 2C). In total 28% of all preterm born children received a prescription for any anti-asthmatic medication in the first year of life.

Pharmacological types of anti-asthmatics prescribed/dispensed (Table 2):

Beta-2-agonists: The RR for receiving or having a prescription for a beta-2-agonist was around 1.3 for all age categories, i.e. 1.29 (95% CI: 1.06-1.56) for ages <1 years, 1.31 (95% CI: 1.14-1.51) for ages 1-4 years and 1.22 (95% CI: 1.10-1.36) for ages 4-9 years.

Glucocorticoids: The RR for being prescribed/dispensed a prescription for a beta-2-agonist was around 1.3 for all age categories, i.e. 1.41 (95% CI: 0.94-2.12) for ages <1 years, 1.34 (95% CI: 1.05-1.70) for ages 1-4 years and 1.28 (95% CI: 1.11-1.48) for ages 4-9 years.

Regional differences in prescription: In three of six regions (United Kingdom: Wales, DK: Funen and Finland) there was a significantly increased RR of prescription for preterm children in the first year of life, whereas in the three other regions no significant difference between term and preterm children was observed (Fig 3C).

Antibiotics

Prescription of antibiotics at each year of age: The RR of preterm children having an antibiotic prescription issued /dispensed compared to term children was slightly lower in the first year of life. There were no significant differences in risk between preterm and term children during the next 9 years of follow-up (Fig 1D).

Impact of preterm birth on prescriptions for antibiotics: In the first year of life children born very preterm (<32 weeks GA) and moderately preterm (32-36 weeks GA) had a lower RR of receiving a prescription for antibiotics than term children (RR 0.86, 95% CI: 0.78-0.95 and RR 0.97, 95% CI: 0.95-1.00). For the age categories 1-4 years and 5-9 years, there was no difference in prescriptions compared to term children. Furthermore we did not observe a dose dependent effect of preterm birth on prescription, i.e. no effect of decreasing GA on RR for prescription (Fig 2D).

Pharmacological types of antibiotics prescribed/dispensed (Table 2):

Any antibiotics: 42.34% (95% CI; 38.81-45.91) received a prescription in their first year of life, 51.05% (95% CI; 47.63-54.46) were issued/dispensed a prescription each year for ages 1-4 years and 29.41% (95% CI; 26.42-32.49) each year for ages 5-9 years.

Penicillins: were prescribed/dispensed for 37.19% (95% CI; 33.58-40.88) of children < 1years, 43.44% (95% CI; 41.72-45.16) had a penicillin prescription each year for ages 1-4 years and 22.79% (95% CI; 21.67-23.94) each year for ages 5-9 years.

Macrolides: 8.43% (95% CI; 5.94-11.30) received a prescription in their first year of life, 13.62 (95% CI; 9.76-18.01) were issued/dispended a prescription for macrolides each year for ages 1-4 years and 6.90% (95% CI; 4.84-9.30) each year for ages 5-9 years.

Regional differences in prescription: A significantly decreased RR for prescription of antibiotics was observed in four of six regions (Fig. 3D).

Discussion

To our knowledge this is the first study to examine medications prescribed/dispensed for cardiovascular diseases, neurological seizures, asthma and infections in a paediatric cohort comparing preterm and term born children up to ten years of age. We show that children born preterm had an increased risk compared to term children of being prescribed/dispensed CVM, ASM and anti-asthmatic medication. For CVM and ASM risks were higher for earlier gestations. For CVM the increased relative risk was most pronounced in the first year of life, whereas for ASM the risk was at a constant level for the first 10 years of life. Although the RR was highest for CVM and ASM, in absolute numbers more children were receiving prescriptions for antibiotics and anti-asthmatics than for CVM and ASM. In the first year of life preterm children had a reduced RR for receiving antibiotics compared to term children.

An important limitation of our study is that all preterm children with a code for PDA are excluded as we excluded all children with congenital anomalies as defined in the method section. There is an inverse relationship between GA and PDA, such that the more preterm an infant is born the higher

the probability that arterial duct will not close spontaneously (16). Furthermore, it has been established that having a PDA is associated with prolonged mechanical ventilation, bronchopulmonary BPD, and necrotizing enterocolitis (16, 17). Therefore, the net effect of excluding infants with a PDA is that we may be underestimating the true burden of morbidity for the group of preterm born children. Also this study only assesses prescription patterns, and as such we are not able to assess whether or not medication are prescribed rationally in accordance with the current standards of evidence, further studies are need to address this question.

Cardiovascular medication: The highest RR in the present study was for diuretics in the first year of life. Although the RR was higher for preterm children with respect to all CVM, it is important to note that in absolute terms few children were prescribed these medications. In preterm born children, development of BPD is the most frequent chronic morbidity and strongly predicts both death and disability in childhood(18-20). The most regularly prescribed medication to infants admitted with an exacerbation in BPD is diuretics(21) and as much as 86% of infants admitted for BPD exacerbation will follow a treatment course for > 5 days with diuretics(22). It therefore seems plausible that the high RR for diuretics in the first year of life most likely reflects either chronic treatment for BPD or shorter periods given in relation to exacerbations in BPD. However, there is a lack of evidence on the efficacy of diuretics in preterm children. For example a Cochrane review examining the risks and benefits of administration of diuretics (furosemide) to preterm children in the NICU at a post menstrual age <40 weeks with ongoing or incipient chronic lung disease found that "furosemide administration has either inconsistent effects or no detectable effect"(23). There are no systematic reviews for long-term use of diuretics to infants/children after discharge from the NICU. In view of this, it is noteworthy that we in the present study find that there is an increased prescription of diuretics to preterm born children up to 10 years of age. The increased RR for prescription of

antihypertensives (which includes ACE-inhibitors) and beta-blockers could reflect chronic heart failure treatment as these are recommended first-line therapies for paediatric heart failure(24). As with diuretics for BPD heart failure treatment in adults with congenital heart defects are generally based on position statements rather than solid evidence(25), a problem that "is even more pertinent in children" (26). The few available studies on heart failure treatments in children have either failed to show an effect or have been underpowered (27-29). Future studies are needed to address whether or not these patterns of increased prescription of CVM can affect clinical course or outcome in preterm children.

Anti-seizure medication: Increased prescription of ASM probably reflects an increased risk for epilepsy among preterm born children. It has previously been shown that there is an inverse dose-response curve with decreasing gestational age increasing epilepsy risk later in life(30), a phenomenon we also observe in our data. A recent meta-analysis estimated that the increased odds ratio (OR) for epilepsy for children born preterm versus term was 2.14 which is consistent with our estimates of increased ASM prescription(31). It is noteworthy, in our data, that while the RR for ASM prescription was relatively stable over the age groups, in absolute terms the number of children receiving treatment roughly doubles from <1 years of age to the age group 5-9 years. The cumulative incidence of epilepsy increases through childhood(32), but it seems that the extra RR conferred by preterm birth is present for at least 10 years after birth. Randomized controlled trials on management of epilepsy in infants are lacking, and as pointed "There is no high-level evidence to support any particular current agents for use in infants with seizures"(33). Treatment strategies are thus based on expert opinion rather than solid evidence(34)., In the present study the RR for prescription of both first/second generation ASM and FAD are remarkably similar, suggesting that

no group is preferred specifically for the epilepsy forms associated with preterm birth. Again studies of medication efficacy are warranted in this patient group.

Anti-asthmatic medication: Preterm birth has been associated with an increased risk of childhood asthma or wheezing disorder with an increased odds ratio of 1.46(35), although considerable heterogeneity across studies have been noted(36). A Danish cohort study reported a strong inverse association with GA and purchase of anti-asthmatics (defined as purchasing both an inhaled beta-2-agonist and glucocorticoids) and found that OR decreased as the age of children increased (37). The waning effect of preterm birth with advancing age has later been shown to progress beyond 11 years of age (38). In the present study preterm birth is associated with an increased risk of being prescribed/dispensed anti-asthmatics at a RR around 1.2 which is similar to that reported in the Danish study, although we did not observe a waning effect with age for the 10 years follow-up after birth. In absolute numbers 28% of preterm children are prescribed anti-asthmatics in their first year of life which then declines to around 13% for ages 5-9 years, so although the RR is lower than for CVM and ASM in absolute numbers far more children were prescribed anti-asthmatics than CVM and ASM. Prescriptions of inhaled beta-2-agonist and glucocorticoids in our study were not substantially different and seems to suggest that children, if treated with anti-asthmatics, are treated with both.

Antibiotics: The present study did not find a dose dependent effect of preterm birth on RR for prescription of antibiotics. Lorch and colleagues looked at the effect of GA on antibiotic prescription in children born <32 weeks GA for the first year of life and did not find an effect of GA on prescription of antibiotics for very preterm born infants (39). In contrast, it has been reported for children from 2 years of age and older that lower GA resulted in higher prescription rates of antibiotics up until ages 10-11 years where an inverse pattern was observed with decreasing prescription(40). The

authors reported a similar pattern with respect to hospital admission for airway infections(40). Several studies have reported higher rates of admissions for respiratory infections both in infancy and childhood for preterm born children (41-43). The study by Lorch et al. did not include a control group, and their finding of lower prescription rates cannot be corroborated by other studies. The higher rates of hospitalizations due to infections for preterm born infants and children reported by other studies might provide some part of the explanation for our data. Our study included prescriptions for children outside hospitals only as we did not include medication given during hospital admissions. Further, preterm born infants stay in hospital for up to three months after birth and therefore they are less "exposed" to prescriptions (as defined in our study) in the first year of life. It is also possible that the lower RR in the first year of life reflects that preterm children are kept more at home and shielded from infections than term children. In teenagers it has been suggested that there is an *ex-preterm behavioral phenotype*(44) that may lead to a more socially isolated life-style with less exposure to infections(40). It can be speculated that there might be a similar behavioral pattern in parents during infancy.

Regional differences: Overall we observed similar trends across all six European regions included in the present study. As there is considerable overlap of confidence intervals between various European regions we cannot for certain identify clinically relevant differences in prescription between geographical regions. Due to a small sample from Tuscany, this sub-cohort failed to find any differences in prescription patterns for preterm vs. term born children.

Conclusion: Children born preterm are at a higher risk of being prescribed/dispensed prescriptions for CVM, anti-seizure medication and anti-asthmatic medication in their first 10 years of life. The higher risk was also present for the moderate preterm born children. While it is known that children

born preterm are vulnerable, this study demonstrates that these children have an excess risk of chronic diseases requiring medication up to age 10 years. Future studies should assess if the excess morbidity associated with preterm birth continues into adolescence/ young adulthood or if it levels off after ten years of age. Preterm born infants have a long life a head of them when they start out the PICU. Optimization of management though infancy and childhood can have profound consequence of quality of life for many years to come, in light of this it seems peculiar that so little of the current prescription practice for ex-preterm infants and children are based on solid scientific evidence.

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The views presented here are those of the authors only, and the European Commission is not responsible for any use that may be made of the information presented here.

Conflict of interest

None declared.

Data Availability Statement

All data from the local registries were sent to a central data repository at Ulster University. A condition for local approval for linking databases was that we are not allowed to share data.

Transparency declaration

The lead author (MD) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; no important aspects of the study have been omitted. Dissemination to patient and public communities: It is anticipated to disseminate the results of this research to wider community via press release, our webpage and social media platforms.

Contributorship statement

Mads Damkjær: wrote first draft of the paper and revised the paper after feedback

Maria Loane: Extraction and analysis of local registry data. Part of steering group and helped design of the study. Gave continuous input in the process of drafting the paper.

Stine Kjaer Urhoj: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Elisa Bellardini: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Clara Cavero-Carbonell: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Alessio Coi: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

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Mika Gissler: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

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Ileuan Scanlon: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Aurora Puccini: Extraction and analysis of local registry data. Gave continuous input in the process of drafting the paper.

Ester Garne: : Extraction and analysis of local registry data. Part of steering group and helped design of the study. Gave continuous input in the process of drafting the paper.

Joan K Morris: Extraction and analysis of local registry data and meta-analysis of pooled data from each individual registry. Help revised paper. Part of steering group who designed the study.

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Legends:

Fig 1: Relative risk (RR) of receiving a prescription for all preterm (< 37 GA) versus term (+37 GA) children for their first 10 years of life. Data plotted are the RR and Error bars indicated 95% confidence intervals. Each point on the graph indicates a child year, i.e. from age 0 until the day before turning 1 year are termed <1 and from 1 till the day before turning 2 is termed <2 etc. The dotted line indicates a RR of 1 which is that of term children. Data are shown for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication; and D) antibiotics. The highest RR is observed for CVM in the first year of life. For CVM, ASM and anti-asthmatics the RR remains elevated compared to term children for all 10 years included in the analysis.

Centres with data on <1000 children <37 GA was excluded from the analysis; for the two first years of life data was included from all six regions, for ages 2 years to <6 years five regions, ages 6 years to <8 years 4 regions and 8 years to <10 years 3 regions.

Fig 2: Relative risk (RR) of receiving a prescription for very preterm (< 32 GA, blue line) and preterm (32-36 GA, red line) versus term children in their 10 years of life. Data are pooled into three age categories; <1 years; 1-4 years and 5-9 years. Error bars indicated 95% confidence intervals. The dotted line indicate a RR of 1 which is that of term children. Please note the logarithmic scale of the y-axis. Data are shown for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication; D) antibiotics. An increased relative risk of prescription is observed for CVM, ASM and anti-asthmatic medication for the three age groups, but not for antibiotics.

Centres with data on <1000 children <37 GA was excluded from the analysis; for the two first years of life data was included from all six regions, for ages 2 years to <6 years five regions, ages 6 years to <8 years 4 regions and 8 years to <10 years 3 regions.

Fig 3: Relative risk (RR) of receiving a prescription for all preterm (< 37 GA) versus term (+37 GA) children in the first year of life. Error bars indicate 95% confidence intervals.Data are shown for all of the six regions individually (black) and the total (red) for A) Cardiovascular medication (CVM); B) anti-seizure medication (ASM); C) anti-asthmatic medication and D) antibiotics. Please note the logarithmic scale of the x-axis in the upper panel, while in the lower panel the scale is linear but the x-axis values varies between graphs.

Table 1: Overview of the prescription databases from which data were extracted for the study and seize of the study population. Information includes the source of prescription data (either community pharmacy or General Practitioner) and the number of children in each group. The reference population are children without congenital anomalies who were born term. For some databases numbers have been rounded to nearest 5 to insure anonymity. Abbreviations; GA, weeks of gestation

Table 2: Percentage of preterm (<37 GA) children with a prescription and relative risk for preterm (< 37 GA) vs term (+37 GA) children for receiving a prescription. Data are shown in three age groups and for each class of medication. The total number of children being prescribed/dispensed medication is indicated by the n number. Due to small numbers data on VWC1, VWC3, and VWC5

are not available. Abbreviations; GA, weeks of gestation; CVM, cardiovascular medication; ASM, anti-seizure medication; FAD, fatty acid derivatives; RR, relative risk; VW1, Vaughn Williams class 1; VW2, Vaughn Williams class 2; VW3, Vaughn Williams class 3; VW5, Vaughn Williams class 5.

Response to reviewer comments

We thank the reviewers and editor for their review and constructive criticism of our paper. A number of relevant points have been raised, all of which have been addressed in the revised version of the manuscript.

All changes in the revised manuscript have been marked with red.

Reviewer: 1
Dr. Imti Choonara, Derbyshire Childrens Hospital Comments to the Author:

An interesting study of drug utilisation in preterm infants through childhood in several European countries. I would like to see the results presented more clearly.
Response: we have revised the presentation of the results

Table 2 should contain actual numbers of infants/children receiving medicines, as well as %.
Response: we have added the numbers of children to the headings in the relevant columns to enable the reader to calculate the numbers of children receiving the medications. This was done to avoid adding an additional 3 columns of data to an already large table.

I would also like to see which antiepileptic drugs (AEDs) were actually prescribed.
Response: when designing the study we did not opt for extracting data on specific antiepileptics (5th level in ATC system), but rather to the 4th level only. The main reason for this is that most national databases have rules that do not allow extraction of small numbers. Even when restricting the analysis to the 4th ATC level numbers for several groups of cardiovascular medication were two low to report. We have clarified this point in the article

Minor point, replace ASM (antiseizure medicine) with antiepileptic drug(AED), as the latter is more frequently used. I
Response: In neonatalogy antiepileptics are frequently prescribed for seizures during early infancy that do not necessarily reflect a diagnosis of epilepsy. As such, in our cohort, prescription of an antiepileptic might well reflect seizure treatment for a shorter duration rather than a diagnosis of epilepsy. We are aware that the term antiepileptic is more widely used in the literature, but opted for the term antiseizure to underscore that receiving this medication does not necessarily reflect an epilepsy diagnosis.

The discussion is too long and can be shortened. Should also mention that studies of drug utilisation need to be followed by studies evaluating whether the medicines are used rationally or not.
Response: we have shortened the discussion.

minor point - is the use of the word "risk " appropriate for receiving a medicine? I think not
Response: In epidemiology, risk has been defined as “the probability of an event during a specified period of time”[1], as such we think that it is the appropriate terminology. We have added this definition in the Methods so that it is clear to the reader

Reviewer: 2

Dr. Anne Louise de Barros Damgaard, Copenhagen University Hospital Rigshospitalet

Comments to the Author:
The article titled “Preterm birth and prescriptions for cardiovascular, anti-seizure, antibiotics and anti-asthmatic medicine in children up to ten years of age: A population-based data linkage cohort study across six European regions” is very promising. The authors make excellent use of unique data from the ambitious EUROlinkCAT project to compare medication use in children born preterm versus children born term all across Europe from birth up to ten years of age. Specifically, the authors studied whether there were differences in prescription patterns for cardiovascular drugs, anti-seizure drugs, anti-asthmatic drugs, and antibiotics throughout childhood.
The authors raise the interesting question of whether the high survival rates at lower gestational ages in high-income countries come “at the price of an increased morbidity in childhood compared to term born children”. While the methods are clear and adequate, results are nicely presented, and the discussion is clearly structured, the introduction and conclusion sections could be even more concise. Lastly, while the subject and contents of this paper show great promise, as it currently stands it necessitates careful spelling and grammar revision to clearly convey its results.

Major concerns:
1. The introduction raises some very relevant points, which could be clearer tied together in the final aim of the study. Since the study is designed to test a hypothesis in the control group of the original cohort, the aim needs to be very clear. Why is it interesting to study medication patterns in preterm born children? And if focus is on children born moderately preterm – why is it important to study prescription patterns for diseases beyond neurodevelopmental and psychiatric disorders? What consequences would higher prescription rates have? The conclusion briefly touches upon the “implications for obstetric and paediatric health care providers as well as to the families of children born preterm” without further elaboration. These implications (or concern for these implications) of a higher disease burden in ex-preemies could be raised in the introduction, elaborated on in the discussion and referred to in the conclusion in order to strengthen the contextualization of this important work.
Response: we have shortened the Introduction and clarified that prescription of medication is used as an indicator of disease burden. We have further clarified that the results we report here do not directly affect patient management, but rather shines light on how much medication is prescribed for ex-preemies despite very low levels of evidence.

2. The methods section presents a nice overview of the provenance of the data in Table 1. The table describes the beginning of data collection in each region, the source of the prescription data (dispensed at pharmacy or prescribed by GP) and the number of children from each region by gestational age group. Do these numbers, specifically the distribution by gestational age, belong in a separate baseline table in the results section? The Tuscan region has provided only a random 10% sample to the data set, resulting in a much smaller sample than the other regions and only 77 children born at a GA <32 weeks. The discussion briefly comments that no significant prescription differences were found in the Tuscan region but does not discuss the potential implications for the data. Is there any way to include the full Tuscan dataset or could the reason for the 10% sample be stated?
Response: The Tuscany registry had concerns about their computational efficiency in handling and manipulating large volumes of data and were unsure that their data providers would give approval to have all their pediatric population data. To address these concerns, the statisticians at SGUL calculated sample size estimates, and a 10% sample size was sufficient to capture rare events in the reference population.

3. Table 2 gives a good overview of the results. In general, data appears to be of very high quality with only 0.7% of missing data on gestational age. Was the missingness evenly distributed throughout the regions?
Response: Yes gestational age is a very well recorded variable in all these data sets.

Fig3 presents regional differences in RRs. The differences are described in the results section, but the discussion does not mention any issues comparing the regions with different definitions of a prescription (GP vs. pharmacy), different inclusion periods (calendar effect) etc.
Response: We have elaborated on this point.

4. The discussion is well-structured and generally well-argued. It does a good job of putting the results into the perspective of current research. However, while it is important to stress the limits of register-based studies on broader clinical conclusions and not overinterpret the data, the results could be understood in a larger context by touching upon possible clinical implications of differences in prescription practices. As a specific example, the last sentence in the discussion of anti-asthmatic drugs (p.20, l. 53 "Management of asthma… cardiac disease") is of unclear relation to the results of the study.
Response: we have deleted the last sentence.

5. The similarity of wording in the "Strengths and limitations of this study" section of this manuscript and the article referenced in number 15 is striking, including the grammar in the sentence starting with "That this is…" and the plural "are" in the second sentence in reference to the single "study". The section should be revised to reflect this independent research project and should reflect points raised in the discussion section, including limits related to the register based nature of the study, possible biases etc. (unless journal requirements state that strengths and limitations should only be presented in this section and not further discussed). In this same "Strengths and limitations" section, anti-seizure is spelled "antis-seizure".
Response: we re-phrased these paragraphs.

Minor issues:
1. In general, the manuscript is understandable. There are some minor terminological inconsistencies.
a. The main outcomes are prescriptions for different drug groups. While the term "medicine" is not technically incorrect, consistent use of the more commonly used terms cardiovascular medication, anti-seizure medication, and anti-asthmatic/asthma medication would avoid any confusion.
Response: We now use medication consistently.

b. The main variable includes both outpatient prescriptions dispensed at pharmacies and prescriptions prescribed by GPs. It could be described more consistently either as "receiving", "prescribed/dispensed", or "issued/dispensed" to avoid confusion.
Response: we have changed it so that prescribed/dispensed is used consistently

c. The main exposure is preterm birth described in weeks of gestation. The gestational ages are divided into 3 groups <32 weeks, 32-36 weeks, and term. There are both comparisons term vs. preterm (<37 weeks) and term vs. 32-36 weeks vs. <32 weeks. The last group is described as "very preterm". To avoid confusion, the 32-36 weeks group could be consistently be described with the term used in the conclusion: "moderately preterm".
Response: we agree and have revised the terminology accordingly

2. Some minor points for clarity:

a. P.8, l.43: According to reference (14), PDA is categorized as a "non-congenital" anomaly. In this study, these patients were excluded. Does this also concern patients with pyloric stenosis and hydrocephalus (from this same category), and if not – was there a reason to treat these diagnoses differently?
Response: Preterm born children with acquired hydrocephaly after neonatal cerebral hemorrhage included in the study population of the correct diagnosis code for acquired hydrocephaly has been used (G91). If a child with acquired hydrocephaly incorrect is given a diagnosis of congenital hydrocephaly (Q03) they will in the case be excluded from the study. This coding problem may have some impact on the group of children with GA < 28 weeks in the same way as the exclusion of PDA, but number of children with hydrocephaly after bleeding is much lower than number of children with PDA. Further, these children are only excluded if a wrong code is given. Children with pyloric stenosis are generally born at term, and the prevalence is low and this would therefore not influence results.

b. P.9, l.19: Could the ATC-codes be "translated" wherever possible, as done in the section for ASM? E.g. beta-blockers, digoxin, calcium-channel blockers etc.
Response: This has been included as requested.

c. P.10, l.14: It is unclear whether combination inhalants were included or excluded, please revise sentence for clarity.
Response: as stated in the paper combination inhalants are excluded.

d. P.10, l.29: The end of the sentence "All topical…" seems to be missing.
Response: has been added.

e. P.14 Results section: could all references to Fig3 include letters for easier reference and a reference be added in the section about ASM?
Response: has been added

f. Fig3: Denmark is presented as a country along with Finland. In the rest of the manuscript it is described as "Denmark: Funen". A, B, and C present a "Total (I-squared)" and D presents a "Subtotal (I-squared)", what is the difference?
Response: the figures terminology has been revised

g. P.15, l.31: seems to describe anti-asthmatics and not "antibiotic prescription".
Response: has been corrected.

h. P.20., l.29: Cited numbers are ORs and represent two different GA groups (28-31 and 32-36 weeks resp.). They are thus not comparable.
Response: has been corrected.

i. P.22, l.7: "the present" study?
Response: has been corrected.

j. P.22, l.7: Last sentence is difficult to understand. Could it read something along the lines of: "however, due to a small sample from Tuscany, this sub-cohort failed to find any differences in prescription patterns for preterm vs. term born children."
Response: has been corrected.

k. P.23, l.15: “A condition…” sentence seems incomplete.
Response: has been corrected.

l. P.29, l.14: ”from 1 till the day before turning 2 is termed <1” should be revised.
Response: has been corrected.

m. P.30, l. 12: Could both sentences starting with “Please note…” be combined into one?
Response: has been corrected.

n. P.30, l.56: Abbreviations HYP and DIU should be removed.
Response: has been corrected.

3. As stated above, manuscript should be carefully checked for spelling and grammar, including commas. Examples of suggestions:
a. P.6, l.32: “that” (who)
b. P.12, l.4: “ss” (as)
c. P.15, l.31: “were” (was)
d. P.18, l.27: “reflect” (reflects)
e. P.18, l.53: “i.e.” (e.g.)
f. P.19, l.7: “at current” (at present, at current times, at the current stage)
g. P.19, l.22: second quotation mark missing
h. P.19, l.44: “relative” (relatively)
i. P.20, l.36: “at an RR” (at a RR)
j. P.20, l.49: “Prescription… were” (Prescriptions)
Response: has been corrected.

4. The reference list is adequate and extensive, however it should be revised and updated:
a. P.5, l.37: Does the statement “in high-income countries, close to 100% of babies born at a GA of 32 weeks are expected to survive infancy” refer to children born at or after 32 weeks of gestation? If so, reference (2) does not support the claim. It states: “"In low-income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties. In high-income countries, almost all of these babies survive." This reads as a description of survival rates of extremely and very preterm infants, not moderately preterm infants. It also states that "yet less than 10% of extremely preterm babies die in high-income settings." contradicting the next sentence in the manuscript citing a mortality rate of 33-50%. While both sentences in the manuscript are probably true, the reference and/or sentences need to be revised.
Response: the references have been updated.

b. P.5, l.49: Could references 4-8 be added after “The few available studies” for clarity?
Response: has been corrected.

c. Reference (15) should be updated to reflect publication details.
Response: has been corrected.

1. Cole SR, Hudgens MG, Brookhart MA, Westreich D. Risk. American Journal of Epidemiology 2015;**181**(4):246-50 doi: 10.1093/aje/kwv001[published Online First: Epub Date]|.