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To Marco

Maternal and Child Health

Abstract

According to the World Health Organization (WHO), every day, worldwide, about 1,000 women die due to causes related to pregnancy or childbirth and, every year, more than eight million children in low and middle income countries die before reaching five years of age. The WHO was clear: maternal and child health is a topic of enormous medical importance and requires investments, projects, energy and commitment; it is an essential part of the public health of human populations.

Improving the approach and access to health care, making qualified assistance, drug treatment and training of the operators more available, but also elementary preventive interventions during pregnancy, childbirth and the early years of a child's life, can prevent avoidable deaths and reduce several neonatal outcomes.

Given the complexity of all the issues and problems concerning births and maternal and child health, through this thesis I propose a path divided into several stages which covers various topics starting from the socio-economic profile of the mother, moving to the pharmacological profile of pregnancy, up to the prevention of stillbirths.

Several statistical methods were implemented to answer the different questions depending on the aim of each study. Log-binomial regression was used for estimating the association between the mother's exposure during pregnancy and the selected neonatal outcomes. The fully conditional specification (FCS) model was performed to generate appropriate values of missing data for those women with missing covariates. The rule-out approach described by Schneeweiss was implemented to make our estimates, which might be affected by unmeasured confounder, more robust. The mediation analysis described by VanderWeele and Vansteelandt was used to assess the role that some adverse neonatal events at presentation (mediator) play in the relationship between the mother's exposure during pregnancy (exposure) and adverse neonatal events later in life (outcome). Lastly, the Propensity Score Stratification derived from the predicted probability of treatment estimated in a logistic-regression model, as well as the high-dimensional propensity score algorithm to evaluate hundreds of inpatient diagnosis, procedures, and pharmacy claims, were completed to account for all potential confounders.

The aim of my thesis is to identify factors to develop and improve the health care related to maternal-fetal and maternal-child world (before and after birth, respectively) from a sociodemographic, farmacoepidemiology, and clinical point of view.

The layout of the thesis has been divided into different sections. I will proceed in the first instance by giving an overview of the methods used in the various studies carried out during my PhD, proceeding with a detailed description of the latter.

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I. Introduction

We know little about the effects of taking most medications during pregnancy. This is because pregnant women are often not included in studies to determine safety of new medications before they come on the market. Fewer than 10% of medications approved by the U.S. Food and Drug Administration (FDA) since 1980 have had enough information to determine their risk for birth defects and other neonatal outcomes.

Nowadays, the awareness that children are not *little adults* increases every day. After all, before research began to show interest in pharmacoepidemiology studies considering the safety of drugs taken during pregnancy as the aim of the studies, the disasters of phocomelia caused by thalidomide and clear cell carcinoma caused by diethylstilbestrol were ringing alarm bells, it was widely believed that the placenta formed an impregnable, protective barrier between the mother and the child. Now we know that this is far from true. Many drugs cross the placenta, as do many pollutants.

Since studies are conducted, in this field, after that medications come on the market, we cannot know the potential risk of taking such medications during pregnancy. Such medications should be avoided by all women who are or might become pregnant. For women who are taking these medications, it is important to discuss the safety or risk of these drugs.

At national and international level, the use of drugs during pregnancy is very common (75% -86% of women) [1]. Despite the increase in the use of drugs during pregnancy, the information about the safety profile of certain medication taken during pregnancy and the potential effects on the fetus are still lacking. In addition, population-based studies related to the consumption of drugs in pregnancy are few, dated and inconsistent.

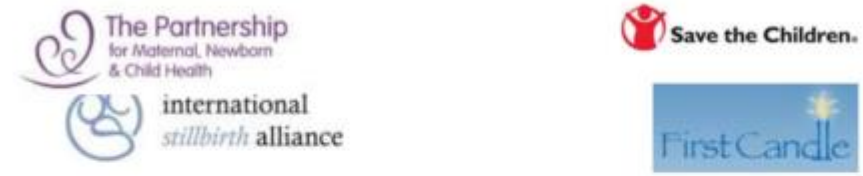
Drugs, unfortunately, are not the only factor that can have harmful consequences on the fetus. For a long time, the intrauterine world has been explored only from a medical point of view, essential to ensure that the fetus would develop normally. Attention was mainly devoted to the physical condition of the mother and the state of her health, omitting all psychological, social, emotional parts that characterized each mother and consequently also their children. David Chamberlain, president of the Association for Pre and Perinatal Psychology and Health (APPPAH), states that "for too long time, the fetal image was as a living creature protected by the mother's womb, that, like a treasure chest, isolates the child from any contact with the outside world" [2]. Several studies have documented that the mortality rate in Italy, as in other states, increases in inverse proportion to the socio-economic status (SES). It was also noted that the SES - measured through the education level of the mother - has an association with the weight of the infant at birth; the probability of low births-weight is 1.5

times higher for mothers with a low educational level (elementary school), than mothers with a level of university studies [1].

Another big challenge in the pregnancy field is the decrease of stillbirths. In 2014, the World Health Assembly endorsed a target of 12 of fewer stillbirths per 1000 births in every country by 2030. By 2015, 94 mainly high-income and middle-income countries have already met this target, although with noticeable variability in the stillbirths' rate within countries (**Figure 1**). Due to this variability, in fact, attention to stillbirths has increased, because it means that a considerable number of stillbirths can be prevented. Within high-income countries, the stillbirth rate (at the third trimester) varies widely, ranging from 1.3 to 8.8 per 1000 births, showing that further reduction is possible, with six countries having a stillbirth rate of 2.0 per 1000 births or lower. Half of all the stillbirths occur during labor and birth. Most result from preventable conditions such as maternal infections, non-communicable disease, and obstetric complications. Hence, it stands to reason that most stillbirths are preventable with health system improvements. Moreover, such inputs result in a quadruple return on investments by preventing maternal and newborn deaths and stillbirths, plus improving child development.

Several population-based studies were performed to identify factors to develop and improve the health care related to maternal-fetal and maternal-child world (before and after birth, respectively) from a sociodemographic, farmacoepidemiology, and clinical point of view.

Figure 1. Country stillbirth rates per 1000 total births for 2009.



Country stillbirth rates per 1000 total births for 2009

	Country	Total births	Total stillbirths	Stillbirth rate per 1000 births		Country	Total births	Total stillbirths	Stillbirth rate per 1000 births
1	FINLAND	59,540	120	2.0	49	KUWAIT	52,400	260	5.0
2	SINGAPORE	37,260	70	2.0	50	ARGENTINA	694,740	3,510	5.0
3	DENMARK	61,800	140	2.2	51	COSTA RICA	76,100	390	5.1
4	NORWAY	58,310	130	2.2	52	KAZAKSTAN	309,520	1,580	5.1
5	ICELAND	4,710	10	2.4	53	ALBANIA	46,950	250	5.3
6	GERMANY	660,790	1,610	2.4	54	COLOMBIA	715,450	3,950	5.5
7	SAN MARINO	290	0	2.5	55	MALAYSIA	553,410	3,290	5.9
8	SWITZERLAND	72,880	190	2.5	56	UZBEKISTAN	562000	3,540	6.3
9	JAPAN	1,016,920	2,670	2.6	57	BRUNEI DARUSSALAM	7,850	50	6.4
10	CZECH REPUBLIC	111,330	300	2.7	58	TFYR MACEDONIA	22,310	140	6.4
11	ITALY	544,120	1,470	2.7	59	OMAN	62,770	410	6.5
12	SWEDEN	108,340	300	2.7	60	BULGARIA	73,390	480	6.6
13	ANDORRA	950	0	2.8	61	ANTIGUA AND BARBUDA	1,630	10	6.9
14	CYPRUS	10,080	30	2.8	62	SAUDI ARABIA	597,810	4,550	7.6
15	AUSTRALIA	270,360	780	2.9	63	CUBA	116,800	890	7.6
16	PORTUGAL	103,690	300	2.9	64	UKRAINE	471,730	3,920	8.3
17	USA	4,425,800	13,070	3.0	65	QATAR	15,790	130	8.4
18	GREECE	106,620	320	3.0	66	TRINIDAD AND TOBAGO	20,080	170	8.5
19	CROATIA	42,610	130	3.0	67	LEBANON	66,720	570	8.6
20	LUXEMBOURG	5,520	20	3.0	68	IRAQ	957,320	8,240	8.6
21	MONACO	390	0	3.0	69	BAHAMAS	5,700	50	8.6
22	BELGIUM	120,070	370	3.1	70	BARBADOS	2,880	30	8.8
23	MALTA	3,710	10	3.1	71	SEYCHELLES	1,190	10	8.8
24	MONTENEGRO	7,560	20	3.2	72	CHILE	254,390	2,260	8.9
25	SPAIN	500,310	1,620	3.2	73	MAURITIUS	18,260	160	8.9
26	CANADA	359280	1,180	3.3	74	BAHRAIN	14,170	130	8.9
27	IRELAND	70,110	230	3.3	75	COOK ISLANDS	430	0	8.9
28	NETHERLANDS	183,490	610	3.3	76	TONGA	2,830	30	9.1
29	ISRAEL	157,310	530	3.4	77	MOLDOVA	45,480	420	9.2
30	SLOVENIA	19,820	70	3.4	78	URUGUAY	50,450	470	9.3
31	POLAND	416,440	1,420	3.4	79	BRAZIL	3,055,520	29,070	9.5
32	REPUBLIC OF KOREA	451,710	1,560	3.5	80	RUSSIAN FEDERATION	1,574,100	15,040	9.6
33	UNITED KINGDOM	751,370	2,630	3.5	81	SAINT KITTS AND NEVIS	960	10	9.7
34	NEW ZEALAND	58,790	210	3.5	82	CHINA	18,500,000	182,150	9.8
35	BELARUS	96,680	340	3.5	83	GUATEMALA	460,820	4,540	9.9
36	UAE	63,280	230	3.6	84	LIBYA	149,150	1,470	9.9
37	AUSTRIA	75,970	280	3.7	85	PERU	611,210	6,060	9.9
38	ESTONIA	16,380	60	3.7	86	TUNISIA	167,020	1,690	10.1
39	SLOVAKIA	55,730	210	3.7	87	ST VINCENT/ THE GRENADINES	1,920	20	10.2
40	HUNGARY	99,190	370	3.8	88	SAMOA	4,130	40	10.2
41	FRANCE	747,440	2,890	3.9	89	KYRGYZSTAN	123,020	1,260	10.2
42	LITHUANIA	31,700	130	4.1	90	PANAMA	70,740	730	10.3
43	LATVIA	23,590	100	4.1	91	GRENADA	2,050	20	10.6
44	ROMANIA	212,800	890	4.2	92	DOMINICA	1,240	10	10.9
45	BOSNIA AND HERZEGOVINA	34,340	140	4.2	93	VENEZUELA	606,300	6,610	10.9

1

The Partnership for Maternal, Newborn & Child Health

international stillbirth alliance

Save the Children.

First Candle

46	THAILAND	980,820	4,270	4.4
47	MEXICO	2,636,110	11,940	4.5
48	SERBIA	114,160	570	5.0
97	ECUADOR	282,250	3,330	11.8
98	DOMINICAN REPUBLIC	226,290	2,680	11.9
99	TAJIKISTAN	197,600	2,370	12.0
100	TUVALU	210	0	12.0
101	NIUE	30	0	12.1
102	AZERBAIJAN	171,060	2,080	12.2
103	BELIZE	7,550	90	12.3
104	SYRIAN ARAB REPUBLIC	603,170	7,470	12.4
105	PALAU	440	10	12.4
106	JAMAICA	52,780	660	12.5
107	DEM. PEOPLE'S REP. OF KOREA	330,870	4,180	12.6
108	KIRIBATI	2,120	30	12.6
109	FIJI	17,730	220	12.7
110	JORDAN	160,420	2,040	12.7
111	VIET NAM	1,503,850	19,120	12.7
112	TURKMENISTAN	112,350	1,430	12.7
113	VANUATU	7,240	90	12.9
114	IRAN	1,408,750	18,380	13.0
115	EGYPT	2,056,450	26,970	13.1
116	MALDIVES	5,910	80	13.4
117	NICARAGUA	142,260	1,930	13.6
118	LAO PEOPLE'S DEM REPUBLIC	174,060	2,450	14.1
119	MICRONESIA	2,790	40	14.2
120	EL SALVADOR	126,360	1,800	14.3
121	TIMOR-LESTE	46,210	660	14.3
122	ARMENIA	48,280	700	14.5
123	INDONESIA	4,236,610	62,290	14.7
124	SAINT LUCIA	3,090	50	14.8
125	PAPUA NEW GUINEA	211,600	3,140	14.8
126	SURINAME	9,880	150	14.9
127	NAMIBIA	59,840	900	15.1
128	MARSHALL ISLANDS	1,340	20	15.1
129	HAITI	278,270	4,300	15.5
130	SOLOMON ISLANDS	15,870	250	15.5
131	CAPE VERDE	12,200	190	15.8
132	PHILIPPINES	2,281,550	36,460	16.0
133	BOTSWANA	48,290	780	16.1
134	GEORGIA	52,600	880	16.7
135	EQUATORIAL GUINEA	26,080	440	16.7
136	BOLIVIA	266,530	4,470	16.8
137	GUYANA	13,520	230	16.9
138	GABON	40,420	700	17.3
139	SRI LANKA	370,250	6,400	17.3
140	NAURU	220	0	17.4
141	HONDURAS	205,840	3,600	17.5
142	CAMBODIA	373,760	6,690	17.9
143	SWAZILAND	35,800	650	18.0
144	PARAGUAY	157,010	3,050	19.4
145	MOROCCO	664,350	12,960	19.5
146	MYANMAR	1,037,050	20,700	20.0
147	ZIMBABWE	387,210	7,740	20.0
148	SOUTH AFRICA	1,108,040	22,560	20.4
94	TURKEY	1,361,500	15,260	11.2
95	ALGERIA	731,620	8,250	11.3
96	MONGOLIA	50,830	580	11.4
155	BHUTAN	15,120	340	22.5
156	RWANDA	422,120	9,620	22.8
157	NIGER	834,400	19,080	22.9
158	YEMEN	881,580	20,380	23.1
159	MALI	564,470	13,090	23.2
160	NEPAL	747,250	17,460	23.4
161	MALAWI	622,430	14,740	23.7
162	GUINEA	406,710	9,660	23.7
163	SUDAN	1,331,630	31,780	23.9
164	CENTRAL AFRICAN REPUBLIC	158,240	3,830	24.2
165	BENIN	357,740	8,710	24.3
166	UGANDA	1,540,230	38,190	24.8
167	TOGO	220,390	5,500	25.0
168	ANGOLA	804,590	20,210	25.1
169	LESOTHO	60,710	1,530	25.3
170	ZAMBIA	563,240	14,380	25.5
171	CONGO	129,030	3,300	25.6
172	TANZANIA	1,859,600	47,550	25.6
173	CAMEROON	729,780	18,660	25.6
174	ETHIOPIA	3,214,640	82,370	25.6
175	GAMBIA	63,570	1,650	25.9
176	BURKINA FASO	757,770	19,870	26.2
177	LIBERIA	152,680	4,110	26.9
178	COMOROS	22,200	600	27.1
179	COTE D'IVOIRE	749,090	20,520	27.4
180	MAURITANIA	112,060	3,070	27.4
181	BURUNDI	291,280	8,060	27.7
182	MOZAMBIQUE	902,400	25,660	28.4
183	DEM. REPUBLIC OF THE CONGO	3,015,670	86,130	28.6
184	CHAD	522,990	15,260	29.2
185	AFGHANISTAN	1,341,210	39,310	29.3
186	GUINEA-BISSAU	67,930	2,010	29.6
187	SIERRA LEONE	234,340	7,030	30.0
188	SOMALIA	414,220	12,450	30.1
189	SENEGAL	493,010	16,660	33.8
190	DJIBOUTI	25,040	850	33.9
191	BANGLADESH	3,529,710	128,550	36.4
192	NIGERIA	6,345,150	264,390	41.7
193	PAKISTAN	5,667,980	264,550	46.7

149	MADAGASCAR	709,260	14,590	20.6
150	ERITREA	188,720	4,000	21.2
151	KENYA	1,564,210	34,130	21.8
152	SAO TOME AND PRINCIPE	5,250	110	21.9
153	GHANA	782,920	17,200	22.0
154	INDIA	27,400,000	605,230	22.1

Source: World Health Organization and Save the Children.

II. Objective

The aim of my thesis is to identify factors to improve child and maternal health in the social, pharmacoepidemiological, and clinical field. In order to reach my goals, I (i) evaluated the role that the mother's social-economic status, measured in term of education level, has on several neonatal outcomes measured at birth and during the first year of the newborn's life (I study), (ii) assessed the association between antidepressants taken during pregnancy and several neonatal outcomes measured at birth and during the first year of the newborn's life (II, III, and IV Study), and (iii) focused my attention on one of the most important recent challenges which brought together more than one hundred authors, investigators, advisers representing countries, and organizations to end preventable stillbirths (V Study).

Different population-based studies were been performed recruiting all live births, except for the stillbirths' project, in Lombardy from 1st January, 2005 through 31st December, 2010.

Specific Aim I Study: To assess whether preterm birth, low birth weight, small for gestational age, low 5-minute Apgar scores, cerebral suffering, respiratory distress, and congenital anomalies varied according to maternal education, and other socioeconomic factors, in a setting where the healthcare system provides essential health services to all women irrespective of their socioeconomic status.

We hypothesized that, because of universal coverage of the healthcare service, the socio-economic status has not affected on the occurrence of selected neonatal outcomes.

Specific Aim II Study: To investigates the effect of antidepressant medications use during pregnancy on risk of preterm birth and low birth weight.

We hypothesized that antidepressants taken during pregnancy, instead of depression, have increased the prevalence ratio of the considered outcomes.

Specific Aim III Study: To determine the effect of antidepressant medications used during pregnancy on the risk of small for gestational age, low 5-min Apgar score, cerebral irritability, neonatal convulsion, intrauterine hypoxia and birth asphyxia, and other respiratory conditions.

We hypothesized that antidepressants taken during pregnancy, instead of depression, have increased the prevalence of the considered outcomes; and that the found association was not explained through a mediation variable (low 5-min Apgar score).

Specific Aim IV Study: To evaluate the risk of low Apgar score (defined as a score <7 at 5 minutes) among infants born to mothers exposed to antidepressants at different stage during pregnancy.

We hypothesized that antidepressants taken during pregnancy increased the risk of the considered outcome.

Specific Aim V Study: Presentation of epidemiological data on timing of stillbirth and on timing of stillbirth specific risk factors. An early detection on specific risk factors could help clinicians in decreasing antepartum and intrapartum risk through monitoring and timely intervention.

III. Methods

1. Study design

The retrospective population-based studies presented in this thesis recruited all live births, except for the stillbirth's project, in Lombardy between 1st January, 2005 and 31st December, 2010. The data used were extracted from the administrative databases of the Lombardy region. In Italy there have been several facilities to collect epidemiological data, both at nationally and regionally level. In 1978, the government established the SSN (*Servizio Sanitario Nazionale*), the Italian version of a National Health Service (NHS), including universal coverage and tax founding. Healthcare is provided to all citizens and residents by a mixed public-private system. The public part is the National Health Service, which is organized under the Ministry of Health and is administered on a regional basis. The Regions have exclusive jurisdiction in the regulation and organization of health services and the funding criteria of the Local Health Authorities and hospitals. Lombardy region accounts for approximately 16% (about ten million) of the entire national population. Since 1997, Lombardy has an automated system of databases to collect a variety of information including (i) an archive of beneficiaries of the Regional Health Service (which it practically coincides with the whole resident population), reporting demographic and administrative data; (ii) the hospital discharge registry, which reports all diagnoses relesed from public or private hospitals; (iii) the outpatient drug prescriptions registry, which reports all dispensations of NHS-reimbursable drugs; and (iv) the Certificates of Delivery Assistance (i.e., the so called CeDAP), which provides detailed information on socioeconomic traits of the mother, and on pregnancy, childbirth, and child presentation at delivery. The linking of records across HUC databases, which is made possible through a unique patient-identifying code included in all database, allows to identify a large and unselected birth cohort and to reconstruct relevant traits and care pathways of mothers and new-borns.

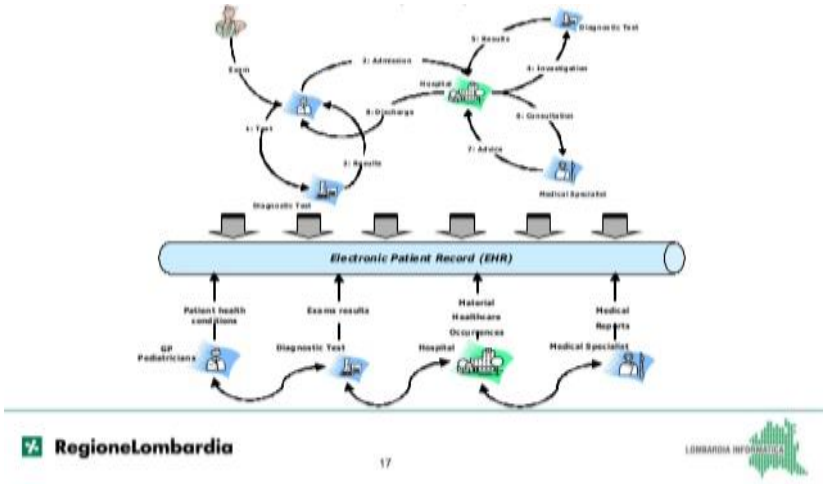


Figure 2. Electronic Health Record (HER): How does it work?

2. Statistical Analysis

- *Conventional statistical analysis*

Standard descriptive statistics including frequencies, percentages, means, and medians were calculated to evaluate the distribution of maternal socio-demographic and clinical features according to maternal exposure. The chi-square test, or its version for the trend, was used when appropriate for testing differences or trends in maternal socio-demographic and clinical features according to mother exposure.

Logistic regressions were fitted to estimate the odds ratio (OR), and the 95% confidence interval (95% CI), of each neonatal outcome associated with the exposure of the mothers during pregnancy Generalized estimating equation was used to account for potential correlation of women contributing with more than one birth during the follow up.

Log-binomial regressions were fitted to estimate the prevalence ratio (PR), and the 95% confidence interval (95% CI), of each neonatal outcome associated with the exposure of the mothers during pregnancy. Generalized estimating equation was used to account for potential correlation of women contributing with more than one birth during the follow up.

- *Accounting for missing data*

Data on maternal characteristics were sometime missing for some women. Multiple imputation provides a useful strategy for dealing with data sets with missing values. Instead of filling in a single value for each missing value, Rubin's (1987) multiple imputation procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute [3]. These multiply imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses. In our cohort, missing data ranged from 1% for previous miscarriages to 13% for marital status. Restricting analyses to the subset of women with all the data observed (complete cases) would have resulted in a significant loss of information and possibly biased estimations. With the aim of generating appropriate values of missing data for those women with missing covariates, an iterative procedure was used known as the Fully Conditional Specification model (FCS) implemented in SAS and involving three distinct phases [4]. First, the FCS imputation method was implemented to generate *n* complete data sets. The imputation method of choice depends on the patterns of missing in the data and the type of the imputed variable. I had data sets with arbitrary missing patterns. Secondly, the log-binomial model was separately fitted to the *n* complete data sets using the GENMOD procedure. Finally, the procedure MIANALYZE was

used to combine the coefficient estimates (and estimations of their variances) from the *n* analyses, in order to obtain valid statistical inferences about the model coefficients that take within and between analysis variances into account.

- *Taking into account for unmeasured confounding*

The robustness of estimates with regard to potential bias introduced by unmeasured confounders was investigated by using the rule-out approach described by Schneeweiss [5]. Although a variety of systematic errors may bias non-experimental research, confounding bias is of particular concern in epidemiologic studies of drug effects. Large health care utilization data sets are often the best sources of data to analyze the relation between prescription drugs and unintended and infrequent health events. A major advantage of health care utilization data is that they reflect routine practice for large and representative populations, in contrast to the much smaller and often healthier patient populations in clinical trials [5]. Nevertheless, information on some potential confounding factors is incomplete (e.g., smoking) or absent (e.g., maternal body mass index, and other life style factors), which may have resulted in residual confounding to the extent that these factors were not accounted. The Rule-Out method, allows to evaluate the strength of an unmeasured confounder necessary to fully explain the observed association. More precisely, this approach allows to quantify the force, expressed through the confounder-exposure association (OR_{EC}) and through the confounder-outcome association (RR_{CD}), that an unmeasured confounder should have to move the observed point estimate (ARR) to the unit, which is the value that represents the lack of association.

We set the possible generic unmeasured confounder: (i) to have a 10% prevalence of exposure among pregnant women; (ii) to increase the neonatal outcome onset up to 10-fold more in mothers exposed than in those unexposed to the confounder and (iii) to be up to 20-fold more common among exposed than among unexposed mothers.

- *Mediation analysis*

The role that adverse neonatal events at presentation (mediator) play in the relationship between exposure during pregnancy (exposure) and adverse neonatal events appearing later in life (outcome) was investigated. In other words, mediation analysis investigates the mechanisms that underlie an observed relationship between an exposure variable and an outcome variable and examines how they relate to a third intermediate variable, the mediator. Rather than hypothesizing only a direct causal relationship between the independent variable and the dependent variable (A→Y), a mediational model hypothesizes that the exposure variable causes the mediator variable, which in turn causes the

outcome variable (A→M→Y). The mediator variable then serves to clarify the nature of the relationship between the exposure and outcome variable.

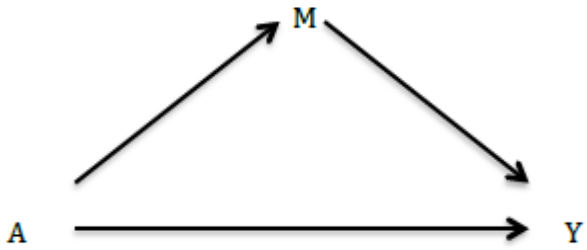


Figure 3. Mediation model in Baron and Kenny 1986 paper

I sought to address whether the increased prevalence of a given neonatal outcome in relation to the exposure of the mother during pregnancy is partially or entirely dependent (i.e., mediated) on an outcome of the newborn appeared at presentation. With this aim the approach described by VanderWeele and Vansteelandt was used [6]. Briefly, the (i) exposure-outcome, (ii) mediator-outcome, and (iii) exposure-mediator associations (each estimated by fitting log-binomial regression, the same model used in Conventional Statistical Analysis) allowed me to assess (i) the natural direct effect (PR_d), i.e., the effect of the exposure on the outcome intervening to set the mediator to the level it would have been under the reference exposure level (e.g., no antidepressant therapy); and (ii) the natural indirect effect (PR_i), i.e., the effect on the outcome when the exposure is present after setting the mediator value to what it would have been with versus without the exposure. The proportion of the exposure-outcome association that was explained by the mediator was computed according to Ananth and VanderWeele [7].

- *Propensity Score Stratification*

Observational studies are frequently used to estimate treatment or exposure effects in settings where the assignment of subjects into intervention or exposure groups is not under control of the study investigator. A major fault of such studies is that treatment preference or the status of exposure is often linked to individual characteristics that are not independent of the outcome of interest. Therefore, comparison groups may differ in their covariate distributions in ways that will confound the results regarding estimated treatment or exposure effects on the outcome. Propensity scores can be used to aggregate information about the predictive role of covariates on treatment assignment or exposure status. The propensity score is the probability of receiving treatment given individual covariate realizations. There are different ways to use propensity scores to address confounding such

as matching based on the propensity score, stratification according to propensity score intervals, ordinary propensity score adjustment in the context of a multivariable binary logistic regression analysis and performing weighted effect estimation (inverse probability of treatment weighting) in the framework of marginal structural models [8]. Propensity scores were derived from two different approaches. In the first one, propensity scores were obtained from the predicted probability of treatment estimated in a logistic-regression model that contained all the covariates considered on the study. In the second approach, propensity scores were estimated using the high-dimensional propensity score algorithm. Using this algorithm, we evaluated hundreds of inpatient diagnoses, procedures, and pharmacy claims and selected the 50 covariates with the highest potential to create confounding based on their prevalence and the strength of their association with the exposure and the outcome. These variables may act as proxies for unmeasured confounders and were combined with the pre-defined covariates in a propensity score model to improve confounding adjustment [9]. After estimating propensity scores, using both the approaches described above, I dropped the observations in non-overlapping areas of the PS, created 25 equally sized PS-strata, after ranking only the exposed patients based on the PS and assigning unexposed patients to these strata based on their PS. Weighted regression models were used to derive an adjusted exposure effect after stratification, in which each exposed patient received a weight of 1 and unexposed patients were weighted in proportion to the distribution of the exposed in the stratum into which they fell [10].

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

IV. Projects

1. I Study (submitted)

Mother's education and the risk of several neonatal outcomes. An evidence from an Italian population-based study

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AC performed statistical analysis, AC and GC wrote the paper, AG had full access to all the data in the study. LM abstracted the data and authorized their utilization. GC was responsible for designing the current study. AC, AG, LM, and GC read and approved the final version of the manuscript.

Conflict of Interest Disclosures: None reported

Abstract

Background: Maternal socioeconomic disparities strongly affect child health, particularly in low and middle income countries. We assessed whether neonatal outcomes varied by maternal education in a setting where healthcare system provides essential health services to all women, irrespective of their socioeconomic status.

Methods: A population-based study was performed on 383,103 single livebirths occurring from 2005 to 2010 in Lombardy, an Italian region with approximately ten million inhabitants. The association between maternal education, birthplace and selected neonatal outcomes (preterm birth, low birth weight, small-for-gestational age, low 5-min Apgar score, severe congenital anomalies, cerebral distress and respiratory distress) was estimated by fitting logistic regression models. Model adjustments were applied for sociodemographic, reproductive and medical maternal traits.

Results: Compared with low-level educated mothers, those with high education had reduced odds of preterm birth (Odds ratio; OR=0.81, 95% CI 0.77-0.85), low birth weight (OR=0.78, 95% CI 0.7-0.81), small for gestational age (OR=0.82, 95% CI 0.79-0.85), and respiratory distress (OR= 0.84, 95% CI 0.80-0.88).
Mothers born in a foreign country had higher odds of preterm birth (OR=1.16, 95% CI 1.11-1.20), low Apgar score (OR=1.18, 95% CI 1.07-1.30) and respiratory distress (OR=1.19, 95% CI 1.15-1.24) than Italian-born mothers. The influence of maternal education on neonatal outcomes was confirmed among both, Italian-born and foreign-born mothers.

Conclusions: Low levels of education and migrant status are important factors associated with adverse neonatal outcomes in Italy. Future studies are encouraged to investigate factors mediating the effects of socioeconomic inequality for identifying the main target groups for interventions.

Key words: Socioeconomic inequality, Maternal education, Adverse neonatal outcomes, Pregnancy and birth

What is already known on this subject?	What does this study add?
• Maternal socioeconomic status, including education level and migrant status, is known to affect birth outcomes • Universal coverage for many healthcare, including obstetric and neonatal services, is provided by the Italian National Health Service	• In spite of universal coverage of healthcare service, education level and migrant status independently affect the occurrence of several neonatal outcomes.

Introduction

Maternal socioeconomic status (SES) strongly affects child health [11-16], likely attributed to delayed prenatal care, preterm delivery and adverse birth outcomes [17-24]. Different SES measures capture unique aspects and pathways of socioeconomic disparities that can relate differently to child health. For example, maternal education reflects life-course SES [25], including parents' SES during childhood and adolescence, access to higher education, work opportunities, and income during adulthood [26]. According to a systematic review of studies in industrialized countries maternal education, rather than its' income, has been found to correlate with birth outcomes [27].

Differential access to good-quality obstetric services and neonatal care is a main reason for socioeconomic disparities in perinatal health. The Italian National Health Service (NHS) provides universal coverage for many areas of healthcare, including obstetric, neonatal and related health care services to women, regardless of their SES [28]. Neonatal outcomes are expected to be only partially affected by socioeconomic inequalities in health systems with universal access to essential health services [12].

We carried out a large population-based study aimed to measure the relationship between maternal education and several neonatal outcomes (i.e., preterm birth, low birth weight, small for gestational age, $Apgar^{5\ min}$ less than 7, severe congenital anomalies, signs of cerebral distress and distress of respiratory functions) in the Italian region of Lombardy. Controlling for other maternal features (i.e., migrant status, sociodemographic factors, reproductive history, and medical conditions), as well as investigating the impact of educational status

Methods

Setting

Data obtained for this study were retrieved from the healthcare utilization (HCU) databases of Lombardy, a region of Italy which accounts for approximately 16% (~ ten million) of the national population. In Italy, the entire population is covered by the National Health Service (NHS), which in Lombardy has been active since 1997 with an automated system of databases to collect a variety of HCU information. For the purpose of the current study, the following databases were considered: (i) the archive of beneficiaries of the Regional Health Service (RHS), i.e., the entire resident population, reporting demographic and administrative data (e.g., municipality, date of birth and date of start and end of being RHS beneficiary), (ii) the database on diagnosis at discharge from public or private hospitals of Italy (diagnoses classified according to the International Code of Disease, 9th Revision, ICD-9); and (iii) the database reporting Certificates of Delivery Assistance (CeDAP) including information self-reported by the mother relating to her socioeconomic traits in the period recent to her current pregnancy, other than medical information relating to pregnancy, childbirth, and child presentation at delivery. In general, information was collected and directly added to the specific database when the specific service was provided, for example, when an individual was recorded for being a RHS beneficiary, a patient discharged from hospital, or a woman who gave birth.

As each single record for the aforementioned databases utilises an univocal identification code, the record linkage between databases was allowed. In order to preserve privacy, however, each identification code was automatically converted into an anonymous code and the inverse process was prevented by the deletion of the conversion table. For the current application, a deterministic procedure of record linkage between the above listed databases was performed so as to select the study cohort and collect data on maternal traits and newborn outcome.

Cohort selection

The 428,715 single live births that occurred in Lombardy from 2005 to 2010 were selected from the CeDAP database, provided that identification codes of both mother and newborn were reported. We sequentially excluded (**Figure 1**) (i) 10,961 newborns (2.6%) because of a missing identification code (CeDAP database); (ii) 26,284 records (6.3%) because the mother was resident outside the Lombardy region (RHS beneficiaries archive); (iii) 6,696 records (1.7%) because the reported hospital admission ICD-9 code of mother and/or newborn was different from that of the delivery and/or birth (hospital discharge database); and (iv) 1,671 records (0.4%) because the mother was younger than 15 years or

older than 55 years of age at delivery (RHS beneficiaries archive). The final study cohort included 383,103 mother-newborn couples.

Collection of data on maternal traits

Information on maternal traits at the time of delivery was obtained from the CeDAP database and included age at delivery (≤25, 25-34 and ≥35 years), sociodemographic factors and reproductive history. Sociodemographic factors included (i) education, measured according to the length of formal education completed and categorized as ≤8 years (low), from 9 to 13 years (intermediate), and ≥14 years (high); (ii) birthplace, categorized as Italian-born and foreign-born, (iii) employment, categorized as employed and unemployed (the latter including women without a job, housewives and students); and (iv) marital status, categorized as married and unmarried. Reproductive history included (i) parity categorized as null parity and multi parity; and (ii) previous spontaneous miscarriages (yes/no). In addition, maternal medical conditions were identified from inpatient diagnoses (hospital discharge database) within the two years prior to date of delivery and included hypertension, dyslipidaemia, diabetes and preeclampsia. Supplementary Material **Table S1** presents the ICD-9 codes used for identifying maternal medical conditions.

Identification of newborn outcomes

Newborn outcomes appearing at presentation and within two years after birth were respectively identified from the CeDAP and the hospital discharge database. At presentation, we considered preterm birth (less than 37 weeks' gestation [29]), low birth weight (below 2,500 grams [30]), small for gestational age (birth-weight less than 10^{th} percentile for infants from 22 to 43 weeks [31] [32]), and low 5-min Apgar score ($Apgar^{5\ min} < 7$ [33]).

From the hospital discharge database the following three categories of neonatal outcomes were considered: (i) severe congenital anomalies, defined according to the EUROCAT classification (www.eurocat-network.eu) and included anomalies of the nervous, respiratory, digestive, urinary and genital systems, and defects of eye, ear, face and neck, heart, abdominal wall and limb; (ii) cerebral distress, including convulsion, other and unspecified cerebral irritability in newborn, cerebral depression, coma, and other abnormal cerebral signs; and (iii) distress of respiratory function, including intrauterine hypoxia, birth asphyxia and other respiratory conditions of foetus and newborn. Supplementary Material **Table S2** summarises ICD-9 codes used for identifying these categories of newborn outcomes. The first appearance of a hospital admission within two years from birth, including hospitalization immediately after birth, reporting anyone of such codes as principal or secondary diagnosis was considered for identifying the onset of outcome onset.

Statistical analysis

The frequency of a given neonatal outcome within strata of the considered maternal traits was evaluated by testing for heterogeneity between strata (of maternal birthplace, employment, marital status, reproductive history and medical conditions) or trend over strata (of educational status and age at delivery) respectively according to chi-square test, or its version for trend.

A logistic regression model was fitted to estimate the odds ratio (OR), and its 95% confidence interval (CI), of a given neonatal outcome in relation to categories of maternal education and birthplace. The influence of maternal education on neonatal outcomes was evaluated by considering the entire sample of mother-newborn couples in addition to stratifying data according to maternal birthplace. Linear trend in ORs for different levels of education was tested by using the contrast statement implemented in SAS [34]. Model adjustments were made for the above reported sociodemographic, reproductive and medical maternal traits.

The following two expedients were used for taking into account the nature of our data. First, because of the potential correlation of women contributing to more than one birth during the considered period, the models were fitted using Generalized Estimating Equations (GEE) for correlated observations with a logit link [12]. Two, because data were missing for some women (ranging missing values from 1% for previous miscarriages to 13% for marital status), 100 multiple imputations were applied by using the fully conditional specification (FCS) method implemented in SAS [4, 35].

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

Results

Just over 1 in 20 newborns were found to be affected from low birth weight (prevalence 5.1%), respiratory distress (5.1%), preterm birth (5.3%), small for gestational age (7.8%) and severe congenital anomalies (5.0%). Lower prevalence was observed for low Apgar score (0.8%) and cerebral suffering (0.3%).

It also emerged that as educational level increases, the frequency of several outcomes (i.e., preterm birth, low birth weight, small for gestational age, cerebral suffering and respiratory distress) decreases proportionally (**Table 1**). Other maternal traits (e.g., older age, foreign-born, unmarried and unemployment status, null parity, previous miscarriages and suffering from medical conditions) were significantly associated with several neonatal outcomes.

The relationship between maternal education and birthplace and selected neonatal outcomes is summarised in **Table 2.** With the exception of severe congenital anomalies, significant trends showing a decrease in adjusted ORs as maternal education increases were observed for all of the considered neonatal outcomes, including those recorded at presentation (preterm birth, low birth weight, small for gestational age), as well as those recorded within the first two years of life (cerebral suffering and respiratory distress). Compared to Italian-born mothers, foreign-born mothers had a higher odds of preterm birth, low Apgar score and respiratory distress, while they had lower odds of being small for gestational age. The influence of maternal education on neonatal outcome was confirmed in both Italian-born and foreign-born mothers (**Table 3**).

Discussion

The main findings from the present study show that even in a country with universal access to essential health care services such as Italy, mothers with higher levels of education were at lower risk of several neonatal adverse outcomes. These differences were cannot to be underestimated, since compared to mothers with lower levels of education, those with high levels of education had 19%, 22%, 18%, and 16% decreased risk of preterm birth, low birth weight, small for gestational age and respiratory distress, respectively. Corroborating our findings, a recent meta-analysis conducted across 12 European countries revealed a 48% risk excess of preterm births associated with low maternal education [36].

Among individual measures of SES, education is considered the most powerful determinant of health [37]. Other mother's traits influencing birth health, however, deserve to be mentioned. One, our study confirms previous observations that in Western countries a high proportion of births are to migrant women [38]. Migrant status has been associated with several adverse neonatal outcomes in some [39-43], but not all studies [44-49], possibly because of differences in access to healthcare services [41, 50, 51], and integration policies of the host countries [52]. Our study shows that, compared to Italian-born mothers, foreign-born ones were at higher risk for preterm birth, low Apgar score and respiratory distress, while they had lower risk of being small for gestational age. Two, our study confirms that advanced maternal age [52-54], null parity [55], and unmarried status are risk factors for some adverse perinatal outcomes [56, 57]. Three, in the current study, unemployed mothers were at a higher risk of some adverse neonatal outcomes, likely because the condition might be a proxy of social inequality uncaptured by education and birthplace. This finding is consistent with studies showing the influence of employment status on preterm birth, small for gestational age and other neonatal outcomes [58, 59]. Finally, we confirmed previous evidence that diabetes, hypertension and to a greater extent pre-eclampsia and drug therapies for managing these concomitant diseases, are leading causes of adverse neonatal outcomes [60-65].

Our study has a number of potential limitations. First, the exclusion of mother-newborn pairs lacking identification codes could mainly affect less healthy women. Second, the cohort included live births only. Several neonatal outcomes that resulted in spontaneous abortion, stillbirth, or termination of pregnancy would therefore have been missed. We did not collect information on income, a factor recognised to be associated with perinatal outcomes [11-13, 15, 16]. More importantly, we did not have data on the country of origin of migrant mothers, so that our estimates likely include the average effect of various migrant groups with an unknown gradient in socioeconomic inequalities. Although it is difficult to assess the impact of the lack of this information, we do not believe this exclusion had

a major effect on the results found. Privacy concerns did not allow of assessing the validity of information recorded in the Certificates of Delivery Assistance, as well as of diagnostic data from hospital charts. Finally, the lack of data on important factors, such as smoking, pre-pregnancy weight and gestational weight gain, may further contribute to some unavoidable source of systematic uncertainty.

Notwithstanding these limitations, our study shows that, despite the availability of essential healthcare services at no out-of-pocket expense, mother's education and other socioeconomic factors are strongly associated with some adverse perinatal outcomes, including preterm birth, low Apgar score, cerebral distress, respiratory distress, and SGA. These findings merit attention from a public health perspective. Future studies are encouraged to investigate factors mediating the effects of socioeconomic inequality on birth outcomes for identifying the main target groups for interventions.

Figure 4. Flow-chart of inclusion and exclusion criteria.

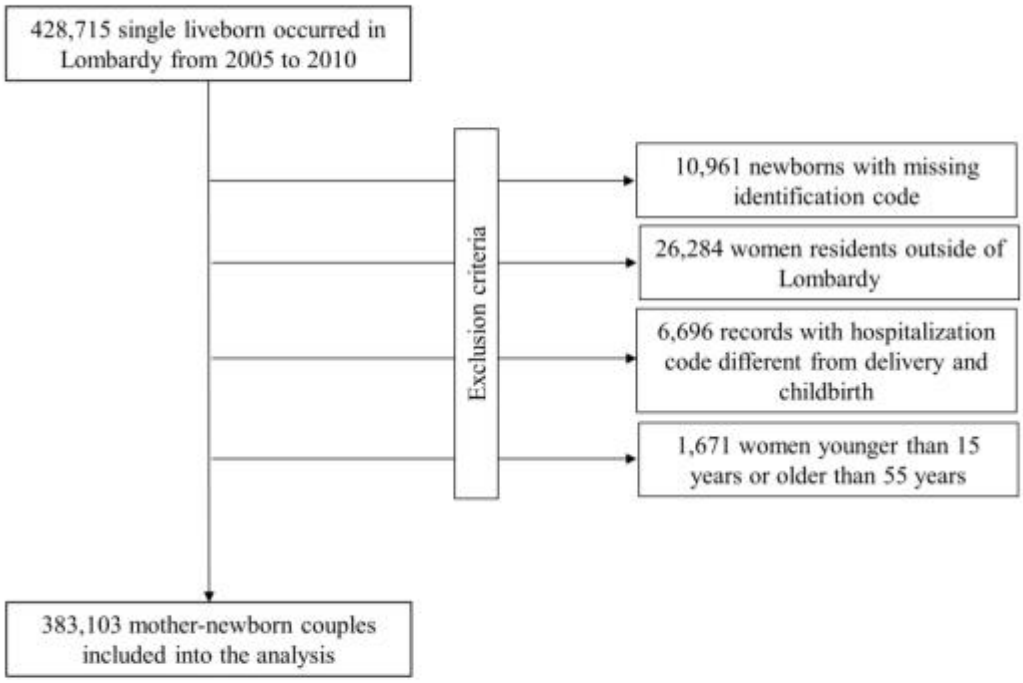

Table 1. Frequency of neonatal outcomes according to selected maternal traits. Italy, Lombardy Region, 2005-2010

Maternal trait	All women (N = 383,103) %	Preterm birth (N = 20,294) %	Low birth weight (N = 19,588) %	Small for Gestational Age (N = 29,800) %	Low Apgar score (N = 3,180) %	Congenital Anomalies (N = 18,997) %	Cerebral distress (N = 996) %	Respiratory distress (N = 15,539) %
Education†								
Low	121,910	5.8%	5.6%	8.1%	0.9%	4.9%	0.3%	5.4%
Intermediate	173,926	5.2%	5.1%	7.7%	0.8%	4.8%	0.3%	5.0%
High	87,267	4.7%	4.6%	7.3%	0.7%	5.2%	0.2%	4.7%
p-value‡		<0.0001	<0.0001	<0.0001	0.0466	0.0044	0.0444	<.0001
Age at delivery								
≤ 25 years	49,803	4.9%	4.9%	8.4%	0.9%	4.8%	0.2%	5.2%
26-35 years	244,037	5.0%	4.9%	7.8%	0.8%	4.8%	0.3%	4.9%
≥ 35 years	89,263	6.2%	5.8%	7.5%	0.9%	5.5%	0.2%	5.4%
p-value‡		<0.0001	<0.0001	0.1739	0.0009	<.0001	0.3189	<.0001
Maternal birthplace								
Italian-born	288,093	5.2%	4.9%	8.1%	0.8%	4.9%	0.2%	4.9%
Foreign-born	95,010	5.6%	5.2%	6.8%	0.9%	4.9%	0.3%	5.6%
p-value‡		<0.0001	0.0009	<0.0001	0.0001	0.1617	0.0200	<.0001
Marital status								
Married	294,606	5.2%	4.9%	7.4%	0.8%	4.9%	0.3%	4.9%
Unmarried	88,497	5.8%	5.9%	9.1%	0.9%	5.1%	0.3%	5.6%
p-value‡		<0.0001	<0.0001	<0.0001	0.0003	0.0245	0.7656	<.0001
Employment								
Employed	270,088	5.2%	5.1%	7.9%	0.8%	5.0%	0.2%	5.0%
Unemployed	113,015	5.4%	5.1%	7.5%	0.9%	4.8%	0.3%	5.2%
p-value‡		0.0170	0.3370	0.0003	0.1516	0.0691	0.0454	0.0068
Parity								
Nulliparous	211,090	5.7%	6.0%	9.7%	0.9%	5.4%	0.3%	5.9%
Multiparous	172,013	4.8%	3.9%	5.5%	0.7%	4.5%	0.2%	4.0%
p-value‡		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<.0001	<.0001
Previous spontaneous abortions								
No	320,274	5.1%	5.0%	7.9%	0.8%	4.9%	0.3%	5.1%
Yes	62,829	6.1%	5.6%	7.0%	0.9%	5.2%	0.3%	4.9%
p-value‡		<0.0001	<0.0001	<0.0001	0.0689	0.0008	0.5183	0.0223

Diabetes								
No	371,227	5.2%	5.1%	7.8%	0.8%	4.9%	0.3%	5.0%
Yes	11,915	9.3%	5.8%	6.1%	1.4%	6.5%	0.4%	6.8%
p-value‡		<0.0001	0.0007	<0.0001	<0.0001	<0.0001	0.0019	<.0001
Hypertension								
No	370,077	5.0%	4.8%	7.6%	0.8%	4.9%	0.3%	5.0%
Yes	13,026	12.9%	14.6%	12.8%	1.4%	5.9%	0.3%	6.9%
p-value‡		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.7711	<.0001
Dyslipidemia								
No	382,202	5.3%	5.1%	7.8%	0.8%	4.9%	0.3%	5.1%
Yes	901	9.7%	6.9%	6.7%	0.9%	5.5%	0.5%	6.7%
p-value‡		<0.0001	0.0158	0.2091	0.8481	0.4135	0.0817	0.0332
Preeclampsia								
No	373,909	4.8%	4.6%	7.5%	0.8%	4.9%	0.3%	4.9%
Yes	9,194	26.0%	27.5%	17.7%	2.2%	7.9%	0.4%	11.5%
p-value‡		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0158	<.0001

† Years of formal education completed categorized as ≤8 years (low), from 9 to 13 years (intermediate), and ≥14 years (high)

‡ According to chi-square test or its version for the trend (education and age at delivery)

Table 2. Relationship between maternal education and birthplace and selected neonatal outcomes. Italy, Lombardy Region, 2005-2010

	Preterm birth	**Low birth weight**	**Small for Gestational Age**	**Low Apgar score**	**Severe congenital Anomalies**	**Cerebral distress**	**Respiratory distress**
	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)
Education †							
Low	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.90 (0.87-0.94)	0.87 (0.84-0.90)	0.88 (0.86-0.91)	0.98 (0.90-1.07)	0.94 (0.91-0.98)	1.00 (0.86-1.16)	0.91 (0.87-0.94)
High	0.81 (0.77-0.85)	0.78 (0.74-0.81)	0.82 (0.79-0.85)	0.92 (0.83-1.03)	1.02 (0.97-1.06)	0.84 (0.69-1.02)	0.84 (0.80-0.88)
p-trend ‡	<0.0001	<0.0001	<0.0001	0.0164	0.1155	0.4745	<0.0001
Birthplace							
Italian-born	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Foreign-born	1.16 (1.11-1.20)	0.98 (0.94-1.03)	0.82 (0.79-0.85)	1.18 (1.07-1.30)	1.01 (0.97-1.06)	1.17 (0.99-1.39)	1.19 (1.15-1.24)

† Years of formal education completed categorized as ≤8 years (low), from 9 to 13 years (intermediate), and ≥14 years (high)

‡ Odds ratios (and 95 % confidence interval) were derived from logistic regression. Full multivariable models for each outcome included as covariates maternal traits (i.e., age at delivery, marital status, employment, parity, previous spontaneous miscarriages, diabetes, hypertension, dyslipidaemia and preeclampsia) categorized as in Table 1.

Table 3. Relationship between maternal education and selected neonatal outcomes according to maternal birthplace. Italy, Lombardy Region, 2005-2010

	Preterm birth	**Low birth weight**	**Small for Gestational Age**	**Low Apgar score**	**Severe congenital Anomalies**	**Cerebral distress**	**Respiratory distress**
	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)
	Italian-born mothers						
	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)	OR ‡ (95% CI)
Education †							
Low	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.88 (0.85-0.92)	0.86 (0.82-0.89)	0.88 (0.85-0.92)	0.95 (0.84-1.08)	0.97 (0.93-1.01)	0.99 (0.83-1.19)	0.90 (0.85-0.94)
High	0.79 (0.76 to 0.84)	0.77 (0.73 to 0.81)	0.82 (0.79 to 0.85)	0.98 (0.88-1.10)	1.06 (0.99-1.12)	0.85 (0.68-1.08)	0.84 (0.80-0.88)
p-trend ‡	<0.0001	<0.0001	<0.0001	0.3129	0.0997	0.6704	<0.0001
	Foreign-born mothers						
Education †							
Low	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Intermediate	0.94 (0.88-1.01)	0.90 (0.84-0.97)	0.88 (0.83-0.94)	0.97 (0.83-1.14)	0.88 (0.82-0.94)	1.00 (0.77-1.31)	0.92 (0.86-0.99)
High	0.84 (0.77-0.92)	0.78 (0.71-0.87)	0.84 (0.77-0.92)	0.81 (0.61-1.07)	0.90 (0.82-0.99)	0.78 (0.52-1.16)	0.81 (0.73-0.90)
p-trend ‡	<0.0001	<0.0001	<0.0001	0.2615	<0.0001	0.9614	<0.0001

† Years of formal education completed categorized as ≤8 years (low), from 9 to 13 years (intermediate), and ≥14 years (high)

‡ Odds ratios (and 95 % confidence interval) were derived from logistic regression. Full multivariable models for each outcome included as covariates maternal traits (i.e., age at delivery, marital status, employment, parity, previous spontaneous miscarriages, diabetes, hypertension, dyslipidaemia and preeclampsia) categorized as in Table 1

Supplementary Materials

Table S1: Chronic maternal medical conditions were defined from inpatient diagnosis database using ICD-9 code. They were measured from 2 years pre-LMP through the end of the delivery.

Condition		Definition
Hypertension	Pre-existing hypertension	401.x-405.x, 642.0x-642.2x, 642.7x, 642.9x
	Gestational hypertension	642.3x
Preeclampsia	Mild preeclampsia	642.4x
	Severe preeclampsia	642.5x, 642.6x, 642.7x
Diabetes	Pre-gestational diabetes	250.x, 648.0x
	Gestational diabetes	648.8x
Dyslipidemia	Disorders of lipoid metabolism	272.x

Table S2: Definition of neonatal outcomes within two years after birth, defined from inpatient diagnosis database using ICD-9 code.

Severe congenital anomalies – EUROCAT classification, www.eurocat-network.eu

Condition	Definition
Nervous system	740, 741, 742
Eye	743
Ear, face and neck	744
Congenital Heart Defects	745, 746, 747.0 – 747.4
Respiratory	748.0, 748.4, 748.50, 748.52, 748.58, 748.6, 748.8
Oro-facial clefts	749.0, 749.1, 749.2
Digestive system	750, 751, 756.6
Abdominal wall defects	756.71, 756.70, 756.79
Urinary	752.61, 753, 756.72
Genital	752.0 – 752.4, 752.60, 752.62, 752.7 – 752.9
Limb	754.3 – 754.8, 755

Sign of cerebral suffering

Condition	Definition
Convulsions in newborn	779.0
Other and unspecified cerebral irritability in newborn	779.1
Cerebral depression, coma, and other abnormal cerebral signs	779.2

Distress of respiratory function

Condition	Definition
Intrauterine hypoxia and birth asphyxia	768
Other respiratory conditions of fetus and newborn	770

2. II Study (published)

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Is the risk of preterm birth and low birth weight affected by the use of antidepressant agents during pregnancy? A population-based investigation

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Abstract

Background: Untreated depression during pregnancy increases the risk of morbidity and mortality in the mother and child. Therefore, specific treatments are required for this population. **Objective:** The study aimed to investigating the effect of antidepressant medication used during pregnancy with reference to the risk of preterm birth (PTB) and low birth weight (LBW). **Methods:** A population-based study was carried out with data provided by the healthcare utilization database of Lombardy, an Italian region with about ten million inhabitants. The study included 384,673 births from 2005 to 2010. Maternal use of antidepressants before and during pregnancy was investigated. Log-binomial regression was used to estimate the association between the use of antidepressants during pregnancy, compared to the non-use or use just before pregnancy, and the prevalence ratio of PTB and LBW. **Results:** Women who used antidepressants during pregnancy had a 20% (95% CI: 10-40%) increased prevalence of both PTB and LBW compared to those who never used antidepressants. There was no evidence that women who used antidepressants during pregnancy had a higher prevalence of the considered outcomes compared to women who used antidepressants before pregnancy, but stopped during pregnancy. Such findings were confirmed by considering separately the effects of SSRIs and other antidepressants together. **Conclusions**: Our findings suggest that depression in itself, rather than antidepressant medication, might be implicated in the causal pathway of PTB and LBW.

Key words. Antidepressant medication; Childbirth; Depression; Healthcare Utilization Database; Neonatal Outcomes; Pregnancy

Introduction

Depression affects up to 13% of women in reproductive age [66]. Untreated antenatal depression has been found to correlate with poor self-care during pregnancy, postpartum depression, impaired maternal–infant attachment and delays in infant development [67, 68], so that antidepressant medication may be required for the effective treatment of maternal depression [69, 70].

Antidepressant drugs, developed since 1950s to treat depressive symptoms, are nowadays widely available with several treatment options. Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs), are the most commonly prescribed antidepressants. Despite their similar effectiveness, however, SSRIs have in part replaced Tricyclic Antidepressants due to better tolerability [71].

Several studies over the past two decades investigated the relationship between the use of antidepressants in pregnancy and the risk of adverse perinatal and birth outcomes [72]. Exposure in utero to antidepressants has been associated with low birth weight and preterm delivery [73-76]. The biological mechanisms explaining the relationship between using antidepressants during pregnancy and delivery outcomes are not entirely known, although some assumptions have been postulated [77-82]. However, as maternal depression may be related to unhealthy behaviors - such as smoking and poor attendance of obstetric care [83-85] - it is still unclear whether the observed adverse perinatal outcomes may be due to direct drug actions or to depression itself [68, 86-88].

The purpose of this population-based study was to investigate the effect of the use of antidepressant medication during pregnancy with reference to the risk of preterm birth (PTB) and low birth weight (LBW).

Methods

Setting

The data used for this study were provided by the healthcare utilization databases of Lombardy, an Italian Region with about 16% of the country's population (almost ten million inhabitants). In Italy, the population is covered by the National Health Service (NHS), which in Lombardy has been associated, since 1997, with an automated system of databases to collect a variety of information including: (1) an archive of those benefitting from the Regional Health Service (practically coinciding with the whole resident population), reporting demographic and administrative data; (2) a database concerning diagnoses at discharge from Italian public or private hospitals; (3) a database concerning outpatient drug prescriptions reimbursed by the NHS and delivered by pharmacies in Lombardy; and (4) a database reporting the Certificates of Delivery Assistance (i.e., the so called CeDAP) providing detailed information on the mother's socioeconomic traits, as well as medical information on the pregnancy, childbirth, and child presentation at delivery. The linking of records among databases, owing to a unique code in all databases, allowed to identify a large and unselected birth cohort and to reconstruct relevant traits and care pathways of mothers and newborns.

Cohort selection

The 579,195 childbirths of women resident in Lombardy from 2005 to 2010 were selected from the CeDAP database. Among these, 182,389 (31.5%) were excluded because the newborn (i) had no identification code (161,514), (ii) was part of multiple birth (20,206), or (iii) was stillborn (669). Further 12,133 records (2.1%) were excluded because the mother (i) had a hospital admission ICD-9 code different from the one expected for childbirth (7,210), (ii) had a too short (<22 weeks) or too long (>46 weeks) gestational age (3,965), or (iii) was under 15 years of age or above 55 years of age (958). The final study population therefore consisted of 384,673 mother-newborn couples (**Fig 1**).

Use of antidepressants and other features concerning the mother

All prescriptions of antidepressant medication dispensed to the women considered during the period of observation, starting from the date corresponding to 9 months before the expected date of conception and stopping at the date of childbirth, were identified. Mothers were thus classified in the following mutually exclusive categories: (i) non-users, if antidepressants were not dispensed during the entire period of observation; (ii) users just before conception, if at least an

antidepressant was dispensed in the 9 months before, but not during, pregnancy; and (iii) users during pregnancy, otherwise.

Maternal traits, including age at delivery, nationality, marital status, education, employment, previous miscarriages and parity, and health conditions, including diabetes, preeclampsia, dyslipidaemia and hypertension, were identified through CeDAPs.

Neonatal outcomes

Two outcomes were considered: "preterm birth" (less than 37 weeks' gestation [29]), and "low birth weight" (less than 2,500 grams [30]) identified from CeDAPs.

Statistical analysis

Chi-squared, or its version for the trend, was used when appropriate for testing differences or trends in maternal socio-demographic and clinical features according to maternal use of antidepressants.

The log-binomial regression model was separately fitted to estimate the prevalence ratio (PR), and the 95% confidence interval (95% CI) of each neonatal outcome associated with the use of antidepressants during pregnancy compared to non-use or use just before pregnancy, as well as of use just before pregnancy compared to non-use. Estimates were adjusted for the maternal traits and health conditions listed above. A generalized estimating equation was used to account for the potential correlation of women contributing with more than one birth during the considered period. Besides the effect of antidepressants as a whole, the separate effects of agents belonging to the class of SSRIs and to other antidepressants was investigated.

Data on maternal characteristics were sometimes missing. Indeed, missing data ranged from 1% for previous miscarriages to 13% for marital status. Restricting analyses to the subset of women with all the data observed would have resulted in a significant loss of information and possibly biased estimations. With the aim to generate appropriate values of missing data for those women with missing covariates, the three-phase iterative procedure known as the fully conditional specification (FCS) was used [4, 35]. First of all, the FCS method was implemented to generate 10 complete data sets. Secondly, the log-binomial model was separately fitted to the 10 complete data sets using the GENMOD procedure. Finally, the MIANALYZE procedure was used to combine the coefficient estimates (and estimations of their variances) from the 10 log-binomial analyses, in order to obtain valid statistical inferences about the model coefficients that take within and between variances into account.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

Results

During the entire observation period (i.e., from 9 months before starting pregnancy until childbirth), antidepressant medication were dispensed at least once to 9,843 women among those the 384,673 included (prevalence: 2.6%). Most women stopped using antidepressants during pregnancy (users just before pregnancy: 6,548 women), while 3,295 mothers kept on following the therapy during pregnancy (users during pregnancy). **Table 1** shows that, compared to both non-users and users just before pregnancy, women who used antidepressants during pregnancy were older, with lower education, and more often were Italian, unmarried, employed, and suffered from the considered medical conditions. Previous pregnancies were significant predictors of the use of antidepressants during pregnancy compared to non-use.

Out of the 384,673 newborns considered in this study, 20,060 (5.2%) and 19,527 (5.1%) had preterm birth and low birth weight, respectively. **Fig 2** shows that mothers who used antidepressants during pregnancy had significant higher prevalence of preterm birth and low birth weight with respect to those who never used antidepressants, but not to those who used antidepressants just before pregnancy. Statistical evidence of higher prevalence of both outcomes among women who stopped using depressant before pregnancy with respect to those who never used them was also found, being the adjusted PRs (and corresponding 95% CI) 1.1 (1.0 to 1.2) and 1.1 (1.0 to 1.3) for preterm birth and low birth weight respectively.

The prevalence of preterm birth among women who used either SSRIs or other antidepressants during pregnancy, as well as the prevalence of low birth weight among women who used SSRIs during pregnancy, were significantly higher with respect to mothers who never used antidepressants, but did not differ from those who used antidepressants just before pregnancy (**Table 2**). Finally, likely due to inadequate power for pointing out the effect of other antidepressants, women using them during pregnancy and those who never used antidepressants did not show significant difference in prevalence of low birth weight.

Table 4. Selected characteristics of the 384,673 mothers considered in the study according to their use of antidepressants before conception or during pregnancy. Italy, Region of Lombardy, 2005-2010

	Use of antidepressants			p-value [2]	
	Never (A) N = 374,830	Just before pregnancy (B) N = 6,548	During pregnancy (C) N = 3,295	A vs. C	B vs. C
Age at delivery					
≤ 25 years	13.3%	8.2%	8.2%	<0.0001	<0.0001
26 - 34 years	56.9%	55.9%	48.9%		
>34 years	29.8%	35.9%	41.9%		
Nationality					
Italy	74.6%	85.6%	86.5%	<0.0001	0.0004
Other	25.4%	14.4%	13.5%		
Marital status					
Married	77.0%	73.2%	72.2%	<0.0001	0.0006
Unmarried	23.0%	26.8%	27.8%		
Education [1]					
Low	31.6%	34.3%	34.4%	<0.0001	0.0037
Intermediate	45.4%	47.1%	46.5%		
High	23.0%	18.6%	19.1%		
Employment					
Employed	70.4%	74.1%	71.7%	<0.0001	<0.0001
Unemployed	29.6%	25.9%	28.3%		
Previous miscarriages					
None	83.6%	82.6%	83.0%	0.0049	0.1207
One or more	16.4%	17.4%	17.0%		
Parity					
Nulliparous	55.3%	52.6%	53.0%	<0.0001	0.3404
Multiparous	44.7%	47.3%	47.0%		
Medical conditions					
Diabetes	5.0%	6.3%	7.2%	<0.0001	<0.0001
Hypertension	9.4%	16.2%	18.2%	<0.0001	<0.0001
Dyslipidaemia	2.1%	3.2%	4.4%	<0.0001	<0.0001
Preeclampsia	1.2%	1.3%	1.5%	0.1510	0.0289

[1] Number of years of formal education completed categorized as 8 or fewer (low), from 9 to 13 (intermediate) and or 14 or more (high)

[2] According to the chi-square test, or its version for the trend (age and education)

Table 5. Adjusted prevalence ratios (and 95% confidence intervals) of selected outcomes associated with dispensing selective serotonin reuptake inhibitors (SSRIs) or other antidepressant medication during pregnancy compared to non-users and users just before pregnancy. Italy, Region of Lombardy, 2005-2010

Neonatal outcome	Comparator	SSRI[1]	Other antidepressants[1]
Preterm birth	Non-users	1.2 (1.1 to 1.4)	1.3 (1.1 to 1.5)
	Users just before pregnancy	1.1 (0.9 to 1.2)	1.0 (0.8 to 1.3)
Low birth weight	Non-users	1.3 (1.1 to 1.5)	1.3 (0.9 to 1.7)
	Users just before pregnancy	1.1 (0.9 to 1.3)	1.1 (0.8 to 1.5)

[1]Prevalence ratio, and 95% confidence interval, estimated with log-binomial regression. Estimates are adjusted for maternal age, nationality, marital status, education, employment, previous miscarriages, parity, and medical conditions

Discussion

Our large population-based study found that women who used antidepressants during pregnancy had a 20% (95% CI: 10-40%) increased prevalence of both preterm birth and low birth weight compared to those who never used antidepressants during the entire period of observation (i.e., from 9 months before pregnancy until childbirth). Such evidence was confirmed by considering separately the effects of SSRIs and other antidepressants together.

These findings confirm and extend the results of (i) meta-analyses showing that prenatal exposure to antidepressant medication as a whole [73, 75], as well as to SSRIs [89], reduces gestational age and birth weight; and (ii) observational studies reporting an association between prenatal use of antidepressants and risks for premature delivery [76, 81, 90-93] and low birth weight [92, 94, 95].

At least two possible explanations are conceivable with our findings. Firstly, the safety of antidepressants on foetal health might be the mechanistic key explaining the higher prevalence of adverse neonatal outcomes among drug users. Although the biological mechanisms are not entirely known, several theories have been postulated on this issue. Antidepressants, mainly SSRIs, pass the placenta barrier increasing the placental secretion of corticotrophin-releasing hormone resulting in an increased activity within the gestational cortisol system [74]. Furthermore, fluoxetine reduces maternal appetite and weight gain causing low birth weight [78, 82]. Moreover, the use of SSRIs alters the 5-TH levels increased risk of intrauterine growth retardation and preterm delivery by impairing placental blood flow [81]. It is also reported that women using antidepressants had higher saliva estriol levels compared to non-users [80] and elevated levels of estriol have been associated with preterm birth [77]. Secondly, antidepressant medications are prescribed to treat depression so that the observed associations could be explained by the residual depressive symptoms. We tried to account for confounding indications by constraining women who took antidepressants during pregnancy with those who interrupted their use during pregnancy. Interestingly, our study did not offer statistical evidence that the considered outcomes differed between using medication before or during pregnancy. In addition, higher prevalence of preterm birth and low birth weight among newborns from women who used antidepressants just before pregnancy than from those who never used them was observed. All these findings taken together suggest that, at least in our setting, depression in itself, rather than antidepressant medication, might be implicated in the causal pathway of these outcomes [94]. The mechanism by which depression may exert its action on the considered neonatal outcomes might be mediated by the presence of epiphenomena, e.g., smoking, alcohol drinking, and other unhealthy behaviours, such as poor attendance to obstetric care [83-85].

Our study has a number of potential limitations. First of all, the exclusion of mother-newborn pairs lacking identification codes could mainly affect less healthy women. Second, the implicit exclusion from our analysis of spontaneous and elective pregnancy terminations affects the possibility for outcomes potentially due to drug foetal-exposure to be selectively excluded. Third, a main limitation in using dispensing data relates to whether or not the medicine was consumed, or consumed as directed, and there is no information in this study for either of these aspects [96]. Fourth, privacy concerns prevented us to assess the validity of the information recorded in the Certificates of Delivery Assistance, as well as the diagnostic data from hospital charts. Fifth, we did not assess when antidepressants were used during pregnancy, a datum which would have provided information concerning possible heterogeneity in outcome risks during the observation period. There are two reasons for the lack of assessment: dispensation data certainly does not correspond to use data; and power considerations did not allow the assessment of rarer exposures than those observed. Finally, the lack of data on important factors - such as smoking, alcohol and illicit drug use - may further contribute to some unavoidable source of systematic uncertainty.

Despite these limitations, our data on drug utilization patterns in the real-world setting offer evidence that the prevalence of preterm birth and low birth weight is increased in pregnant women who use antidepressants during pregnancy compared to pregnant women who never use antidepressants. However, rather than a direct action of these agents, our findings suggest that depression in itself may explain the observed adverse neonatal outcomes, possibly due to the effect of maternal unhealthy behaviours, such as smoking, alcohol abuse, unhealthy diet, and poor attendance to obstetric care. Much more research is needed to better understand risks and benefits of therapeutic strategies for depression care during pregnancy.

Acknowledgment

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Figure 5. Flow-chart of inclusion and exclusion criteria

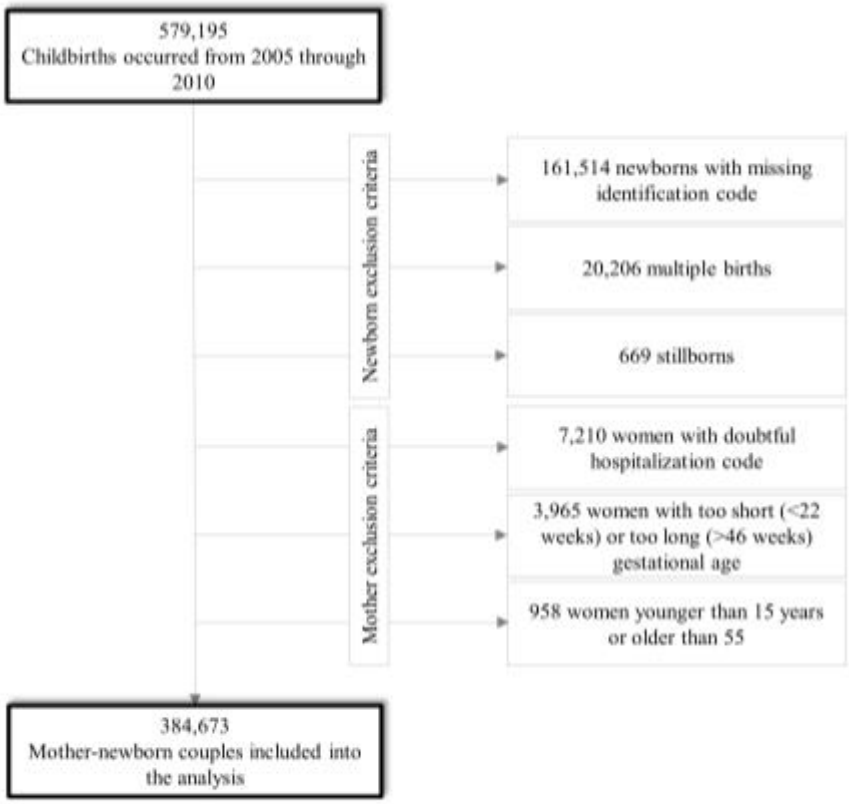
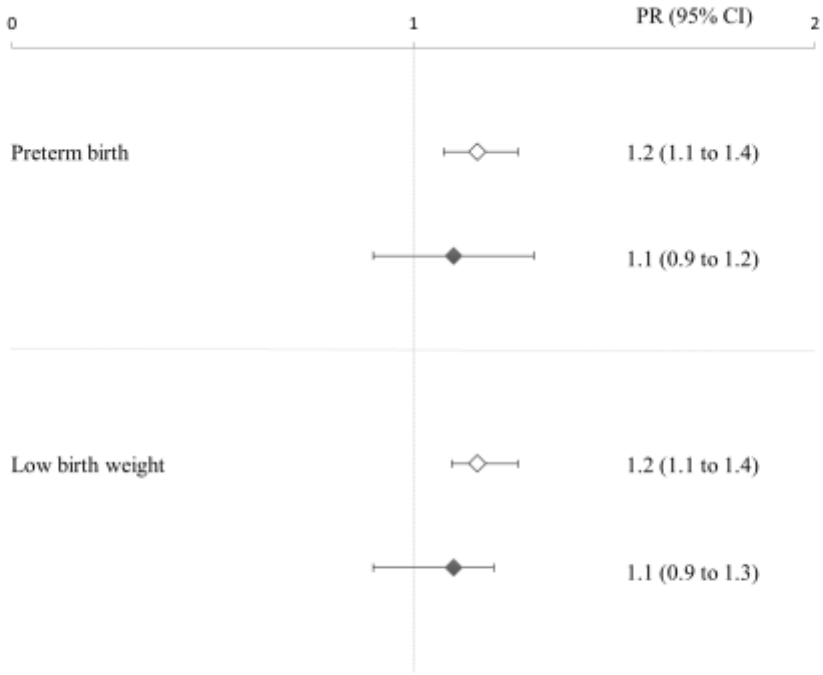


Figure 6. **Adjusted prevalence ratios (and 95% confidence intervals) of selected outcomes associated with the use of antidepressants during pregnancy, compared to the non-use as well as to the use just before pregnancy.** Prevalence ratio, and 95% confidence interval, estimated with log-binomial regression. Estimates are adjusted for maternal age, nationality, marital status, education, employment, previous miscarriages, parity, and medical conditions.

Figure 2



◇ Users of antidepressant medications during pregnancy compared to never users

◆ Users of antidepressant medications during pregnancy compared to use just before conception

3. III Study (submitted)

Use of antidepressant medications in pregnancy and adverse neonatal outcomes. A population-based investigation

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Authors' Contributions:

AC performed the statistical analyses, AC and GC wrote the paper. LM authorized data utilization. CG assisted in interpreting the results under a clinical perspective. GC was responsible for designing the study. AC, LM, CG and GC read and approved the final manuscript.

Conflict of Interest Disclosures: None

Abstract

Background: Untreated depression during pregnancy may have negative consequences for births. There are still conflicting data on potential harmful effects of prenatal antidepressant treatment on the child health.

Objective: To investigate the relationship between use of antidepressant medications during pregnancy and selected neonatal outcomes.

Methods: The 384,673 births occurred from 2005 to 2010 from women resident in Italian Region of Lombardy were included. Maternal exposure to antidepressants during and before pregnancy was investigated. Neonatal outcomes were identified at presentation (small for gestational age and low 5-min Apgar score) and within two years after birth (cerebral irritability, neonatal convulsion, intrauterine hypoxia and birth asphyxia, and other respiratory conditions). Log-binomial regression was used to estimate the prevalence ratio of neonatal outcomes as a result of antidepressant exposure during pregnancy. A set of sensitivity analyses was performed in order to account for sources of systematic uncertainty.

Results: Women who used antidepressants during pregnancy had significant higher prevalence of the considered outcomes than those who never used antidepressants (with prevalence ratio, 95% CI, ranging from 1.3, 1.1 to 1.6, for intrauterine hypoxia and birth asphyxia to 2.6, 1.4 to 4.8, for cerebral irritability) and those who used antidepressants only before pregnancy (with prevalence ratio, 95% CI, ranging from 1.3, 1.0 to 1.6, for other respiratory conditions to 3.4, 1.2 to 9.1, for neonatal convulsions). These findings were reasonably robust to confounding and mediation.

Conclusions. Use of antidepressants during pregnancy may be harmful for several neonatal outcomes.

Key words. Antidepressants; Childbirth; Depression; Healthcare Utilization Database; Neonatal Outcomes; Pregnancy

Introduction

Untreated antenatal depression is associated with poor self-care during pregnancy, postpartum depression, impaired maternal–infant attachment and delays in infant development [67, 68]. It follows that antidepressant medications may be required for the effective treatment of maternal depression [69, 70].

Several studies over the past two decades investigated the relationship between use of antidepressants in pregnancy and risk of adverse birth outcomes [[68, 70, 72]. Although these studies provided inconsistent and sometimes conflicting findings, two recent meta-analyses showed that antidepressant use in pregnancy was significantly associated with preterm birth and low birth weight [73, 75]. Other adverse neonatal outcomes, including low Apgar score, congenital anomalies, respiratory distress and other outcomes, have been investigated [72, 78, 87, 97-100], but final judgments of the role of antidepressants on their appearance are still premature.

Antidepressant medications, mainly the class of selective serotonin reuptake inhibitors (SSRIs), are known to cross the human placenta [79] thus explaining some of their consequences on neonatal health. However, maternal depression itself is also associated with adverse outcomes, such as obstetric complications [88], stillbirth, prematurity, impaired growth [68, 87, 88], malformations, cognitive deficits, and psychopathology [86]. Finally, common behaviours among women who suffer from depression, including smoking during pregnancy [101], are known themselves risk factors for adverse offspring outcomes. [85, 102].

The purpose of this large population-based study is to further investigate the relationship between use of antidepressant medication during pregnancy and neonatal outcomes appearing at presentation (i.e., small for gestational age and low 5-min Apgar score) and within two years after birth (i.e., cerebral suffering and distress of respiratory function). Distinguishing the effects of depression per se from those of antidepressant medications, controlling for unmeasured confounding, and taking into account the possibility that adverse outcomes appeared at presentation may act as mediator of outcomes appeared later in life, were of particular concern in this study.

Methods

Setting

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, a Region of Italy which accounts for about 16% (almost ten millions) of its population. In Italy, the population is covered by the National Health Service (NHS), which in Lombardy has been associated, since 1997, with an automated system of databases to collect a variety of information including: (1) an archive of beneficiaries of the Regional Health Service (practically coincide with the whole resident population), reporting demographic and administrative data; (2) a database on diagnoses at discharge from Italian public or private hospitals; (3) a database on outpatient drug prescriptions reimbursed by the NHS and delivered by pharmacies of Lombardy; and (4) a database reporting the Certificates of Delivery Assistance (i.e., the so called CeDAP) providing detailed information on the mother's socioeconomic traits, as well as medical information on the pregnancy, childbirth, and child presentation at delivery. Record linkage between databases performed via a single identification code allowed us fitting out a large and unselected birth cohort and of reconstructing relevant traits and care pathways of mothers and newborns.

Cohort selection

The 579,195 childbirths occurred from women resident in Lombardy from 2005 to 2010 were selected from the CeDAP database. Among these, 161,514 records were excluded because the lack of identification code. Exclusions in addition regarded multiple births (20,206), stillborns (669), hospital ICD-9 code different from the one expected for childbirth (7,210), too short (<22 weeks) or too long (>46 weeks) gestational age (3,965), and mothers younger less than 15 years or older 55 years (958). The final study population therefore consisted of 384,673 mother-newborn couples (**Figure 1**).

Use of antidepressants and other maternal traits

All prescriptions of antidepressant medications dispensed during the period of observation, i.e., from the date corresponding to 9 months before the expected date of conception to the date of childbirth, were identified. Mothers were thus classified in the following mutually exclusive categories: (i) never users, if antidepressants were not dispensed during the entire period of observation; (ii) users just before pregnancy, if at least an antidepressant was dispensed in the 9 months before, but not during pregnancy; and (iii) users during pregnancy, otherwise.

Maternal traits, including age at delivery, nationality, marital status, education, employment, previous miscarriages and parity, and health conditions, including diabetes, preeclampsia, dyslipidaemia and hypertension, were recorded.

Neonatal outcomes

Health conditions of newborn at presentation and within two years after birth were respectively identified from CeDAP and hospital discharge databases. At presentation we considered small for gestational age (SGA - identified from ICD-9 code 656.5x, 764.0 and 764.1 [103]) and low 5-min Apgar score (7 or less [33]). Within two years after birth the following neonatal outcomes were considered: signs of cerebral suffering, including (i) cerebral irritability (779.1), and (ii) neonatal convulsion (779.0), and distress of respiratory function, including (iii) intrauterine hypoxia and birth asphyxia (768), and (iv) other respiratory conditions of foetus and newborns (770).

Conventional statistical analysis

Chi-squared, or its version for the trend, was used when appropriate for testing differences or trends in maternal socio-demographic and clinical features according to maternal use of antidepressants.

The log-binomial regression model was fitted to estimate the prevalence ratio (PR), and the 95% confidence interval (95% CI) of each neonatal outcome associated with the use of antidepressants during pregnancy compared to never use or use just before pregnancy. Estimates were adjusted for maternal traits and health conditions listed above. Generalized estimating equation was used to account for potential correlation of women contributing with more than one birth during the considered period.

Accounting for missing data

Data on maternal characteristics were sometime missing for some women. Indeed, missing data ranged from 1% for previous miscarriages to 13% for marital status. Restricting analyses to the subset of women with all the data observed would have resulted in a significant loss of information and possibly biased estimations. With the aim to generate appropriate values of missing data for those women with missing covariates, an iterative procedure was used known as the fully conditional specification (FCS) implemented in SAS and involving three distinct phases [4]. First, the FCS imputation method was implemented to generate 10 complete data sets. Secondly, the log-binomial model was separately fitted to the 10 complete data sets using the GENMOD procedure. Finally, the procedure MIANALYZE was used to combine the coefficient estimates (and estimations of their variances) from the 10 log-binomial analyses, in order to obtain valid statistical inferences about the model coefficients that take within and between analysis variances into account.

Taking into account for unmeasured confounding

The robustness of estimates with regard to potential bias introduced by unmeasured confounders was investigated by using the rule-out approach described by Schneeweiss [5]. Briefly, the approach involves of detecting the extension of the overall confounding required to fully account for the exposure-outcome association, thus moving the observed point estimate to the null. We set the possible generic unmeasured confounder: (i) to have a 10% prevalence of exposure among pregnant women; (ii) to increase the neonatal outcome onset up to 10-fold more in mothers exposed than in those unexposed to the confounder and (iii) to be up to 20-fold more common among exposed than among unexposed mothers.

Mediation analysis

The role that adverse events at presentation (mediator) play in the relationship between use of antidepressant during pregnancy (exposure) and newborn adverse events appearing later in life (outcome) was investigated. In other words, we sought to address whether the increased prevalence of a given neonatal outcome (e.g., neonatal convulsion or birth asphyxia) in relation to antidepressants use during pregnancy is partially or entirely dependent (i.e., mediated) on an outcome appeared at presentation (e.g., low 5-min Apgar score). With this aim we used the approach described by VanderWeele and Vansteelandt [6]. Briefly, the (i) exposure-outcome, (ii) mediator-outcome, and (iii) exposure-mediator associations (each estimated by fitting log-binomial regression after correcting for the above listed covariates) allowed us to assess (i) the natural direct effect (PR_d), i.e., the effect of the exposure if the mediator were set to what it would have been without the exposure; and (ii) the natural indirect effect (PR_i), i.e., the effect on the outcome when the exposure is present after setting the mediator value to what it would have been with versus without the exposure. The proportion of the exposure-outcome association that was explained by the mediator was computed according to Ananth and VanderWeele [104].

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

Results

Table 1 shows that, of the 384,673 included women, antidepressant medications were dispensed to 9,843 of them (prevalence: 2.6%). Among them, almost two third stopped the therapy during pregnancy (6,548) while antidepressant treatment was kept by the remaining one third (3,295). Compared with never users, women who used antidepressants were older, Italian, poorly educated, unmarried and employed, previously experienced other pregnancies, and suffered from the considered medical conditions. With the exception of previous pregnancy, the same maternal traits were associated with more frequent antidepressant use during pregnancy than just before pregnancy. Prevalence of neonatal outcomes was 3.2% for SGA (12,212 newborns), 0.86% for low 5-min Apgar score (3,300), 0.12% for cerebral irritability (466), 0.13% for neonatal convulsion (482), 2.6% for intrauterine hypoxia and birth asphyxia (10,052), and 2.7% for other respiratory conditions (10,341). Compared with women who never use antidepressants, those who used these medications during pregnancy showed significant higher prevalence of almost all the considered neonatal outcomes (except SGA), prevalence ratios (95% CI) ranging from 1.3 (1.1 to 1.6) for asphyxia to 2.6 (1.4 to 4.8) for cerebral irritability (**Figure 2**). Similarly, compared with antidepressant users just before pregnancy, women who used these medications during pregnancy showed significant higher prevalence of almost all the considered outcomes (SGA and cerebral irritability), prevalence ratios ranging from 1.3 (1.0 to 1.6) for other respiratory conditions to 3.4 (1.2 to 9.1) for neonatal convulsions (**Figure 2**). Very similar findings were obtained by considering the exposure to SSRIs, rather than all antidepressants together as in the main analyses (**Supplementary Table S1**).

The effect of a generic unmeasured confounder which might overinflate the observed harmful effect of antidepressants use during pregnancy is shown in **Figure 3**. Assume pregnancy smoking be the confounder of interest and that antidepressants users had 3-fold higher smokers' prevalence than no users (exposure-confounder odds ratio = 3). In these conditions, pregnancy smoking should increase the risk of intrauterine hypoxia and birth asphyxia by 5-fold (confounder-outcome relative risk = 5) in order to nullify the observed harmful effect of antidepressants use during pregnancy. On the other hand, admitting that smoking during pregnancy increases the risk of neonatal convulsions by 5-fold, prevalence of smokers among antidepressants users should be 16-folds higher than no users in order to nullify the observed effect.

The results of portioning the observed effect of use of antidepressants during pregnancy (exposure) on selected outcomes into natural direct and indirect effects mediated through low Apgar score are shown in **Table 2**. The exposure-outcome prevalence ratios were stronger for natural direct effects than indirect effects. The proportion of excess neonatal outcomes following antidepressant use during

pregnancy that were mediated through low Apgar score were estimated to be 4%, 15%, and 22% for neonatal convulsions, intrauterine hypoxia and birth asphyxia and other respiratory condition, respectively.

Discussion

Our large population-based study offers evidence that use of antidepressant medications during pregnancy increases the risk of several neonatal adverse events such as low Apgar score, cerebral irritability, neonatal convulsion, intrauterine hypoxia and birth asphyxia, and other respiratory condition. These effects are not negligible since, compared to newborns whose mothers didn't used antidepressants, the excess of risk ranged from 30% (intrauterine hypoxia and birth asphyxia) to 160% (cerebral irritability). These findings confirm and extend the results of several investigations showing that antenatal SSRI-exposure involves poor neonatal adaption (e.g., respiratory distress, feeding difficulties, neonatal convulsions and rigidity) [76, 81, 89, 90, 92, 93, 95, 105-108].

Several possible explanations are conceivable with our findings. First, safety of antidepressants on foetal health might be the mechanistic key for interpreting our findings. As expected, selective serotonin reuptake inhibitors (SSRIs) were the more common antidepressant medications prescribed in our setting and we showed that the considered neonatal outcomes were associated with use of SSRIs. Although little is known about neonatal psychopharmacology of SSRIs [75], the possible role of SSRIs on neonatal cerebral suffering is of particular concern [87, 109-115]. However, power considerations prevented us of investigating possible differential effect between SSRIs and other antidepressant classes, so that a direct effect of antidepressants on the considered outcomes remains an open key in interpreting our findings.

Second, antidepressant medications are prescribed to treat depression, thus the observed associations could be explained by the residual depressive symptoms. We tried to account for confounding by indication by constraining women who used antidepressants during pregnancy with those who used they before pregnancy. Interesting, our study did not offer statistical evidence that cerebral irritability differently affected women who used antidepressants during pregnancy or just before pregnancy, so suggesting a role of depression itself rather than antidepressant medications. On the contrary, low 5-min Apgar score, neonatal convulsion, intrauterine hypoxia and birth asphyxia, and other respiratory conditions, affected women who used antidepressants during and just before pregnancy. However, confounding by severity of the underlying depression might still be present, because women who used antidepressant drug therapy during pregnancy might have more severe depression than those who interrupt it. On the other hand, it is possible that past depression affects maternal physiology lastingly and thus could also affect foetal development [116].

Third, the mechanism by which depression may exert its action on the considered neonatal outcomes might be mediated by the presence of epiphenomena, e.g., smoking, alcohol drinking, and other unhealthy behaviours, such as poor attendance to obstetric care [84, 102, 117, 118]. We attempted to

adjust for the available socioeconomic variables, as well as for the mother's reproductive history, but unmeasured residual confounding could still be present. For this reason, we attempted to take into account the extension that a generic factor should exert on both exposure (antidepressant use during pregnancy) and neonatal outcome to entirely explain the observed exposure-outcome association. For example, one might consider smoking during pregnancy as a possible (unmeasured) confounder since depressed women are more likely smokers, and prenatal smoke exposure likely increases the risk for the considered neonatal adverse outcomes [73, 117, 118]. Prevalence of women who smoke during pregnancy has been reported to be 8.4% in Italy [118]. While assuming higher smokers' prevalence (say 10%), our sensitivity analysis revealed that the observed antidepressant-outcome relationship was not annulled by correcting for an unmeasured confounder of great potential importance such as smoking, even when the worst scenario was simulated.

Fourth, some of the neonatal effects appeared during the first two years of the child's life might be substantially explained by effect of antidepressants that occurs early at birth. For example, exposure to antidepressant medications might act directly on the foetus development, so that frail newborns might be more susceptible to adverse events such as cerebral suffering and distress of respiratory function. However, in our setting women who did use antidepressants during pregnancy did not give birth with small for gestational age. In addition, our mediation analysis revealed that the effect of antidepressants during pregnancy on neonatal convulsion and respiratory distress are unlikely mediated by frailty of child's at birth just as it is synthesized by low Apgar score.

Our study has a number of potential limitations. First, the exclusion of mother-newborn pairs lacking of identification code could mainly affect less healthy women. Second, the implicit exclusion from our analysis of spontaneous and elective pregnancy terminations affects the possibility for outcomes potentially due to drug foetal-exposure to be selectively excluded. Third, a main limitation in using dispensing data relates to whether or not the medicine was consumed, or consumed as directed, and there is no information in this study for either of these aspects [96]. Fourth, privacy concerns do not allow to assess the validity of information recorded in the Certificates of Delivery Assistance, as well as of the diagnostic data from hospital charts. Fifth, we could not assess when antidepressants were used, a figure which would have provided information concerning possible heterogeneity in outcome risks during the observation period. There are two reasons for the lack of assessment: (i) dispensation data certainly does not correspond to use data; and (ii) power considerations did not allow the assessment of rarer exposures than those observed. Finally, the lack of data on important factors - such as depression severity, alcohol and illicit drug use - may further contribute to some unavoidable source of systematic uncertainty.

Despite these limitations, our data on drug utilization patterns in the real-world setting offer evidence that the use of antidepressants during pregnancy is harmful for several neonatal outcomes. It remains to be determined whether maternal antidepressant medications use is more beneficial or has adverse effects beyond the underlying depression. In the meantime, the clinician and the woman herself need to balance the degree of severity of the depressive disorder and the risk of relapse, with the emerging safety profile of antidepressant drugs.

Acknowledgment

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Figure 7. Flow-chart of inclusion and exclusion criteria

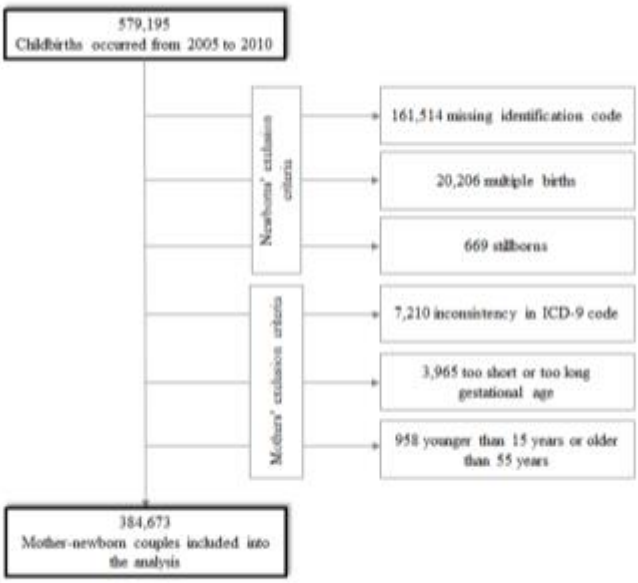

Table 6. Selected characteristics of the 384,673 mothers included in the study according to their use of antidepressants just before or during pregnancy. Italy, Region of Lombardy, 2005-2010

	Use of antidepressants			p-value [b]	
	Never (A) N = 374,830	Just before pregnancy (B) N = 6,548	During pregnancy (C) N = 3,295	A vs. C	B vs.C
Age at delivery					
≤ 25 years	13.3%	7.7%	8.2%	<0.0001	<0.0001
26 - 34 years	56.9%	55.6%	48.9%		
>34 years	29.8%	36.6%	41.9%		
Nationality					
Italy	74.6%	86.4%	86.5%	<0.0001	0.0004
Other	25.4%	13.6%	13.5%		
Marital status					
Married	77.0%	73.0%	72.2%	<0.0001	0.0006
Unmarried	23.0%	27.0%	27.8%		
Education [a]					
Low	31.6%	32.3%	34.4%	<0.0001	0.0037
Intermediate	45.4%	48.2%	46.5%		
High	23.0%	19.5%	19.1%		
Employment					
Employed	70.4%	75.1%	71.7%	<0.0001	<0.0001
Unemployed	29.6%	24.9%	28.3%		
Previous miscarriages					
None	83.6%	81.6%	83.0%	0.0049	0.1207
One or more	16.4%	18.4%	17.0%		
Parity					
Nulliparous	55.3%	53.4%	53.0%	<0.0001	0.3404
Multiparous	44.7%	46.6%	47.0%		
Medical conditions					
Diabetes	5.0%	6.6%	7.2%	<0.0001	<0.0001
Hypertension	9.4%	16.5%	18.2%	<0.0001	<0.0001
Dyslipidaemia	2.1%	3.3%	4.4%	<0.0001	<0.0001
Preeclampsia	1.2%	1.5%	1.5%	0.1510	0.0289

Figure 8. Adjusted prevalence ratios (and 95% confidence intervals) of selected outcomes associated with use of antidepressants during pregnancy, with respect to never use and use just before pregnancy

Prevalence ratio, and 95% confidence interval, estimated with log-binomial regression. Estimates are adjusted for the covariates listed in Table 1

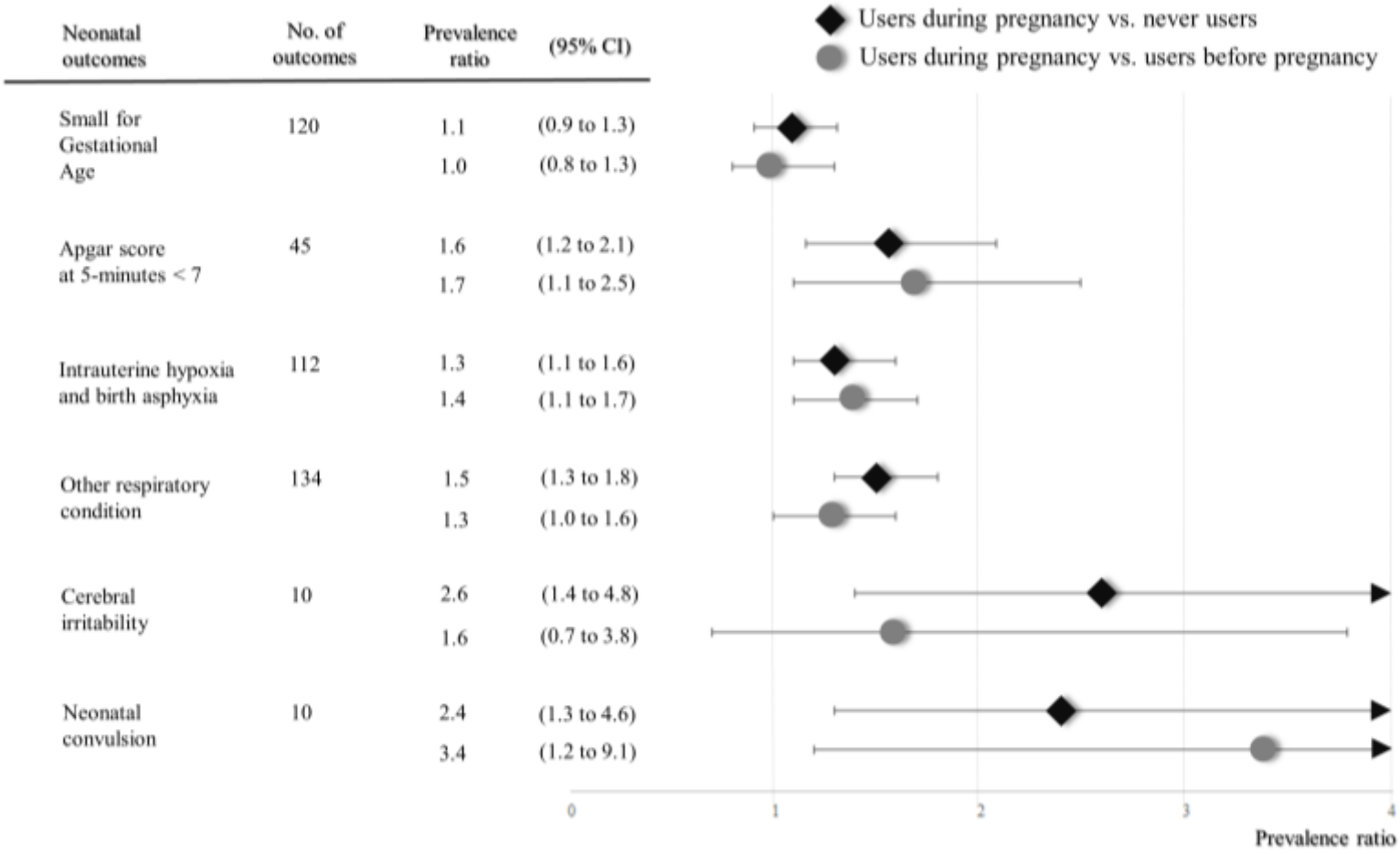

Figure 9. Influence of a generic unmeasured confounder on the relationship between use of antidepressants during pregnancy (exposure) and the risk of selected neonatal outcomes. The graph indicates the combinations of confounder–outcome and exposure-confounder associations that would be required to move the observed effect of antidepressant medications towards the null

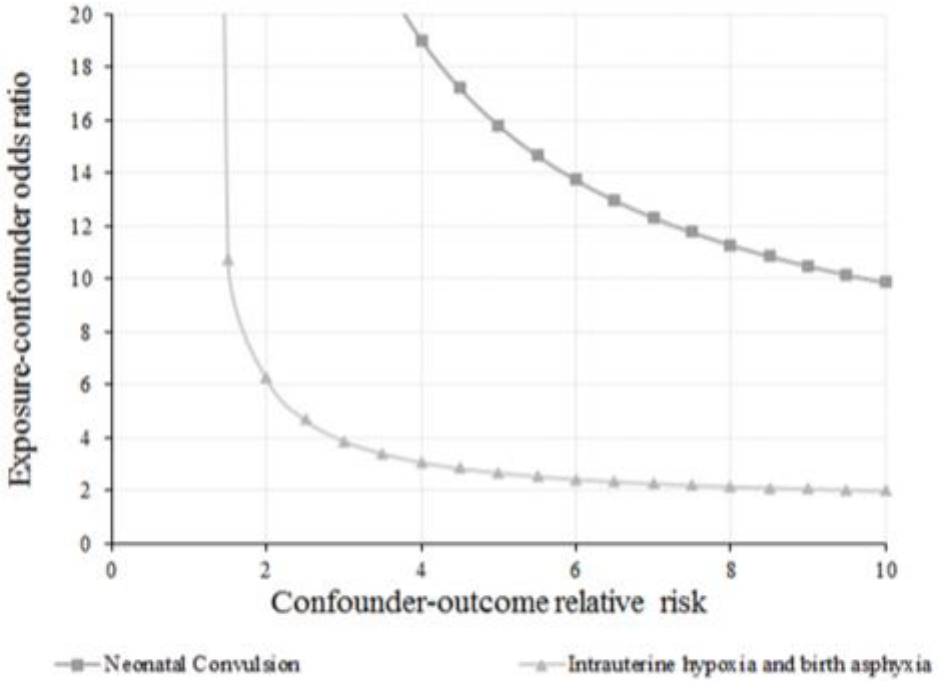

Table 7. Estimates of direct and indirect effects (mediated through Apgar score < 7 at 5-minutes) of the association between selected neonatal outcomes and use of antidepressants during pregnancy with respect to use of antidepressants just before pregnancy, Italy, Region of Lombardy, 2005-2010

Neonatal Outcomes	Adjusted prevalence ratio[a]						Proportion mediated[b] through low Apgar score, %
	Natural Direct Effect		Natural Indirect Effect		Total Effect		
	PR_d	95% CI	PR_i	95% CI	PR	95% CI	
Neonatal convulsion	3.4	(1.1 to 10.3)	1.03	(0.4 to 2.5)	3.5	(0.8 to 14.6)	4.1
Intrauterine hypoxia and birth asphyxia	1.3	(1.0 to 1.7)	1.04	(0.4 to 2.6)	1.3	(0.5 to 3.5)	15.1
Other respiratory condition	1.2	(0.9 to 1.5)	1.05	(0.4 to 2.9)	1.2	(0.4 to 3.6)	21.6

[a] Prevalence ratios were adjusted for the covariates listed in Table 1

[b] Outcome proportions mediated through low Apgar score were estimated as follows: $(PR_d \times (PR_i - 1)/(PR_d \times PR_i - 1))$, where PR_d and PR_i refer to the corresponding prevalence ratios for natural direct and indirect effect, respectively [26]

Supplementary Materials

Table S3. Adjusted prevalence ratios (and 95% confidence intervals) of selected outcomes associated with use of selective serotonin reuptake inhibitors during pregnancy, with respect of using any antidepressant medication just before pregnancy

	N. of outcomes	Prevalence ratio	(95% confidence interval)
Small for Gestational Age	107	1.0	(0.8 to 1.3)
Apgar score at 5-minutes < 7	43	1.9	(1.2 to 2.9)
Intrauterine hypoxia and birth asphyxia	100	1.4	(1.1 to 1.8)
Other respiratory condition	116	1.5	(1.1 to 1.7)
Cerebral irritability	9	2.1	(0.8 to 5.3)
Neonatal convulsion	9	2.8	(1.0 to 7.7)

Prevalence ratio, and 95% confidence interval, estimated with log-binomial regression. Estimates are adjusted for the covariates listed in Table 1

The following two projects, are made in collaboration with the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. I worked in this department as research scholar from 20th July, 2016 to 27th January, 2017. During this period, I worked in the following two projects with the collaboration of Krista Huybrechts and Elisabetta Patorno.

4. IV Study (working in progress)

Antidepressant use in pregnancy and the risk of low Apgar score: an Italian population-based study

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Running head: Low Apgar score and antidepressant use in Italy

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Conflict of Interest Disclosures: The authors have no conflict of interest to declare.

Abstract

Background: Several studies reported a low Apgar score at 5 minutes in infants exposed to antidepressants during pregnancy. However, antidepressants at different stages and maternal psychiatric illness during pregnancy has not always been assessed.

Objective: To evaluate the association between antidepressants during pregnancy and low Apgar score at 5 minutes in infants.

Study design: We conducted a population-based cohort study including 356,671 deliveries that occurred from January 2005 to December 2010 in the Lombardy region of Italy. We evaluated the risk of low Apgar score (defined as a score <7 at 5 minutes) among infants born to mothers exposed to antidepressants at different stages during pregnancy. Logistic-regression analysis was used to estimate the relative risk for low Apgar score and 95% confidence intervals. Propensity score stratification was used to account for all potential confounders (N= 23). In sensitivity analyses, we stratified the study population by underlying depression, and we restricted to women who did not undergo C-section and to those who had full-term births.

Results: In the overall population, we identified 1883 cases of low Apgar score. A total of 3309 women (0.93%) filled at least one prescription of antidepressant during pregnancy. Compared to other infants, newborns with late exposure to antidepressants had an increased risk of a low Apgar score (propensity score adjusted relative risk (aRR): 2.68, 95% CI 1.65-4.37). When analyses were restricted to children born to mothers with depression, the aRR of low Apgar score was 4.80 (1.37-16.80). Results remained consistent when analyses were restricted to mothers without C-section and to full-term births (aRR:3.94, 2.13-7.32; aRR:3.71, 2.20-6.26, respectively).

Conclusion: In this population-based study, which accounted for many potential confounders, late exposure to antidepressants in pregnancy was associated with increased risk of low Apgar score. Results were robust across sensitivity analyses.

KEY WORDS: Antidepressant medications, low Apgar score, pregnancy, depression.

Background

The Apgar score is a method for determining an infant's condition at birth by scoring the heart rate, respiratory effort, muscle tone, reflex irritability, and color [119]. The infant is rated from 0 to 2 on each of the five items, the highest possible score being 10. Each of the items is rated 1 minute after birth and again after five minutes. The Apgar score at 5 minutes after birth is an objective way of assessing and describing an infant's adaptation to extrauterine life. An Apgar score of less than 7 at 5 minutes (i.e., low Apgar score) has been associated with neurological disability, including cerebral palsy, epilepsy, and cognitive impairment that can persist many years post birth [119].

Previous studies have reported an increased risk ranging from 6.6 to 1.6 of low Apgar score in neonates with antidepressant exposure during pregnancy [95, 119-122]. Furthermore, it is stated that infant exposed to antidepressants, mainly SSRIs, during pregnancy had a lower 5-minute Apgar score as compared to unexposed infants with median of Apgar score in the range 8.4-8.9 and 9.0-9.9, respectively for exposed and unexposed to antidepressants *in utero* [116, 123-127]. However, it remains unclear as to whether there is a causal relationship between exposure to antidepressant medication *in utero* and poor neonatal adaptation, or whether maternal depression is itself responsible for this increased risk.

Mental disorders and psychotropic drugs may both influence the development of the fetus. Like most drugs, antidepressants cross the placenta which could lead to disruption of the normal maturation of the serotonin system and could alter the serotonin-dependent neuronal process in the fetus [111, 128]. In addition, maternal depressive illness and unhealthy behaviors associated with depression, such as smoking, alcohol intake, illicit drug use, and poor attendance for obstetric care, may also influence the new-born’s health [119].

We conducted a population-based cohort study in the Lombardy region of Italy, to evaluate the potential association between the use of antidepressants during pregnancy and low Apgar score at 5 minutes, taking into account potential confounding by underlying depression and associated factors.

Methods

Data Source and Study Cohort

The study cohort consisted of all live born infants in Lombardy from 1st January 2005 to 31st December 2010. Lombardy is a region in Italy which accounts for approximately 16% of the country's population (almost ten million inhabitants). The health care use of all residents of Lombardy is covered by the government-funded National Health Service (NHS) which in Lombardy has been associated with an automated system since 1997. All NHS-covered healthcare is documented in the HealthCare Utilization (HUC) databases of Lombardy. The HUC system of databases records demographic and administrative data for all beneficiaries of the Regional Health Service (approximately coinciding with the entire resident population), as well as their health care use. It includes (i) the hospital discharges registry, which reports all diagnoses released from public or private hospitals, (ii) the outpatient drug prescriptions registry, which reports all dispensations of NHS-reimbursable drugs, and (iii) the Certificates of Delivery Assistance, which provides detailed information on pregnancy, childbirth, and child presentation at delivery. The linking of records across HUC databases, which is made possible through a unique patient-identifying code included in all databases, allows to identify a large and unselected birth cohort and to reconstruct relevant traits and care pathways of mothers and new-borns.

We identified all pregnancies in women aged 12 to 55 years with gestational age between 22 and 46 weeks. To ensure the complete ascertainment of exposures, outcomes, and covariates, we required that all women had at least 3 months of continuous enrolment before the last menstrual period (LMP) through to at least 1 month after delivery. We excluded pregnancies of mothers who were not beneficiaries of the NHS (25,474 pregnancies), and who had a hospital admission ICD-9 code different from the one expected for deliveries (6,688 pregnancies). We excluded pregnancies in which the infant did not have an identification code (124,505 pregnancies) and did not have an Apgar score (1,530 pregnancies) (**Figure 1**).

Antidepressant medication during pregnancy

The Lombardy outpatient drug prescriptions registry holds information on all redeemed prescriptions. Antidepressant exposure was defined as redemption of a prescription for medicines with the Anatomical Therapeutic Code N06A. Women were considered exposed if they filled at least one prescription for an antidepressant medication during pregnancy. Two mutually exclusive exposure windows were considered. Late exposure was defined as filling at least one prescription for an antidepressant during the third trimester of pregnancy, with or without exposure before the third trimester. The reference group consisted of women without such late exposure. Early exposure was

defined as filling at least one prescription for an antidepressant during the first and/or the second trimester of pregnancy, but not during the third trimester. The reference group consisted of women without exposure at any time during pregnancy (Supplemental Material **Figure S1**).

Low Apgar Score

The Lombardy Certificates of Delivery Assistance registry records data on pregnancy, childbirth, and child presentation at delivery, including information on Apgar score (1-10) at 5 minutes. A low Apgar score was defined as an Apgar score of less than 7 at 5 minutes.

Covariates

Information on covariates that were used for confounding adjustment or for stratification was obtain from the hospital discharges registry and from the outpatient drug prescriptions registry. Maternal covariates were measured from any time before LMP through to the end of the first trimester, while concomitant medication and healthcare utilization variables were measured from any time before LMP through LMP. We considered several baseline maternal characteristics that may affect low Apgar score at 5 minutes. Demographic variable (i.e., maternal age), psychiatric comorbidities (i.e., depression, epilepsy, bipolar disorder, personality disorders, other psychiatric disorders, psychosis or schizophrenia, sleep disorder and/or anxiety), medical comorbidities (i.e., preeclampsia, hypertension, diabetes, obesity, migraine and/or headache, neuropathic, non-neuropathic, and other pain), and obstetric characteristics (i.e., Caesarian delivery, preterm birth). In addition, we considered concomitant medication (benzodiazepines, triptans, non-steroidal anti-inflammatory drugs (NSAIDS) and antiepileptics), and healthcare utilization measures, including the proportion of hospitalizations and the number of distinct prescription drugs used, excluding antidepressants, as a general marker of comorbidity [129].

Statistical analysis

We compared the distribution of maternal covariates, concomitant medication use, and healthcare utilization measures among women with late exposure and early exposure.

For each contrast of interest, we used logistic-regression analysis to estimate the odds ratio for low Apgar score (<7 at 5 minutes) and their corresponding 95% confidence intervals. Use of the robust variance estimator to account for correlations within women with multiple pregnancies did not change the confidence intervals considerably, so correlation structures were omitted from all analyses. Since the odds ratio is an excellent estimate of the risk ratio in the case of rare outcomes, the results are reported as relative risks.

Results are presented according to three levels of adjustment. The first analysis was an unadjusted analysis. In the second analysis, we used propensity score stratification to account for all predefined covariates that may act as confounders. Propensity scores (PS) were derived from the predicted probability of treatment estimated in a logistic-regression model that contained all the covariates described above. We dropped the observations in non-overlapping areas of the PS, created 25 equally sized PS-strata, after ranking only the exposed patients based on the PS and assigning unexposed patients to these strata based on their PS.
Weighted regression models were used to derive an adjusted exposure effect after stratification, in which each exposed patient received a weight of 1 and unexposed patients were weighted in proportion to the distribution of the exposed in the stratum into which they fell [10]. In the third analysis, propensity scores were estimated using the high-dimensional propensity score algorithm. Using this algorithm, we evaluated hundreds of inpatient diagnoses, procedures, and pharmacy claims and selected the 50 covariates with the highest potential to create confounding based on their prevalence and the strength of their association with the exposure and the outcome. These variables may act as proxies for unmeasured confounders and were combined with the pre-defined covariates in a propensity score model to improve confounding adjustment [9].

Sensitivity analyses

We conducted several sensitivity analyses to evaluate the effect of potential misclassification of exposure. We redefined exposure as (i) having filled at least 2 prescriptions of antidepressants, or (ii) as having days of supply that overlap with the exposure window of interest.
To avoid differential opportunity for exposure in preterm versus full term deliveries, we re-defined late exposure as having filled at least one prescription during the last 90 days of pregnancy as opposed to during the third trimester.
We compared the risk of low Apgar score between women who were treated with antidepressants during the three months before the start of pregnancy and in the third trimester (late use), and women who discontinued treatment before the start of pregnancy (pre-pregnancy use). The rationale for this analysis is that women who have been treated with antidepressants but discontinue because of their pregnancy might be more comparable to women who continue treatment into their third trimester than women who were never treated with antidepressants, ultimately possibly resulting in less confounding.
Given the importance of depression and its associated behaviors, we stratified the analyses by the presence of a diagnosis of depression identified in the hospital discharges registry measured from any time before the LMP through to the end of the first trimester.

Finally, since was reported an excess risk of low Apgar score in women with cesarean section procedures [130, 131], as well as in preterm births [132, 133], to evaluate if the outcome occurs through these variables, we restricted the outcome to cases of no C-section and full-term births.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level.

Results

Out of 356,671 deliveries that met the inclusion criteria, 3309 women (0.93%) used an antidepressant during pregnancy: 986 (0.28%) were exposed to the third trimester and 2323 (0.65%) to the first and/or the second trimester only. Among the 256,671 pregnancies, 1883 (0.5%) had an Apgar score after 5 min between 0 and 6 whereas 354,788 children had an Apgar score from 7 to 10.

Table 1 shows the baseline maternal covariates, concomitant medication and healthcare utilization according to the mother's antidepressant utilization. There were substantial differences in the baseline characteristics of women exposed to antidepressants compared with those unexposed.

Women who filled at least one prescription for an antidepressant during the third trimester, as well as, in early pregnancy, were more likely to have a diagnosis of psychiatric illness, mainly of depression, and of pain. They were more likely to be obese or overweight, and to deliver by C-section and to deliver preterm.

Prior to pregnancy, a consistent number of women who redeemed prescriptions for antidepressants during pregnancy, redeemed also prescriptions for Triptans, NSAIDs, and Antiepileptic.

Figure 2 shows the unadjusted, adjusted propensity score stratified (PSS), and adjusted high-dimensional propensity score stratified (HDPSS) relative risk (RR) for a low Apgar score among the risk groups. Stratification according to the propensity score ensured that comparisons were made between groups with nearly identical characteristics. The only risk group with a significantly increased risk for a low Apgar score was for children born of women with late exposed (unadjusted RR, 3.09; 95% CI, 1.90-5.03 – adj. PSS RR, 2.68; 1.65-4.37 – adj. HDPSS RR, 2.20; 1.25-3.86). Infants exposed to antidepressants in early pregnancy didn't have an increased risk of low Apgar score at 5 minutes (unadj. RR, 1.23; 0.74-2.04 – adj. PSS RR, 1.05; 0.63-1.74 – adj. HDPSS RR, 0.96; 0.53-1.73).

The overall findings were not affected when we changed the exposure definitions (Figure 3). Redefined the exposure requiring women to have filled at least 2 prescriptions, according to the days of supply, and redefining late pregnancy exposure as exposure filling a prescription during the last 90 days of pregnancy, did not affect the results that remained consistent with the main analyses.

The increased risk of low Apgar score associated with later pregnancy exposure to antidepressants was confirmed in analyses stratified by the presence of a depression diagnosis, and in subgroup analyses restricted to vaginal deliveries and full terms births. Likewise, the null finding for early exposure was seen in the stratified and subgroup analyses.

Discussion

In this cohort study including 356,671 deliveries in the Lombardy region in Italy, we found that antidepressant exposure during the third trimester of pregnancy was associated with a more than doubling of the risk of being born with a low Apgar score (<7) at 5 minutes. There was no evidence of a significantly increased risk of low Apgar score with antidepressant exposure during the first or second trimester only. These results were confirmed in sensitivity analyses conducted to address potential residual confounding (i.e., continuers versus discontinuers, stratification by a recorded diagnosis of depression) and misclassification of the exposure (i.e., >1 dispensing, days supply overlap), as well as in subgroup analyses restricted to vaginal deliveries and to full-term deliveries.

Previous studies have shown increased risks of low Apgar score in children exposed to antidepressants *in utero*, especially that of SSRIs [95, 116, 119-125, 127, 134]. Our findings are supported by Reis & Kallen and by Smith et al, who demonstrated increased risk of low Apgar score among women who used antidepressants in late pregnancy and a lower Apgar score for infants exposed to SSRIs during the last trimester than for unexposed infants, respectively [95, 116, 120, 122, 134]. Moreover, Colvin et al, supported a contrast results finding an increased risk of low Apgar score for infants exposed to SSRIs during the first trimester but not for children exposed during the second or third trimester only [121]. Most of the studies compared the Apgar score in women treated with antidepressants during pregnancy with those without such exposure finding a general increased risk for children born of women exposed to antidepressants during pregnancy and a lower Apgar score in such group of children compared with infants unexposed [95, 116, 119, 120, 123-125, 127].

The importance of distinguishing the effects of maternal depressive disease from the effects of antidepressants has been highlighted in recent reviews [99, 135-137]. To assess whether the association could be due to confounding by indication, we evaluated exposure at different stages throughout pregnancy, and stratified analyses by the presence of a recorded diagnosis of depression. The fact that we only observed an association for late pregnancy exposure and that we observed an association in the subgroup where both exposed and unexposed women had a diagnosis of depression suggest the findings is unlikely to be due to confounding by depression. This is consistent with the finding from Jensen et al. who stated that maternal depression, without prescription of antidepressants, was not associated with a low Apgar score [119]. In contrast, Lory et al. found no evidence of low Apgar score when the control group was depressed mothers without antidepressant exposure during pregnancy [138].

Several studies have highlighted an increased risk of low Apgar score associated with a decrease in gestational age [130, 131]. Since antidepressants have been found to be associated with preterm birth,

we conducted a subgroup analysis restricting the cohort to full-term births (weeks' gestation ≥37) to remove the possible mediator effect of short gestational age. The results remained consistent. In addition, it has been reported that delivery by C-section was a potentially important factor for low Apgar score [132, 133]. Restricting the cohort to women with vaginal deliveries did not change the results.

Conducting research in this area is extremely complex, especially in understanding the biological mechanism to explain how the exposure affects the risk of low Apgar score. Surely, some women may have a greater biological risk for mental disorders, and thus their children may have an increased biological risk for adverse childhood outcomes, such as low Apgar score [126]. Another possible explanation for the increased risk of low Apgar score associated with intrauterine exposure to antidepressants could be a direct effect of transient neonatal toxicity or withdrawal among infants with late exposed to antidepressant in pregnancy, several cases reported these findings [139-143]. Moreover, the findings that antidepressant during fetal development might have subtle effects on motor development and motor control, infant characteristics measured through Apgar score, are consistent with the pharmacologic properties of the drugs [123].

The large population-based sample and the powerful statistical methodology to control for important confounding variables are the peculiarities of this study.

This study has several strengths. First of all, the CeDAP database, used to select our cohort, established by the Ministry of Health on 2001, is the main source of current data available in Italy on maternal and child health, gathering information on socio-demographic characteristics and on pregnancy, delivery, and birth. The cohort includes a large and unselected population with prospective assessment of exposure that can be linked with clinical information including chronic maternal illness, obstetric characteristics, concomitant medication use, and healthcare utilization. The large size of the cohort allowed us to evaluate the effect of the timing of antidepressant exposure, and to test the robustness of the findings in a number of sensitivity and subgroup analyses.

Our study also has a number of potential limitations. Most importantly, confounding variables are based on inpatient information only. Less severe comorbid conditions that do not result in hospitalization or are not recorded as one of the patient diagnoses in hospitalizations for delivery or other medical problems are therefore missed. This is likely why the proportion of women with a recorded diagnosis of depression is lower in our cohort than in other similar population-based cohorts. Moreover, lifestyle factors (e.g., smoking, alcohol use, obesity) are known to be under-recorded in administrative databases. This could result in residual confounding. It is reassuring, however, that (1) we did not find an association for early pregnancy exposure, (2) results were confirmed in the subgroup of women with a recorded depression diagnosis, (3) results were confirmed when

comparing late use to pre-pregnancy use of antidepressant medication which are more likely to be similar than users versus non-users, (4) high-dimensional PS analyses where we screen a large number of empirically defined potential confounding variables did not attenuate the findings.

Redeeming a prescription does not necessarily imply that the women actually took the medication, and we have no information available in this study to address this aspect [96]. We were not able to look at individual antidepressants (SSRIs vs tricyclic drugs vs other antidepressants) but seems to be not certain difference between women using tricyclic drugs, SSRIs, or other antidepressants [122].

Privacy concerns prevented us to assess the validity of the information recorded in the Certificates of Delivery Assistance, as well as the diagnostic data from hospital charts. Nevertheless, the Annual Reports established by Decree of the Minister of Health stated that the quality of the data is good for most variables, both in terms of correctness both of completeness.

In conclusion, our results suggest that use of antidepressants late in pregnancy, but not in early pregnancy, increases the risk of low Apgar score. This effect seems to be attributable to the treatment and not to the disease itself. Adequate control for maternal smoking is essential to clarify the relationships between depression, antidepressant treatment, and low Apgar score. Such controls will provide information useful for clinicians and their patients on the use of antidepressant medication during pregnancy. Furthermore, future studies are needed to distinguish between individual SSRIs to find the safest medication for the treatment of depression during pregnancy.

Figure 10. Study cohort

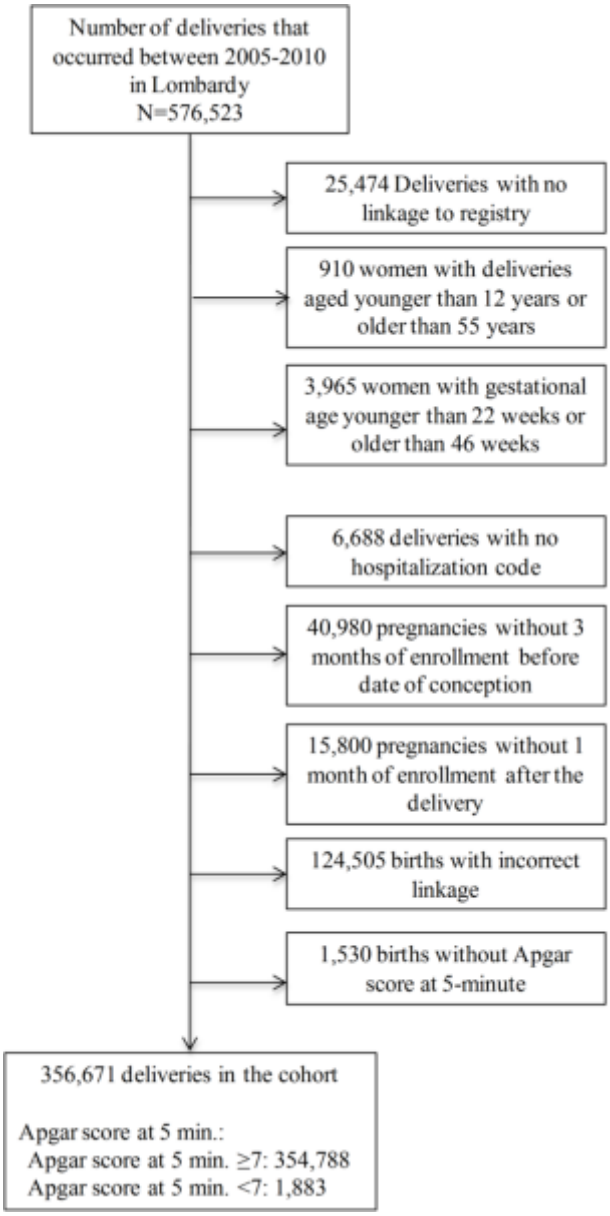


Table 8. Selected Cohort Characteristics of Women among the various Exposure Groups. Italy, Region of Lombardy, 2005-2010.

Characteristics	Unadjusted		Adjusted†			Unadjusted		Adjusted†		
	Late exposure (N=986)	Unexposed (N=355 685)	Late exposure (N=985)	Unexposed (N=352 154)	*Standardized Difference*	T1/T2 exposure (N=2323)	Unexposed (N=353 362)	T1/T2 exposure (N=2322)	Unexposed (N=352 773)	*Standardized Difference*
Maternal covariates										
Age, mean (SD), yr	34 ±4.8	32 ±4.9	34 ±4.7	34 ±4.8	-1,9	33 ±5.2	32 ±4.9	33 ±5.2	33 ±5	-1,7
Depression - no. (%)§	91 (9.2)	1795 (0.5)	91 (9.2)	31761 (9)	0,8	150 (6.5)	1645 (0.5)	149 (6.4)	20167 (5.7)	2,9
Epilepsy - no. (%)§	8 (0.8)	1102 (0.3)	8 (0.8)	2984 (0.8)	-0,4	16 (0.7)	1086 (0.3)	16 (0.7)	2306 (0.7)	0,4
Preeclampsia - no. (%)§	25 (2.5)	8670 (2.4)	25 (2.5)	8555 (2.4)	0,7	62 (2.7)	8608 (2.4)	62 (2.7)	9700 (2.7)	-0,5
C - section - no. (%)∫	365 (37)	109 298 (30.7)	365 (37.1)	132527 (37.6)	-1,2	867 (37.3)	108 431 (30.7)	866 (37.3)	134556 (38.1)	-1,7
Preterm Birth - no. (%)∫	75 (7.6)	20 985 (5.9)	75 (7.6)	27194 (7.7)	-0,4	175 (7.5)	20 810 (5.9)	175 (7.5)	26840 (7.6)	-0,3
Hypertension - no. (%)§	40 (4.1)	12 503 (3.5)	40 (4.1)	14577 (4.1)	-0,4	113 (4.9)	12 390 (3.5)	113 (4.9)	17677 (5)	-0,7
Diabetes - no. (%)§	36 (3.6)	11 127 (3.1)	36 (3.7)	12883 (3.7)	0	102 (4.4)	11 025 (3.1)	102 (4.4)	15803 (4.5)	-0,4
Obesity or overweight - no. (%)§	13 (1.3)	2948 (0.8)	13 (1.3)	5172 (1.5)	-1,3	65 (2.8)	2883 (0.8)	65 (2.8)	10455 (3)	-1
Migraine/ headache - no. (%)§	18 (1.8)	3117 (0.9)	18 (1.8)	6615 (1.9)	-0,4	69 (3)	3048 (0.9)	68 (2.9)	9986 (2.8)	0,6
Bipolar disorder - no. (%)§	21 (2.1)	325 (0.1)	21 (2.1)	4922 (1.4)	5,6	29 (1.3)	296 (0.1)	28 (1.2)	3321 (0.9)	2,6
Other Personality disorder - no. (%)§	50 (5.1)	792 (0.2)	50 (5.1)	13649 (3.9)	5,8	91 (3.9)	701 (0.2)	90 (3.9)	10279 (2.9)	5,3
Neuropathic, Non-neuropathic, and Other Pain - no. (%)§	98 (9.9)	20 158 (5.7)	98 (9.9)	36147 (10.3)	-1	199 (8.6)	19 959 (5.7)	198 (8.5)	30227 (8.6)	-0,1
Psychiatric disorders - no. (%)§	31 (3.1)	2145 (0.6)	31 (3.1)	10526 (3)	0,9	113 (4.9)	2032 (0.6)	113 (4.9)	15230 (4.3)	2,6
Psychosis or Schizophrenia - no. (%)§	15 (1.5)	515 (0.1)	15 (1.5)	4303 (1.2)	2,6	23 (1)	492 (0.1)	23 (1)	2840 (0.8)	2
Sleep disorder or Anxiety - no. (%)§	62 (6.3)	2190 (0.6)	62 (6.3)	22222 (6.3)	-0,1	115 (5)	2075 (0.6)	114 (4.9)	16178 (4.6)	1,5
Substance dependence - no. (%)§	24 (2.4)	1043 (0.3)	24 (2.4)	7297 (2.1)	2,5	62 (2.7)	981 (0.3)	62 (2.7)	7471 (2.1)	3,6
Concomitant medication¶										
Benzos - no. (%)	18 (1.8)	317 (0.1)	18 (1.8)	3454 (1)	7,2	23 (1)	294 (0.1)	22 (0.9)	2028 (0.6)	4,3
Triptans - no. (%)	78 (7.9)	13 895 (3.9)	78 (7.9)	29746 (8.4)	-1,9	218 (9.4)	13 677 (3.9)	217 (9.3)	36414 (10.3)	-3,3
NSAIDs - no. (%)	367 (37.2)	77 540 (21.8)	367 (37.3)	134086 (38.1)	-1,7	804 (34.6)	76 736 (21.7)	804 (34.6)	127436 (36.1)	-3,1
Antiepileptic	36 (3.6)	1107 (0.3)	36 (3.7)	11103 (3.2)	2,8	59 (2.5)	1048 (0.3)	58 (2.5)	7579 (2.1)	2,3
Healthcare utilization‡										
Indicator variable if there was a hospitalization - no. (%)	37 (3.7)	13 940 (3.9)	37 (3.8)	12961 (3.7)	0,4	120 (5.2)	13 820 (3.9)	120 (5.2)	17493 (5)	1
No. of distinct prescription drugs, excluding antidepressants										
=1	282 (28.6)	96 119 (27)	282 (28.6)	99872 (28.4)	0,6	696 (30)	95 423 (27)	696 (30)	104288 (29.6)	0,9
≥2	377 (38.2)	72 876 (20.5)	377 (38.3)	136912 (38.9)	-1,2	833 (36)	72 043 (20.4)	832 (35.8)	130052 (36.9)	-2,2

† To account for propensity score, the untreated observations were weighted using the distribution of the treated among propensity score strata. Propensity score strata that did not contain at least 1 treated women and 1 untreated women (i.e., uninformative strata) were removed.

§ Maternal covariates measured from any time before LMP through the end of the first trimester.

∫ Data related to the current pregnancy.

¶ Concomitant psychotropic medication use measured during any time pre-LMP.

‡ Healthcare utilization variables measured during three months pre-LMP.

Figure 11. Risk of Apgar score of less than 7 at 5 minutes, according to maternal exposure to antidepressants. Odds ratios and 95% confidence intervals are presented with different levels of confounding to show the risk of low Apgar score at 5 minutes among infants born to mothers exposed to antidepressants at different stages during pregnancy.

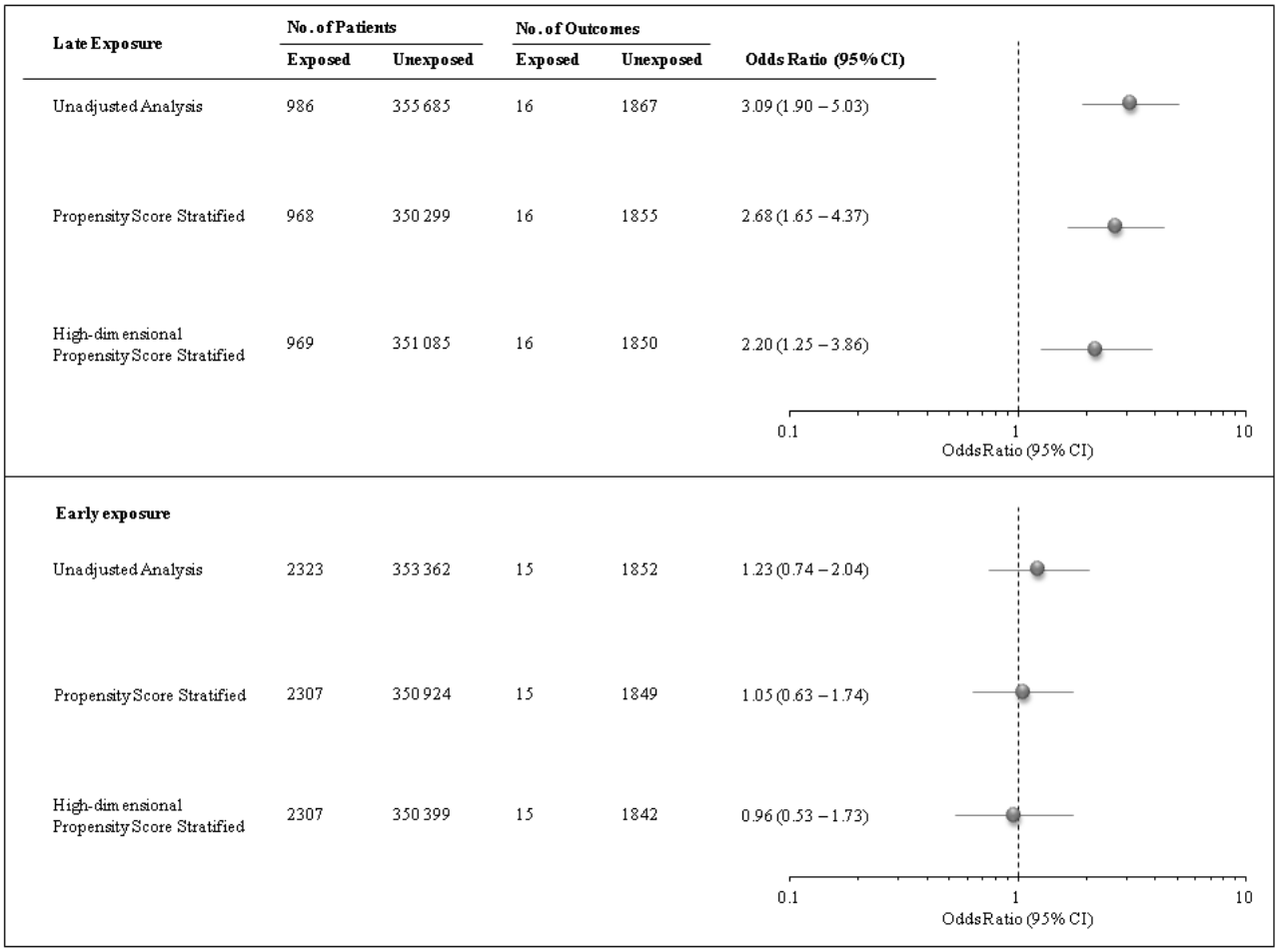
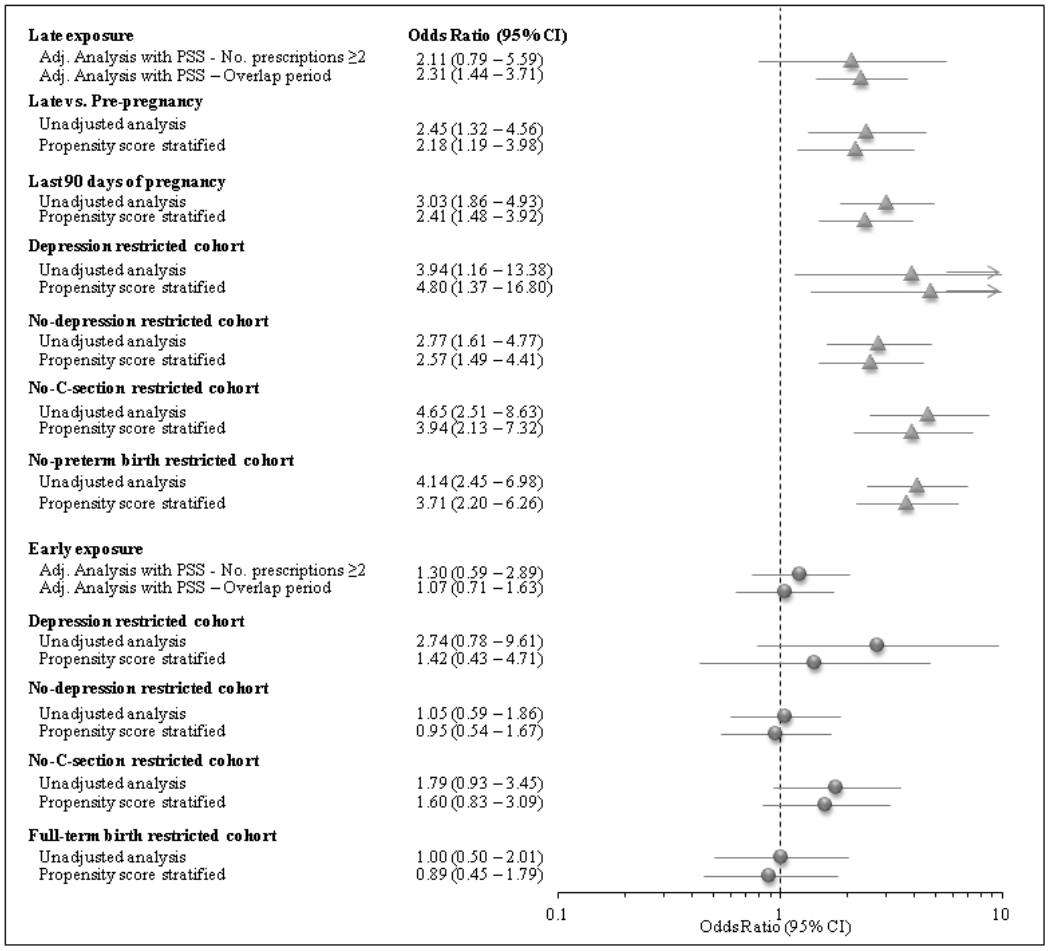


Figure 12. Sensitivity analyses and subgroup**.** Risk of Apgar score of less than 7 at 5 minutes, according to maternal exposure to antidepressants. Odds ratios and 95% confidence intervals are presented with different levels of confounding to show the risk of low Apgar score at 5 minutes among infants born to mothers exposed to antidepressants at different stages during pregnancy.



Supplementary Materials

Figure S1. Definition of risk groups.

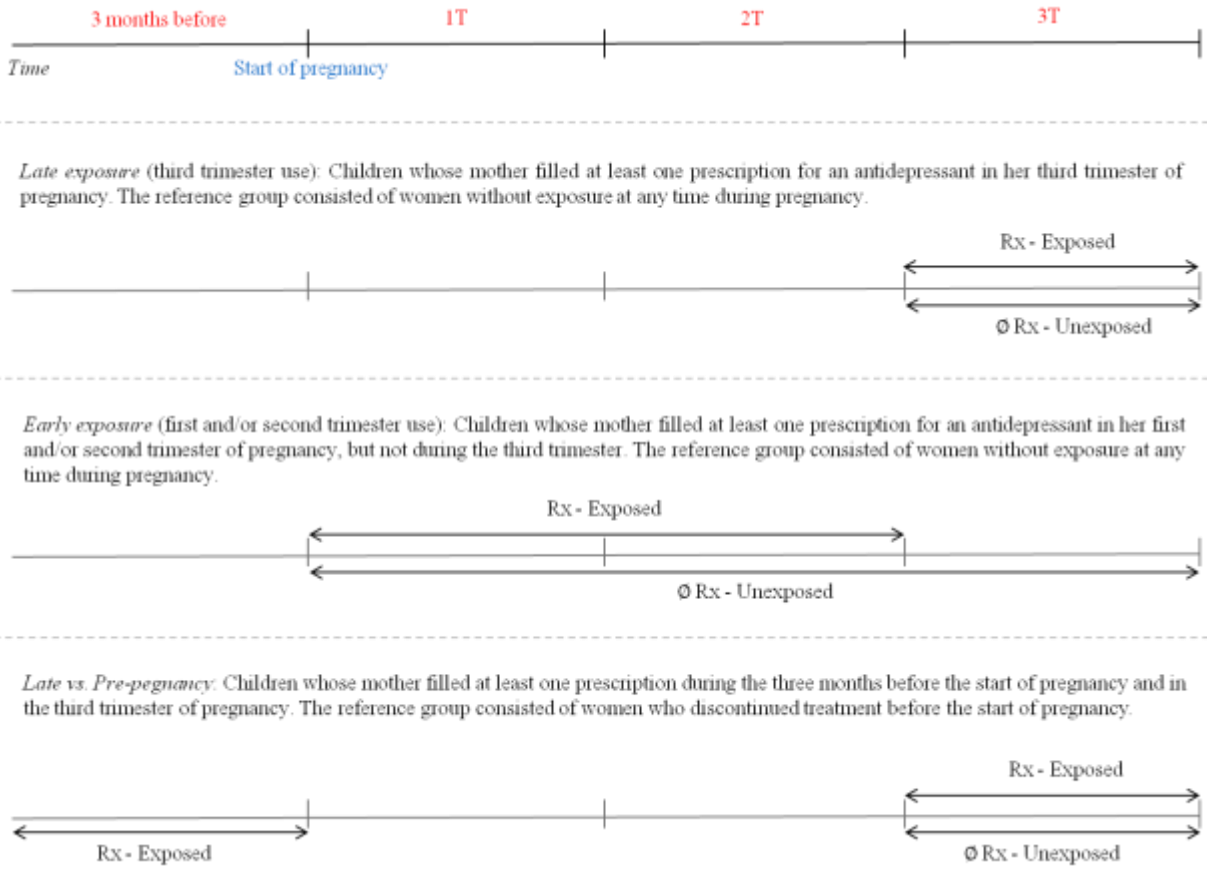


Table S4. Risk of Low Apgar score among the various exposure groups. Sensitivity Analysis. Data from the Lombardy region, Italy, 2005-2010.

	No. of Patients		No. of Outcomes		
Exposure Definition	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**OR (95% CI)**
Late exposure					
Adj. PSS – No. prescriptions ≥2	338	347 266	4	1801	2.11 (0.79 - 5.59)
Adj. PSS – Overlap period	1171	350 242	17	1854	2.31 (1.44 – 3.71)
Late vs. Pre-pregnancy					
Unadjusted Analysis	986	4073	16	27	2.45 (1.32 - 4.56)
Propensity Score Stratified	968	4026	16	27	2.18 (1.19 - 3.98)
Last 90 days of pregnancy					
Unadjusted Analysis	1007	355 664	16	1867	3.03 (1.86 - 4.93)
Propensity Score Stratified	990	351 473	16	1856	2.41 (1.48 - 3.92)
Depression restricted cohort					
Unadjusted Analysis	91	1795	3	15	3.94 (1.16 - 13.38)
Propensity Score Stratified	86	1633	3	12	4.80 (1.37 - 16.80)
No-depression restricted					
Unadjusted Analysis	895	353 890	13	1852	2.77 (1.61 - 4.77)
Propensity Score Stratified	880	348 619	13	1839	2.57 (1.49 - 4.41)
No-C-section restricted cohort					
Unadjusted Analysis	621	246 387	10	853	4.65 (2.51 - 8.63)
Propensity Score Stratified	610	245 265	10	852	3.94 (2.13 - 7.32)
No-preterm birth restricted cohort					
Unadjusted Analysis	911	334 700	14	1242	4.14 (2.45 - 6.98)
Propensity Score Stratified	896	330 128	14	1231	3.71 (2.20 - 6.26)
Early exposure					
Adj. PSS – No. prescriptions ≥2	650	351 948	6	1861	1.30 (0.59 - 2.89)
Adj. PSS – Overlap period	3380	350 166	22	1844	1.07 (0.71 - 1.63)
Depression restricted cohort					
Unadjusted Analysis	150	1645	3	12	2.74 (0.78 - 9.61)
Propensity Score Stratified	145	1503	3	10	1.42 (0.43 - 4.71)
No-depression restricted					
Unadjusted Analysis	2173	351 717	12	1840	1.05 (0.59 - 1.86)
Propensity Score Stratified	2159	348 692	12	1831	0.95 (0.54 - 1.67)
No-C-section restricted cohort					
Unadjusted Analysis	1456	244 931	9	844	1.79 (0.93 - 3.45)
Propensity Score Stratified	1447	243 544	9	841	1.60 (0.83 - 3.09)
No-preterm birth restricted cohort					
Unadjusted Analysis	2148	332 552	8	1234	1.00 (0.50 - 2.01)
Propensity Score Stratified	2139	331 033	8	1234	0.89 (0.45 - 1.79)

Results are presented with different levels of confounding adjustment

Figure S2. Distribution of Apgar score at 5 minutes among exposure to antidepressants during pregnancy.

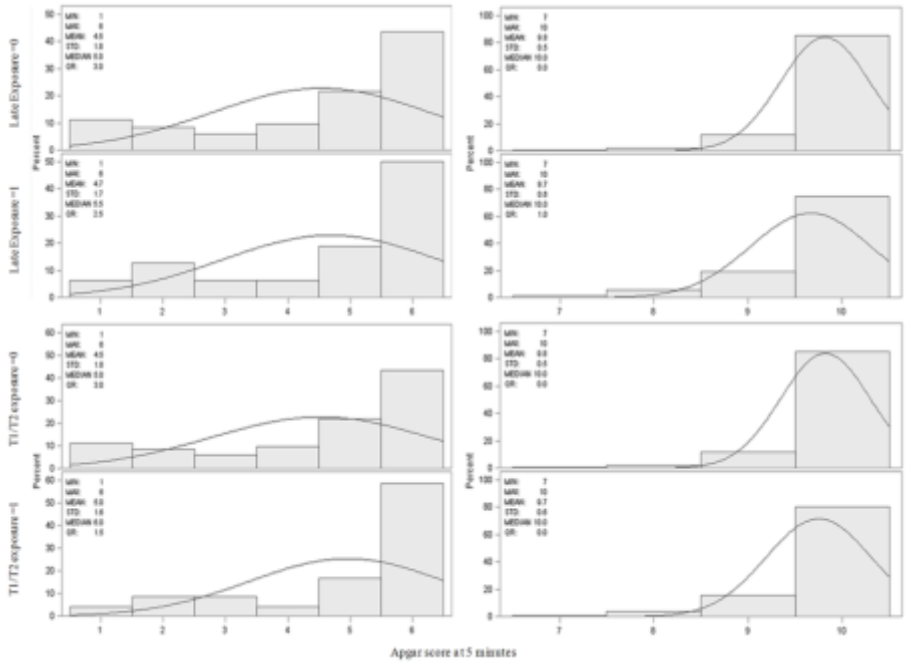


Figure S3. Distribution of Apgar score at 5 minutes among exposure to antidepressants during pregnancy within vaginal vs. C-section deliveries.

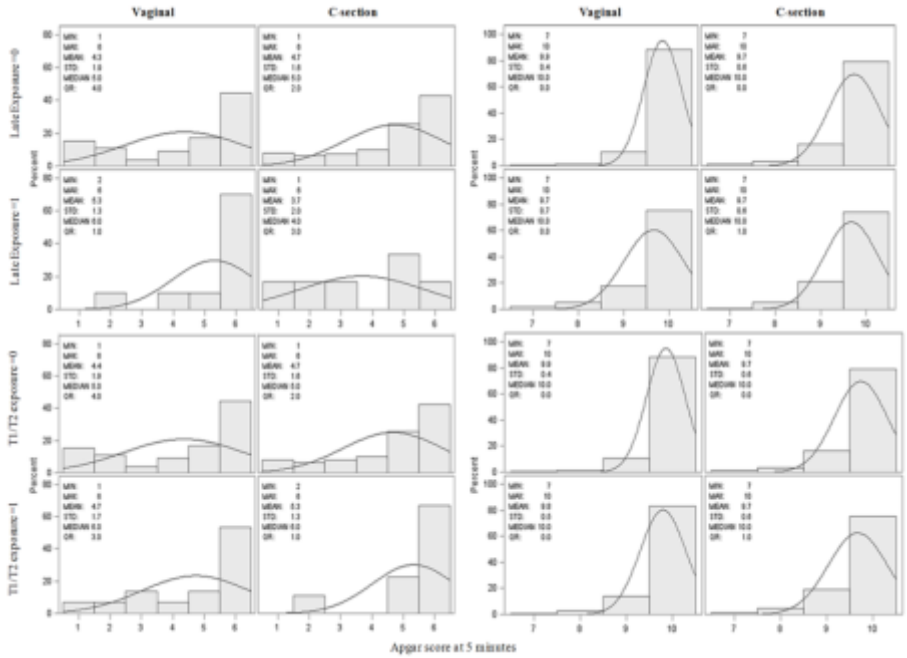
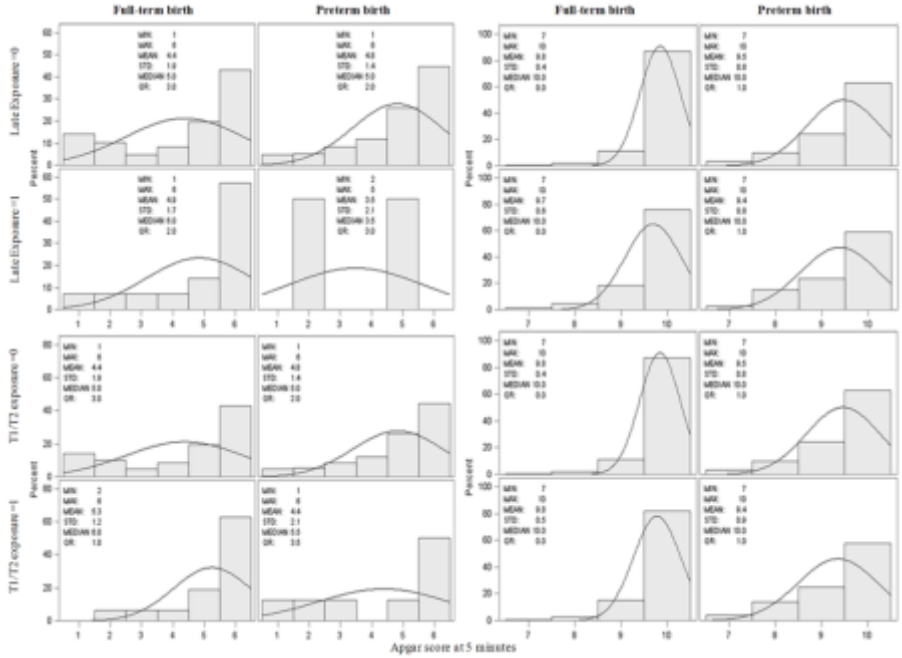


Figure S4. Distribution of Apgar score at 5 minutes among exposure to antidepressants during pregnancy within Full-term vs. Preterm birth.



5. V Study (working in progress)

Epidemiological data on timing of stillbirth and on timing of stillbirth specific risk factors with an Italian population-base data

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Authors' Contributions:

Conflict of Interest Disclosures: The authors have no conflict of interest to declare.

Introduction

Although stillbirth rates in high-income countries have decreased significantly since the 1940s, ending preventable stillbirth is still one of the major global public health challenges [144].

The International Federation of Gynecology and Obstetrics (FIGO), the International Pediatric Association (IPA), and the International Confederation of Midwives (ICM) defined stillbirth as the most common adverse pregnancy outcome worldwide with about 2.6 million or more stillbirths happening every year [145].

Several studies have reported multiple risk factors associated with stillbirth, including advance maternal age (>35 years old), which is associated with a 65% increase in the odds ratio of stillbirth [7, 146-150], and low educational level (<10 years), which doubles the odds of stillbirth [148, 150]. Maternal smoking during pregnancy [146-148, 150], multiparity [150, 151], obesity [146-150], multiple pregnancies [148], and the use of assisted reproductive technology are also important risk factors in high-income countries [147, 152]. Maternal hypertension is often connected with obstetric disorders with placental origins such as abruptions, infections, and other placental pathology linked with stillbirths [144, 146-148, 153]. It has been reported that 7% of still births are due to maternal medical disorders, with the most frequent reported associated conditions as hypertension and diabetes [146, 147]. Fetal growth restriction owing to placental insufficiency is the cause of 40-60% of stillbirths [144, 146, 147, 153]. Another important risk factor is infection, such as parvovirus B19, group-B streptococcus, Listeria, Escherichia coli, eteroviruses, cytomegalovirus, and influenza virus, which are more often related with stillbirths in early pregnancy [147]. Finally, preterm and post-term labor are associated with the occurrence of stillbirths [147].

However, previous studies of risk factors for stillbirth used limited data and population-based studies are required. Furthermore, knowledge on timing of stillbirth and on timing of stillbirth specific risk factors are unknown. An early detection on specific risk factors could help clinicians in decreasing antepartum and intrapartum stillbirth risk through monitoring and timely intervention; indeed, gestational age at the decision of screening and intervention is crucial.

In this paper, we present epidemiological data on timing of stillbirth and on timing of stillbirth specific risk factors with population-based data.

Methods

Study design

We conducted a population-based study among pregnancies that occurred between January 1, 2005, and December 31, 2010, in Lombardy, Italy.

Data were obtained from the healthcare utilization databases (HUC) of Lombardy, an Italian Region with about 16% of the country's population (almost ten million inhabitants). The HUC system of databases records demographic and administrative data for all beneficiaries of the Regional Health Service (practically coinciding with the entire resident population), as well as their health care use. It includes (i) the hospital discharges registry, which reports all diagnoses released from public or private hospitals, (ii) the outpatient drug prescriptions registry, which reports all dispensations of NHS-reimbursable drugs, and (iii) the Certificates of Delivery Assistance (CeDAP), which provides detailed information on pregnancy, childbirth, and child presentation at delivery. The linking of records across HUC databases made possible through a unique patient-identifying code included in all databases, allows to identify a large and unselected birth cohort and to reconstruct relevant traits and care pathways of mothers and new-borns.

We identified all pregnancies in women aged 12 to 55 years with gestational age between 22 and 46 weeks from CeDAP. Gestational age in this data file was clinically estimated. To ensure the complete ascertainment of exposures, outcomes, and covariates, we required that all women had at least 3 months of enrolment before the last menstrual period (LMP) through to at least 1 month after delivery. We excluded pregnancies from mothers who were not beneficiaries of Lombardy's NHS (25,474 pregnancies), and pregnancies from mothers with at least an ICD-9 code for birth defects and/or Chromosomal anomalies (295 pregnancies) (**Figure 1**).

Stillbirth definition

Stillbirth was defined based on the presence of inpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) diagnostic codes for stillbirth (V27.1, V27.3, V27.4, V27.6, V27.7, V35, and V36) in the maternal records during 30 days before or after the date of delivery.

Chronic Risk Factors and Proximal Causes definition

Factors that were consider to be associated with stillbirth were categorized in two macro groups define as (i) chronic risk factors, included maternal age (≤25 yr, 26-34 yr, 35-39, and ≥40 yr), use of assisted reproductive technology, pre-existing hypertension, gestational hypertension, pre-gestational

diabetes, gestational diabetes, systematic lupus erythematosus, and multiple births; and (ii) proximal causes, included pre-eclampsia, infections, abruption placentae, and fetal growth restriction.
Information on chronic risk factors and proximal causes were obtained from the hospital discharges registry and from the Certificates of Delivery Assistance database.

Statistical analysis

Missing values for *use of assisted reproductive technology* variable, the only one retrieved from Certificates of Delivery Assistance database, were imputed once with single imputation using the fully conditional specification model (FCS) [4, 35], because only a small percentage of data were missing (1%). As a rule of thumb, the number of imputed datasets should be at least equal to the percentage of incomplete cases [154]. Using only complete cases would cause the loss of all the information that is in the incomplete cases. Moreover, excluding observations with missing values also ignores the possible systematic difference between the complete cases and incomplete cases, and the resulting inference might not be applicable to the population of all cases, especially with a smaller number of complete cases.
Chronic risk factor and proximal causes were described in term of numbers and percentages among stillbirths and live births. Timing of stillbirth and timing of stillbirth specific chronic risk factors and proximal causes were evaluated comparing the median and the interquartile range of gestational age among stillbirths and live births. This approach was used to identify the useful timing of monitoring and intervention in decreasing stillbirth risks.
First, a logistic regression model was used to develop a model for prediction for stillbirths derived from chronic risk factors (Overall model). A nomogram for risk assessment of overall stillbirth was designed using a linear predictor method to assign points [155].
Second, the timing of stillbirth in relation to chronic risk factors and proximal causes were investigated by categorizing the outcome in three mutually exclusive groups: (i) stillbirths at weeks of gestation ≤32, (ii) stillbirths at weeks of gestation between 32 and 37, and (iii) stillbirths at weeks of gestation ≥37. Five multivariate distinct models for each categorization of the outcome were evaluated. The first one includes all chronic risks, and the remaining were performed separately for each proximal cause adjusted for maternal age and multiple births.
To assess the impact of increasing number of chronic risk factors on stillbirths, we classified women according to the number of chronic risk factors (zero, one, two, or ≥ three chronic risk factors). We contrasted the distribution of gestational age of stillbirths and live births among each group. A logistic regression model was used to develop a model for prediction for stillbirths derived from the number of chronic risk factors.

Results

Of the 486,518 pregnant women who were recorded to have given a birth in the delivery registry between January 1, 2005 and December 31, 2010, 1,517 (0.31%) were stillbirths. **Table 1** shows the descriptive characteristics of the study population. Roughly more than half of the women were 25 years or younger. Chronic risk factors and proximal causes were more likely to be recorded among women with a stillbirth, especially for gestational diabetes, multiple births, infection, abruption placentae, and fetal growth restriction. The distribution of gestational age was quite different among stillbirths and live births with a median and interquartile range of 35.0 (8.0) and 39.0 (2.0), respectively (**Figure 2**). **Figure 3** shows the timing of stillbirth specific risk factors. Neither the timing of chronic risk factors nor the timing of proximal causes were statistically different among stillbirths and live births. Chronic risk factors were ordered according to the median of timing of stillbirth.

A prediction model for overall stillbirth was developed considering all chronic risk factors. As we can see from the model (**Table 2**), risk for overall stillbirth was strongly associated with multiple births (OR, 6.93; 95% CI, 5.86-8.19), pre-gestational diabetes (2.06; 1.66-2.57) and gestational diabetes (1.48; 1.14-1.93), pre-existing hypertension (2.00; 1.55-2.06), and advanced maternal age (≥40 yr, 1.47; 1.22-1.77). Weaker associations were found for maternal age ≤25 years and between 35-39 years. Stillbirth can occur across the whole range of gestational age. As the primary means to prevent stillbirths is to deliver the baby, the consequences of inappropriate intervention differ profoundly throughout the gestational age. To understand which of the chronic risk factors and proximal causes are important to detect and prevent a stillbirth, and the best timing to detect these factors for an adequate intervention, we performed several models across different stages of gestational age. The risk factors that deserve attention, after advanced maternal age known as risk factor for stillbirth, are pre-existing hypertension, gestational diabetes, pre-eclampsia, infections, abruption placentae, and fetal growth restriction.

Chronic risk factors

Advanced maternal age

Advanced maternal age was considered as one of the most prevalent risk factors for stillbirth. Even after accounting for hypertension, diabetes, and multiple births, medical conditions that are more likely to occur an advanced age, advanced maternal age remains a significant risk factor throughout pregnancy resulting as an independent risk factor for stillbirth.

Hypertension and Diabetes

Hypertension and diabetes have been associated with an increased risk of stillbirth throughout pregnancy. It seems that the provision of quality preconception care for women with pre-existing hypertension and diabetes that guarantees a normal level for both the conditions should decrease the risk of stillbirth for these women [148]. Weight management, monitoring, and intervention to achieve optimum levels of glycemic control and blood pressure throughout pregnancy is crucial to ensuring the best possible outcomes for women with these diseases. Blood pressure seems to be more associated with stillbirths with week of gestation <37, whereas pre-gestational diabetes and gestational diabetes are more associated with stillbirths in late pregnancy (Table 2). Moreover, the optimal management of these diseases is crucial since they increase the risk of abruption placentae, intrauterine growth restriction, and preeclampsia; all medical and obstetrical conditions related to stillbirth [156-158].

Multiple births

Given the increased use of assisted reproductive technology, mostly in women of advanced maternal age, there is an increase in multiple births with a consequent increase in stillbirth. This variable plays an important role on the risk of stillbirth increasing the risk of 8-fold in women with multiple pregnancy compared with women with singleton pregnancy, throughout the whole pregnancy (Table 2).

Systemic Lupus Erythematosus

Systemic lupus erythematosus onsets in a very few pregnancies but the risk of stillbirth, especially those with weeks of gestation ≥37, is very high. Women affected with this disease are also more likely to have hypertension, preeclampsia, and fetal growth restriction [148]. It seems that the use of heparin and aspirin, which is considered the optimum management of patients with the systemic lupus erythematosus, was associated with an improved outcome [159].

Proximal causes

Hypertension and diabetes increased risk of abruption placentae, intrauterine growth restriction, and preeclampsia, which always necessitates early delivery increasing the risk of stillbirths. Stillbirth related to growth restriction and placenta disorder are the 2 categories of death that contribute the most to fetal losses. A significant risk factor for stillbirth, mainly in stillbirths at gestational age >32 weeks, are infections. Despite the adoption of a strategy to reduce the risk of infections, there is still a huge number of stillbirths due to these.

Number of Chronic Risk Factors

To assess the impact of the number of risk factors on timing of stillbirth we evaluated the timing of stillbirths among women with zero, one, two, or three or more chronic risk factors (**Figure 4**). The association between number of chronic risk factors and stillbirths are reported in **Table 3**. Unifying the results from Figure 4 and Table 3, it seems that there is an increased in risk of stillbirths directly proportional to the growth of the number of chronic risk factors, but this trend is not associated with the timing of stillbirth.

Discussion

Stillbirth is one of the most common adverse pregnancy outcomes worldwide and there is currently no method of screening the general population for stillbirth risk which has been shown to reduce perinatal mortality [160]. Stillbirth was associated with multiple maternal and pregnancy characteristics including maternal age, maternal medical complications, as well as obstetrical conditions. Identification and management of those medical and socioeconomic risk factors that contribute to stillbirth are important and gestational age at the time of intervention is crucial. Previous studies focused their attention on the causes of stillbirth looking at risk factors for that outcome. Our study was designed to evaluate timing of stillbirth and timing of stillbirth specific risk factors categorized by chronic risk factors and proximal causes. An early detection of specific risk factors could help clinicians in decreasing antepartum and intrapartum stillbirth risk through monitoring and timely intervention, as the gestational age at the decision of screening and intervention is crucial. We tried to capture information useful to the clinicians to perform a risk assessment for each individual patient, which could give realistic estimates of anticipated obstetric outcomes. The nomograms for risk assessment of overall stillbirth gave an easy direct interpretation of the impact that each chronic risk factor has on stillbirth. Multiple pregnancy and chronic and gestational medical conditions of the mother are the most important risk factors for the considered outcome (Supplementary material **Figure S1**) without affect the timing of stillbirth. Fretts et al, reviewed the causes of stillbirth by performing a systematic review of the literature. Our findings are in line with the findings from previous studies. Screening for hypertension and diabetes of course are essential to prevent stillbirths, but several other factors should be taken in consideration in any risk assessment. It should be useful to remember the increased risk of stillbirth in women with advance maternal age. Moreover, in the last 2 decades, the rate of pregnancies with multiple gestations in advanced maternal age women are increased considerably owed to the wide use of assisted reproductive technology, all conditions that increase the risk of stillbirth [161, 162]. Women with medical conditions and in advanced maternal age should be monitored to optimize their treatment and ensure fetal well-being.

In term of reducing potentially preventable stillbirth, an adequate intervention and monitoring for those women with a diagnosis of fetal growth restriction and abruption placentae should be considered. Deaths due to these obstetric conditions represent one of the most common types of stillbirth [163, 164].

However, it is also clear the impact that the number of chronic risk factors have on stillbirth without affecting the time of stillbirth. The risk of stillbirth increased in a directly proportional way to the growth of the number of chronic risk factors. We tried to capture if there was a path between the

presence of specific chronic risk factors (Supplementary material **Table S1**). Our results claim what was stated in previous studies showing an increased for the combination of advanced maternal age-multiple births, and advanced maternal age-use of assisted reproductive technology-multiple births.

To conclude, knowledge on timing of stillbirth and of stillbirth specific risk factors could help clinicians in an early detection of women at high-risk of stillbirth decreasing stillbirths risk through monitoring and timely intervention. A method of screening the general population for stillbirth risk should be implemented to prevent avoidable stillbirths. A useful information that we can capture from our results, is that all the chronic risk factors and proximal causes that we considered increase the risk of stillbirth but they do not affect the timing of stillbirths. It means that screening for the chronic risk factors, as proximal causes are almost always a consequence of them, are essential to prevent stillbirth.

Figure 13. Study Cohort

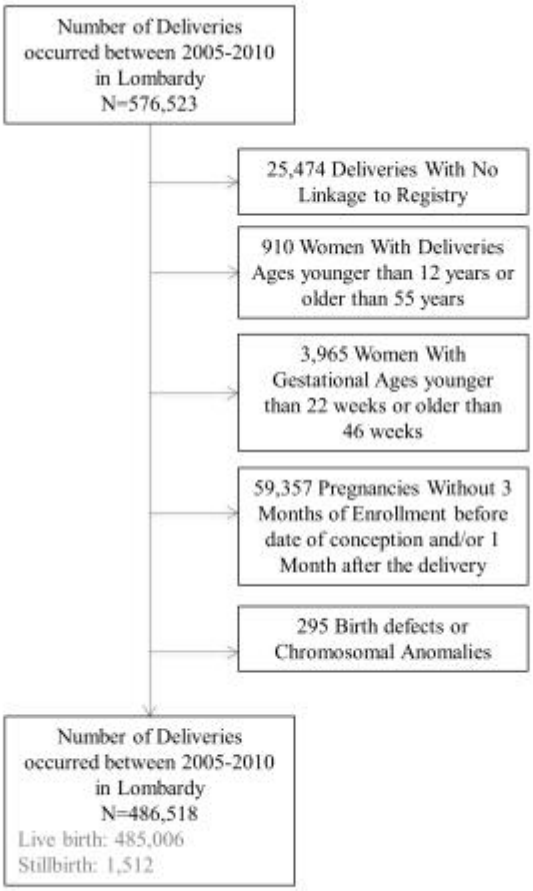


Table 9. Distribution of maternal characteristics among live births and stillbirth. Lombardy, 2005-2010

	Stillbirth		**Live birth**	
	n= 1512		n= 485 006	
Weeks' gestation - no. (%)				
<32	472	(31.22)	3631	(0.75)
32-37	423	(27.98)	26 645	(5.49)
≥37	617	(40.81)	454 730	(93.76)
Chronic risk Factors				
Maternal Age - no. (%)				
≤25 yr	787	(52.05)	277 369	(57.19)
26-34 yr	436	(28.84)	130 655	(26.94)
35-39 yr	161	(10.65)	48 400	(9.98)
≥40 yr	128	(8.47)	28 582	(5.89)
Use of Assisted Reproductive Technology - no. (%)	44	(2.91)	6730	(1.39)
Pre-existing hypertension - no. (%)§	64	(4.23)	8684	(1.79)
Gestational hypertension - no. (%)§	61	(4.03)	10 719	(2.21)
Pre-gestational diabetes - no. (%)s§	26	(1.72)	3974	(0.82)
Gestational diabetes - no. (%)§	93	(6.15)	13 019	(2.68)
Systematic Lupus Erythematosus - no. (%)§	3	(0.2)	361	(0.07)
Multiple births - no. (%)§	171	(11.31)	8610	(1.78)
Proximal Causes				
Preeclampsia - no. (%)§	89	(5.89)	11 847	(2.44)
Infection - no. (%)§	108	(7.14)	18 867	(3.89)
Abruption Placentae - no. (%)§	136	(8.99)	4208	(0.87)
Fetal Growth Restriction - no. (%)§	254	(16.8)	21 424	(4.42)

§ from LMP+91day through delivery date+30day

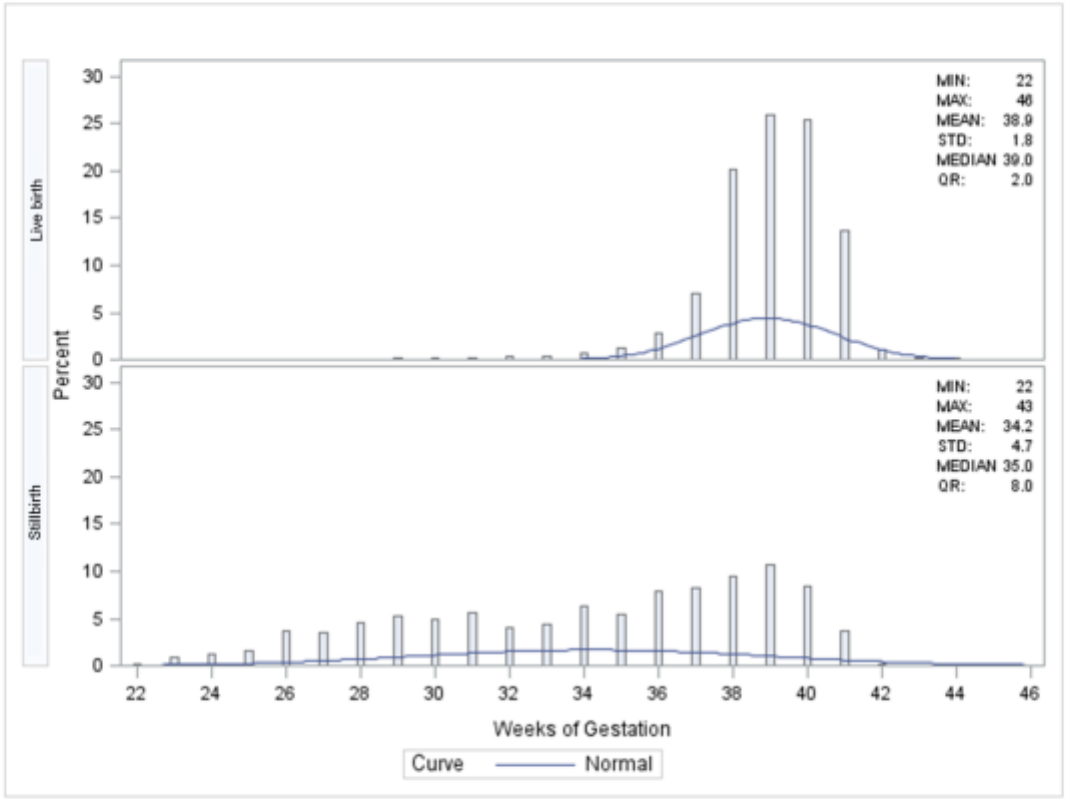


Figure 14. Distribution of Gestational Age in Live birth and Stillbirth. Lombardy 2005-2010.

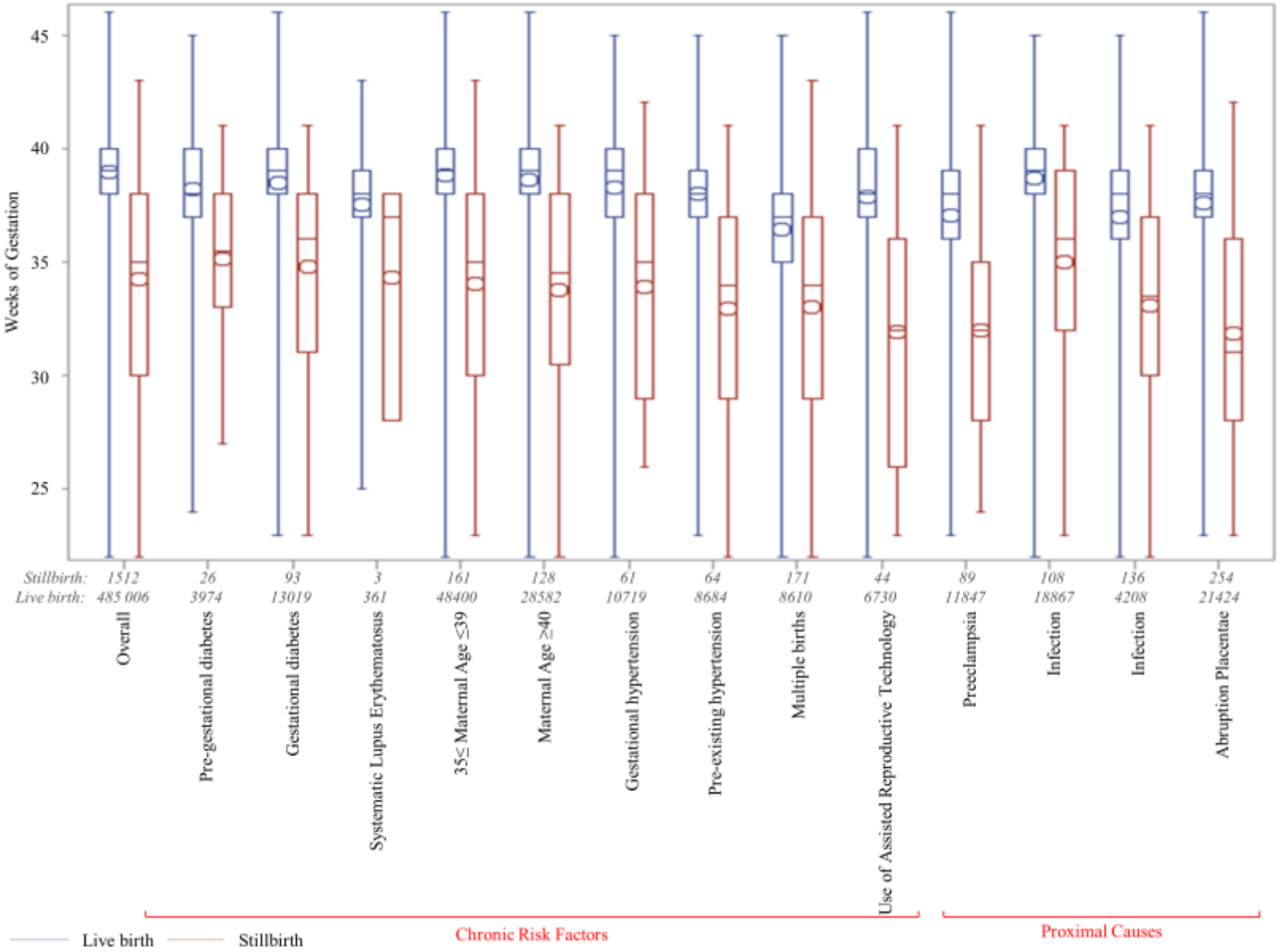


Figure 15. Timing of Stillbirth specific risk factors. Lombardy 2005-2010.

Table 10. Association between maternal factors and stillbirths. Lombardy, 2005-2010

Stillbirths at:	Overall		Weeks' Gestation ≤32		32< Weeks' Gestation <37		Weeks' Gestation ≥37	
Characteristics	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Chronic Risk Factors‡								
Maternal Age								
≤25 yr	1.23	(1.04-1.46)	1.28	(0.94-1.73)	1.26	(0.91-1.75)	1.19	(0.92-1.54)
26-34 yr		Ref.		Ref.		Ref.		Ref.
35-39 yr	1.14	(1.01-1.28)	1.24	(1.01-1.53)	1.25	(1.00-1.55)	1.01	(0.83-1.21)
≥40 yr	1.47	(1.22-1.77)	1.36	(0.96-1.93)	1.93	(1.40-2.67)	1.3	(0.95-1.77)
Use of Assisted Reproductive Technology	1.01	(0.74-1.38)	1.35	(0.84-2.18)	1.03	(0.59-1.80)	0.81	(0.43-1.54)
Pre-existing hypertension	2.00	(1.55-2.06)	2.42	(1.58-3.71)	2.41	(1.53-3.79)	1.58	(0.99-2.52)
Gestational hypertension	1.48	(1.14-1.93)	1.67	(1.07-2.59)	1.12	(0.65-1.93)	1.72	(1.14-2.59)
Pre-gestational diabetes	1.41	(0.94-2.11)	1.04	(0.46-2.39)	1.62	(0.81-3.24)	1.65	(0.89-3.07)
Gestational diabetes	2.06	(1.66-2.57)	1.84	(1.22-2.76)	2.29	(1.55-3.39)	2.12	(1.50-3.00)
Systematic Lupus Erythematosus	2.29	(0.73-7.17)	2.33	(0.32-16.68)	-	-	4.86	(1.2-19.64)
Multiple births	6.93	(5.86-8.19)	8.14	(6.16-10.75)	8.77	(6.54-11.75)	8.09	(6.00-10.92)
Proximal Causes†								
Preeclampsia			3.18	(2.29-4.41)	3.68	(2.64-5.13)	0.82	(0.44-1.53)
Infection			1.32	(0.87-1.99)	2.09	(1.46-2.98)	2.27	(1.70-3.02)
Abruption Placentae			11.76	(8.70-15.91)	16.59	(12.39-22.21)	8.97	(6.36-12.65)
Fetal Growth Restriction			7.41	(6.05-9.09)	4.61	(3.61-5.9)	1.79	(1.31-2.46)

‡ Odds ratios were adjusted for the Chronic Risk Factors

† Odds ratios were adjusted for maternal age and multiple births

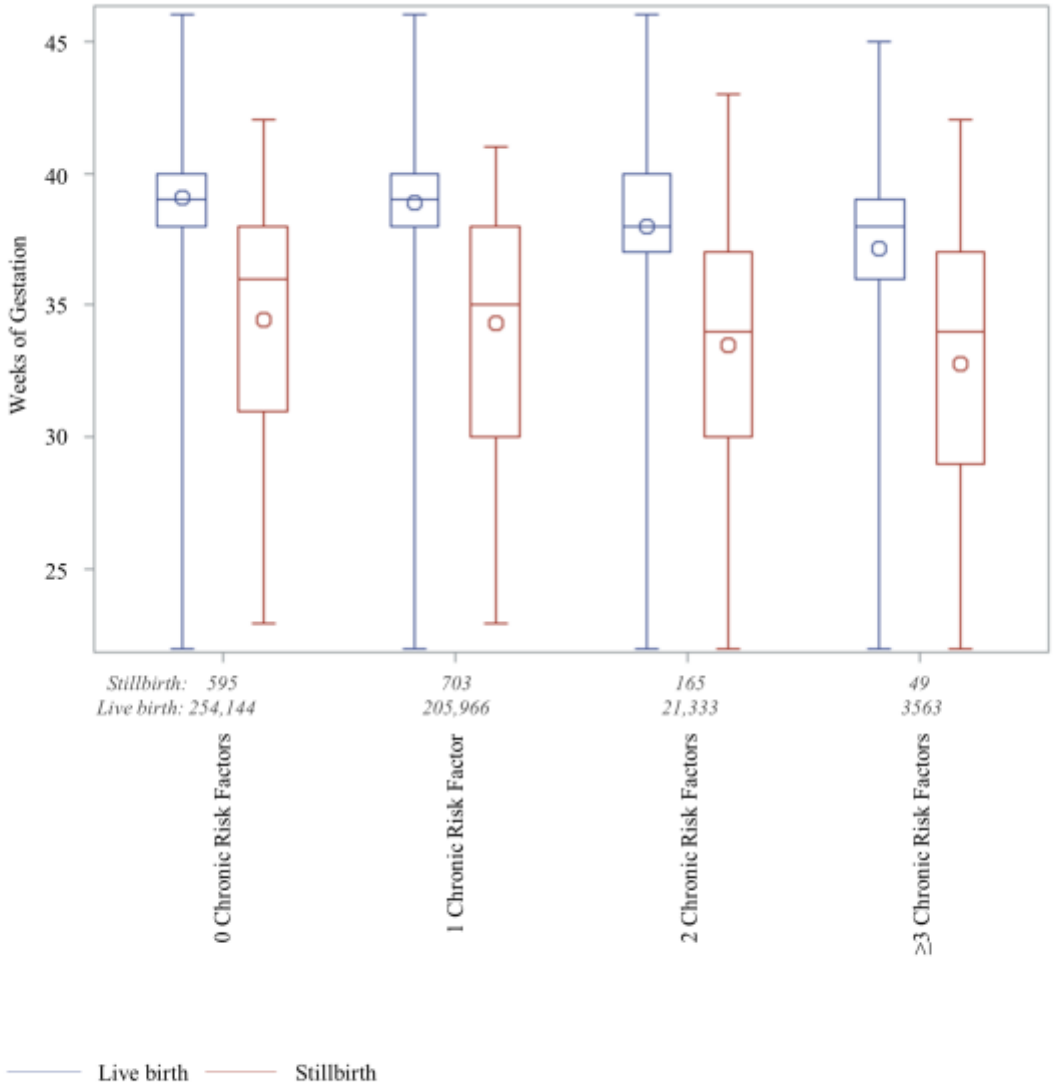


Figure 16. Gestational Age at Stillbirth among number of Chronic Risk Factors. Lombardy 2005-2010.

Table 11. Association between no. of Chronic Risk Factors and Stillbirths. Lombardy, 2005-2010

	Stillbirths at:	Overall	
Characteristics		**OR**	**(95% CI)**
0 Chronic Risk Factors		Ref.	
1 Chronic Risk Factor		1.46	(1.31-1.63)
2 Chronic Risk Factors		3.30	(2.78-3.93)
≥3 Chronic Risk Factors		5.88	(4.39-7.88)

Supplementary Materials

Figure S5. Nomogram for Risk Assessment of Overall Stillbirth. Lombardy 2005-2010.

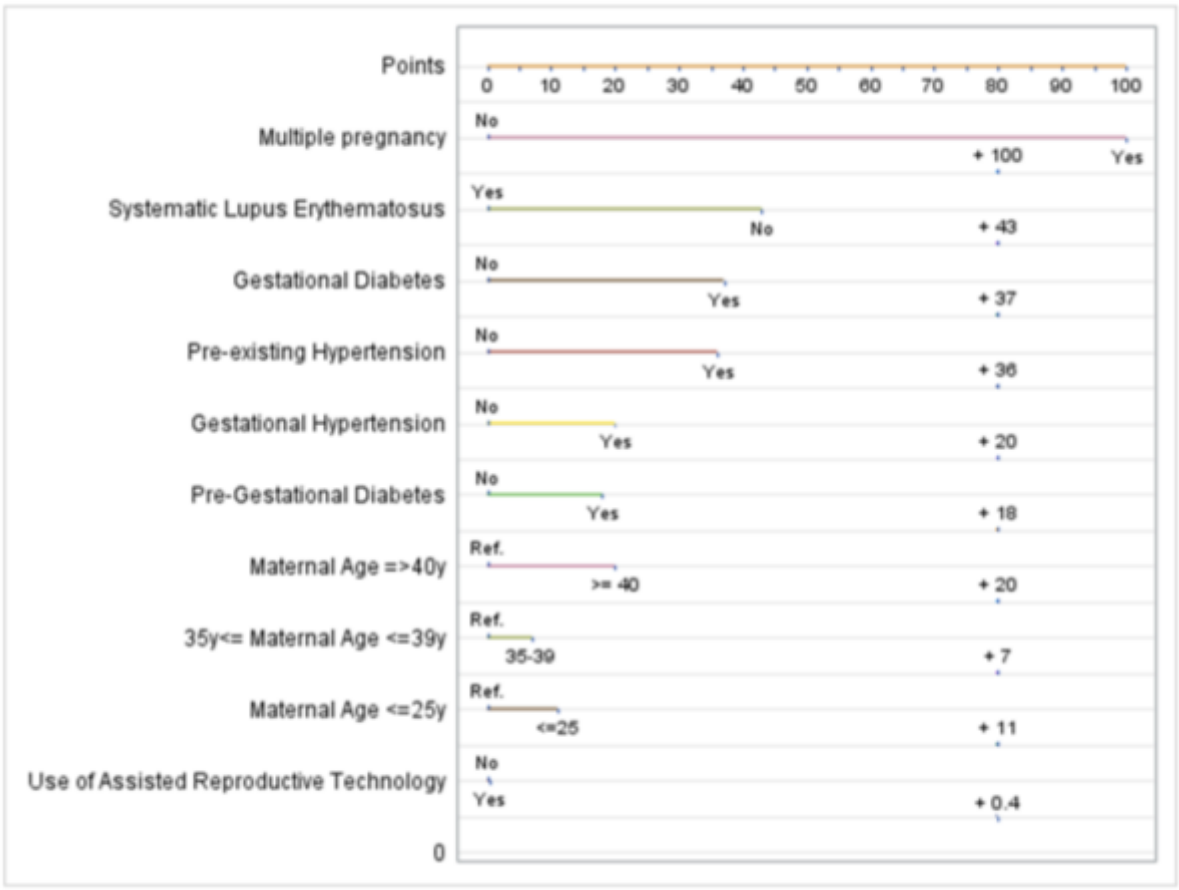
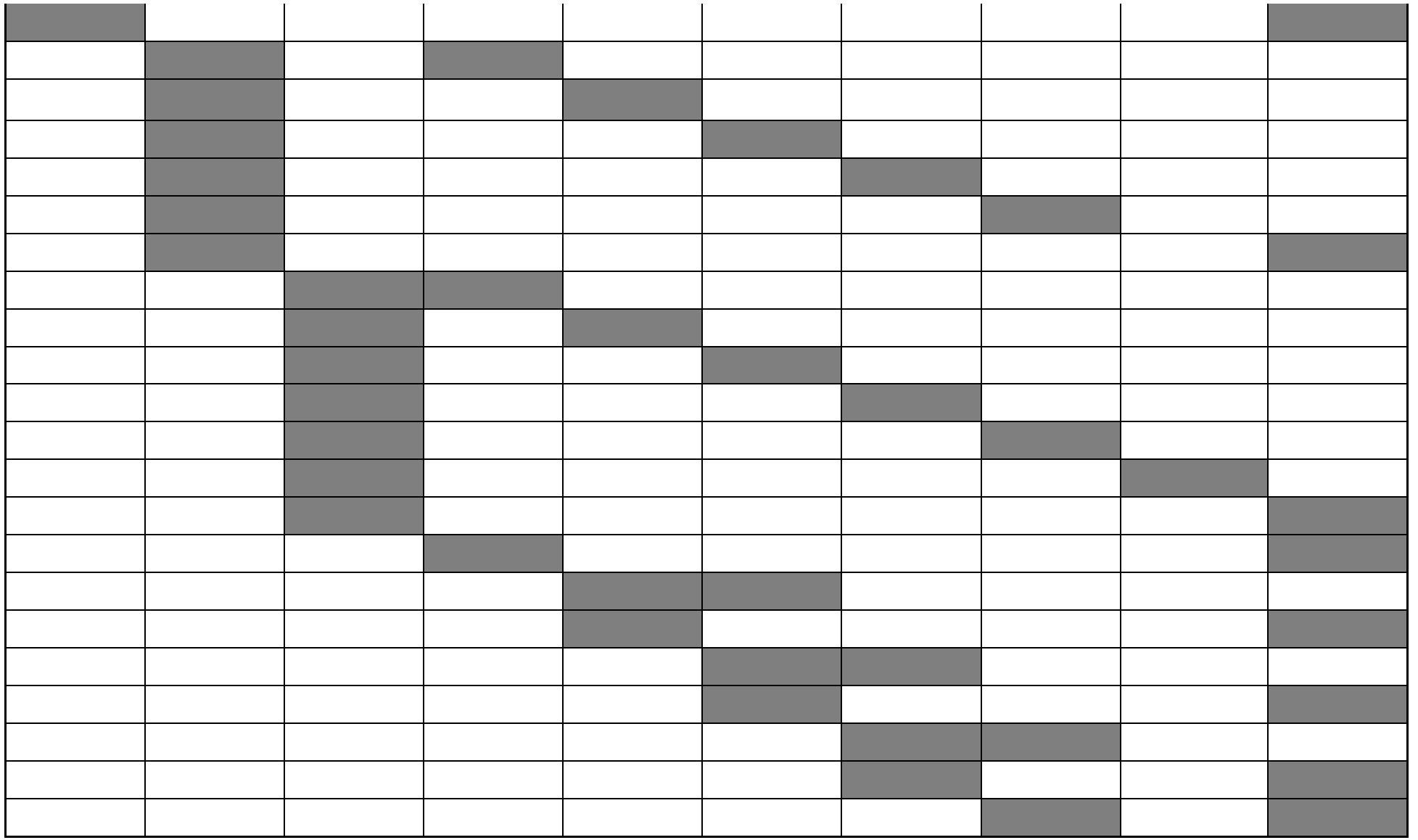


Table S5. All possible combination of Chronic Risk Factors

Maternal Age ≤25 yr	Maternal Age 35-39 yr	Maternal Age ≥40 yr	Use of Assisted Reproductive Technology	Pre-existing hypertension	Gestational hypertension	Pre-gestational diabetes	Gestational diabetes	Systematic Lupus Erythematosus	Multiple births	
■										134
	■									318
		■								88
			■							8
				■						17
					■					22
						■				8
							■			39
								■		2
									■	67

Maternal Age ≤25 yr	Maternal Age 35-39 yr	Maternal Age ≥40 yr	Use of Assisted Reproductive Technology	Pre-existing hypertension	Gestational hypertension	Pre-gestational diabetes	Gestational diabetes	Systematic Lupus Erythematosus	Multiple births	
■				■						5
■					■					1
■						■				2
■							■			6



11
8
13
6
3
16
42
2
5
2
1
6
1
12
5
5
1
1
4
4
1
2

Maternal Age ≤25 yr	Maternal Age 35-39 yr	Maternal Age ≥40 yr	Use of Assisted Reproductive Technology	Pre-existing hypertension	Gestational hypertension	Pre-gestational diabetes	Gestational diabetes	Systematic Lupus Erythematosus	Multiple births	
■						■	■			1
■							■		■	1
	■		■		■					1
	■		■				■			1
	■		■						■	10
	■			■	■					5
	■			■			■			1
	■			■					■	1
	■				■		■			3
	■				■				■	3
	■					■	■			3
	■						■		■	1
		■	■						■	4
		■		■			■			2
		■		■					■	1
			■	■						1
			■			■	■			1
				■	■		■			3
					■	■	■			1

Maternal Age ≤25 yr	Maternal Age 35-39 yr	Maternal Age ≥40 yr	Use of Assisted Reproductive Technology	Pre-existing hypertension	Gestational hypertension	Pre-gestational diabetes	Gestational diabetes	Systematic Lupus Erythematosus	Multiple births	
										1
										1
										1

Maternal Age ≤25 yr	Maternal Age 35-39 yr	Maternal Age ≥40 yr	Use of Assisted Reproductive Technology	Pre-existing hypertension	Gestational hypertension	Pre-gestational diabetes	Gestational diabetes	Systematic Lupus Erythematosus	Multiple births	
										1
										1

V. Discussion

The aim of my thesis is to identify factors to develop and improve the health care related to maternal-fetal and maternal-child world (before and after birth, respectively) from a sociodemographic, farmacoepidemiology, and clinical point of view.

The sociodemographic aspect analysis shows that, despite the availability of essential healthcare services at no out-of-pocket expense, the mother's education and other socioeconomic factors are strongly associated with some adverse perinatal outcomes, including preterm birth, low Apgar score, cerebral distress, respiratory distress, and SGA. From a public health perspective, more attention should be given to the wider social determinants of health, such as maternal education. Improvements in the level and quality of antenatal and obstetric instructions should be made so as to reduce several neonatal outcomes. Future studies are encouraged to investigate factors mediating the effects of socioeconomic inequality on birth outcomes for identifying the main target groups for interventions.

Studies which focus on the use of antidepressants taken during pregnancy offer evidence that the prevalence of preterm birth and low birth weight is increased in pregnant women who use antidepressants during pregnancy compared to pregnant women who never use antidepressants. Furthermore, our findings suggest that the depression itself explains the observed preterm birth and low birth weight, possibly due to the effect of maternal unhealthy behaviour, such as smoking, alcohol abuse, unhealthy diet, and poor attendance at obstetric care.

Moreover, our data regarding drug utilization patterns in the real-world setting offer evidence that antidepressant medications taken during pregnancy increase the risk of low Apgar score, cerebral irritability, neonatal convulsion, intrauterine hypoxia and birth asphyxia, and other respiratory conditions. These effects are not negligible since, compared to newborns born from mothers who did not use antidepressants, the excess of risk ranged from 30% (intrauterine hypoxia and birth asphyxia) to 160% (cerebral irritability). It remains to be determined whether the use of maternal antidepressant medications is more beneficial or has adverse effects beyond the underlying depression. In the meantime, the clinician and the woman herself need to balance the degree of severity of the depressive disorder and the risk of relapse, with the emerging safety profile of antidepressant drugs.

The last study on antidepressants utilization developed the research by looking at the use in different stages of pregnancy. Our results state that the use of antidepressants late in pregnancy, but not in early

pregnancy, increases the risk of low Apgar score. This effect seems to be attributable to the treatment and not to the disease itself. Adequate controls regarding maternal smoking and other life style factors should be carried out to clarify the relationships between depression, antidepressant treatment, and low Apgar score. Such controls will provide useful information for clinicians and their patients on the use of antidepressant medication during pregnancy.

The last study adds knowledge in one of the most important challenges of public health: how to end preventable stillbirth. Evidences on timing of stillbirth and of stillbirth specific risk factors could help clinicians with an early detection of women at high-risk of stillbirth decreasing stillbirth risk through monitoring and timely intervention. Most stillbirths should be preventable by introducing a method of screening the general population for stillbirth risk and improving quality health care during pregnancy. A piece of useful information which we can gain from our results is that all the chronic risk factors and proximal causes that we considered increase the risk of stillbirth but they do not affect the timing of stillbirths. This means that screening for chronic risk factors as well as screening for proximal causes, which are almost always a consequence of chronic risk factors, are essential to prevent stillbirth.

The Partnership for Maternal and Child Health brings together more than 260 member organizations worldwide working together to achieve the Millennium Development Goals 4 and 5 for the survival of children and women's health.
In September 2007, a new and important opportunity for global health was introduced with the launch of the Global Campaign for the Health MDGs, a campaign created to align governments and donors on a national and strengthening health service plan with particular attention to the accessibility of its services for women and children. Jens Stoltenberg, Prime Minister of Norway, has committed to allocate a billion dollars for maternal and child health for ten years and, in order to give greater impetus, he has created a Network of Global Leaders, which includes more than 10 heads of state.

To conclude, Maternal and Child health is a priority area of public health and investments, projects, energy and commitment are required and necessary in order to reach all the targets of an efficient health systems that focuses on high-service interventions, remove barriers that may impede access to health for all women and children, and monitor adherence to achieving the results.

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