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Maternal medically diagnosed infection and antibiotic prescription during pregnancy and risk of childhood cancer: A population-based cohort study in Taiwan, 2004 to 2015

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Abstract

While associations between maternal infections during pregnancy and childhood leukemia in offspring have been extensively studied, the evidence for other types of childhood cancers is limited. Additionally, antibiotic exposure during pregnancy could potentially increase the risk of childhood cancers. Our study investigates associations between maternal infections and antibiotic prescriptions during pregnancy and the risk of childhood cancer in Taiwan. We conducted a population-based cohort study using the Taiwan Maternal and Child Health Database (TMCHD), linked with national health and cancer registries. The study included 2 267 186 mother-child pairs, and the median follow-up time was 7.96 years. Cox proportional hazard models were utilized to estimate effects. Maternal infections during pregnancy were associated with a moderate increase in the risk of childhood hepatoblastoma (adjusted hazard ratio [HR] = 1.34; 95% confidence interval [CI]: 0.90-1.98) and a weaker increase in the risk of childhood acute lymphoblastic leukemia (ALL) (adjusted HR = 1.15; 95% CI: 0.99-1.35). Antibiotic prescriptions during pregnancy were also associated with an elevated risk of childhood ALL (adjusted HR = 1.30; 95% CI: 1.04-1.63), particularly with tetracyclines (adjusted HR = 2.15; 95% CI: 1.34-3.45). Several specific antibiotics were also associated with an increased risk of hepatoblastoma and medulloblastoma. Children exposed in utero to antibiotic prescription or both infections and antibiotics during pregnancy were at higher risk of developing ALL. Our findings suggest that there are associations between maternal infections, antibiotic use during pregnancy and the risk of several childhood cancers in addition to ALL and highlight the importance of further research in this area.

KEYWORDS
antibiotic, childhood cancer, cohort study, infection, pregnancy

Abbreviations: ALL, acute lymphoblastic leukemia; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; ICD, International Classification of Diseases; ICD-9, International Classification of Diseases, Revision 9; ICD-10, International Classification of Diseases, Revision 10; ID, identification; IQR, interquartile range; NIRD, National Insurance Research Database; TMCHD, Taiwan Maternal and Child Health Database; TWD, Taiwan dollar.

What's new?

Maternal infection and antibiotic exposure during pregnancy are potential risk factors for childhood cancer. Previous studies of possible associations between these factors and childhood cancer risk, however, have focused mainly on European and U.S. populations. Here, relationships between childhood cancer and medically diagnosed maternal infection and antibiotic use during pregnancy were explored in a Taiwanese population. Analyses reveal moderate associations between maternal infection during pregnancy and childhood hepatoblastoma risk and risk of childhood acute lymphoblastic leukemia (ALL). Maternal use of certain antibiotics during pregnancy increased childhood hepatoblastoma and ALL risk, with ALL risk especially linked to maternal tetracycline use.

1 | INTRODUCTION

Potential links between maternal infections during pregnancy and childhood cancers, especially leukemia, have been the subject of investigations for a considerable period of time.[1-3] However, there remains limited evidence available regarding associations between maternal infections during pregnancy and less common types of cancers, such as central nervous system tumors, including medulloblastoma, and hepatoblastoma.[4-6] Additionally, there is concern that exposure to antibiotics during pregnancy may be a potential risk factor for some childhood cancers, either acting as a mediator of infection or as an independent cause of the cancer.[7-9]

Greaves studied the associations between infection and childhood acute lymphoblastic leukemia (ALL),[10] and developed a theory that ALL development occurs in two distinct stages: during fetal development and after birth.[10] This two-stage process is influenced by a combination of common infections and inherited genetic factors. While Greaves' theory highlighted the importance of common infections over specific types of infection,[10] several studies concentrated on specific groups of infections that occur during pregnancy, for instance, infections affecting the genitourinary tract, influenza and varicella were found to be associated to a higher risk of childhood leukemia.[1-3]

Similar to infections, maternal exposure to antibiotics during pregnancy has been extensively studied in relation to risk of childhood leukemia. However, most of the findings have not provided sufficient evidence to establish associations conclusively,[11,12] with only a few studies demonstrating moderate to strong links.[7,9] While the presence of infections can complicate the interpretation of these results due to confounding by indication for antibiotics, there remains a possibility that the antibiotics themselves contribute to the development of childhood cancer through different mechanisms. Certain types of antibacterials, such as some quinolones and metronidazole, have been shown to act as carcinogens or genotoxins in animal studies.[13,14] Furthermore, many antibiotics are considered nitrosatable drugs, which have been associated with certain types of childhood cancer.[15]

On the other hand, several studies explored the potential links between maternal infections during pregnancy and the risk of childhood brain and nervous system tumors, which represent the second most common type of childhood cancer. However, findings have been inconclusive due to limited statistical power.[4,6] Some studies have identified a positive association between viral infections during pregnancy and the risk of childhood nervous system tumors.[4,6] A case-control study reported an increase in risk of childhood brain tumors associated with influenza infection in pregnant women.[6] Additionally, research investigating the use of antibiotics by mothers during pregnancy has provided additional evidence for childhood brain tumor associations.[16]

Hepatoblastoma is more frequently observed in children in Taiwan compared to other populations,[17] which highlights the importance of studying the potential relationship with maternal infections and antibiotic prescriptions during pregnancy in this specific context. Additionally, a recent cohort study has reported associations between parental hepatitis B infection and risk of childhood hepatoblastoma.[18]

The objective of our study is to explore possible associations between maternal medically diagnosed infections and antibiotic prescriptions during pregnancy and the risk of childhood cancer in the Taiwanese population.

2 | METHODS

We performed a population-based cohort study using the Taiwan Maternal and Child Health Database (TMCHD). Established in 2004, this database contains information including health status and healthcare utilization of mothers and children born between 2004 and 2015, with a total population of 2 385 071 mother and child pairs.[19] The database was linked with the Registry for Beneficiaries of the National Insurance Research Database (NIRD) (2002-2017), Taiwanese Cancer Registry (1979-2017) and birth registry (2004-2015; Figure S1). Notably, the Taiwanese government has ensured universal healthcare coverage through the National Health Insurance Program since 1995, thus these datasets comprise information on >99% of Taiwanese residents, including inpatients, outpatients and prescription information. All of these datasets were accessed through the Health and Welfare Data Science Center, which operates under the Ministry of Health and Welfare in Taiwan.

Children who had incomplete information regarding their mother's identification (ID), International Classification of Diseases (ICD) code, age or sex at baseline were excluded from the analysis

(n = 17 174). Additionally, any children with missing or duplicated registration records were excluded (n = 73 718). Children born with extremely low birth weights (<500 g), who have a lower likelihood of surviving until the development of cancer, were also excluded from the analysis (n = 1071). Moreover, children diagnosed with Down syndrome, a condition strongly associated with specific cancer types,[20,21] were excluded from the analysis as well (n = 1006). Finally, children who had missing information regarding their mother's Anatomical Therapeutic Chemical (ATC) code (n = 24 916) were excluded due to uncertainty regarding their exposure status.

The presence of maternal infection during pregnancy was determined by extracting information from the linkage of TMCHD with the NIRD. Diagnoses recorded in the database were categorized using the International Classification of Diseases, Revision 9 (ICD-9) and Revision 10 (ICD-10) coding systems. Maternal infection diagnoses were grouped based on their type (viral or bacterial) and the affected organ system (such as the respiratory, enteric or urinary tract) using the categorization developed by Atladóttir et al.[22] (Table S1).

We determined exposure to antibiotics during pregnancy by utilizing the ATC code for antibacterials for systemic use (J01) and intestinal anti-infectives (A07A). The specific subcategories of antibiotics are described in Table S2.

The exposure period was defined as the estimated date of conception until the date of birth. The estimated date of conception was calculated by subtracting the gestational age in days from the date of birth. Within this exposure period, episodes of infection were counted. If a pregnant woman received multiple diagnoses of the same disease within a span of 2 weeks, we considered it a single episode. To identify exposure status, we included both inpatient and outpatient diagnoses as well as primary and secondary ICD codes.

The main outcome of our study was the offspring's cancer diagnosis. The specific types of cancer that were of interest in our study were ALL, central nervous system (CNS) tumors (including medulloblastoma) and hepatoblastoma. We established a linkage between the databases above and the Taiwan Cancer Registry, which is a comprehensive and reliable population-based cancer registry.[23] This linkage allowed us to identify children within the database who were diagnosed with cancer between 2004 and 2017.

Cox proportional hazard models with age (in days) as the time scale were used to estimate effects for medically diagnosed infections and antibiotic prescriptions during pregnancy and the risk of childhood cancer. Premature death was treated as a censoring event, and we assumed the independency of this completing risk. Additional analyses were conducted to explore the number of infection episodes, both as categorical variables (0, 1, 2-3 and 4 or more episodes) and as a continuous variable. We also examined the combined effects of infections and antibiotic exposure during pregnancy in separate models, using those without infections and antibiotic use during pregnancy as the reference group.

Based on modified disjunctive cause criteria,[24] we adjusted all models for birth year, sex, maternal age in years, family income (divided into quartiles), urbanization level (categorized as high, middle or low) and parity (categorized as 1, 2 or 3 or more). Some of these factors including child's age (as birth year) and sex,[25-27] maternal age[21,28-30] and parity[26,27] have been suggested as potential risk factors for certain types of childhood cancer. Family income and urbanization level were considered proxies for confounding by socioeconomic status.[26,31] Furthermore, some factors, such as birth year, parity, family income and urbanization level, may be associated with exposures of interest, that is, infections and antibiotic use during pregnancy in our study population. We ensured the proportional-hazards assumption was met through graphical evaluation. Models with fewer than five exposed cases are not being presented due to the limited number of events occurring. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Table 1 shows the general characteristics of the maternal and child cohort. A total of 2 292 102 individuals were initially considered eligible for the study. After excluding those with incomplete information regarding maternal exposure during pregnancy (n = 24 916), the final analysis includes 2 267 186 participants (Figure S1). The median follow-up time for children after live birth was 7.96 years (interquartile range [IQR] = 6.2 years) while the median age at cancer diagnosis was 2.72 years (IQR = 4.06 years).

We observed a moderate increase in the risk of childhood hepatoblastoma among children whose mothers were diagnosed with infections during pregnancy, but the confidence interval was wide and included the null (adjusted hazard ratio [HR] = 1.34; 95% confidence interval [CI] 0.90-1.98). Similarly, we found a small increase in the risk of childhood ALL among children whose mothers had an infection during pregnancy (adjusted HR = 1.15; 95% CI: 0.99-1.35). However, we did not observe an association between any type of infection during pregnancy and the risk of childhood CNS tumors or medulloblastoma. Additionally, while for some of the specific types of infection we saw positive associations with the four types of childhood cancers examined, the data were not informative enough to draw firm conclusions (see Table 2).

Table 3 shows an increased risk of childhood ALL among children whose mothers were prescribed antibiotics during pregnancy (adjusted HR = 1.30; 95% CI: 1.04-1.63). The association was even stronger for children whose mothers were prescribed tetracyclines during pregnancy (adjusted HR = 2.15; 95% CI: 1.34-3.45). The use of aminoglycosides during pregnancy was associated with an increased risk of hepatoblastoma in offspring (adjusted HR = 2.05; 95% CI: 1.11-3.80), as were other antibacterials with different modes of action not classified in the preceding groups (adjusted HR = 5.26; 95% CI: 2.29-12.12). However, there was not sufficient evidence to conclusively establish an association between antibiotic prescriptions during pregnancy and childhood CNS tumors including medulloblastoma.

In Table 4, we show our results from examining relationships between medically diagnosed infections, antibiotic prescriptions during pregnancy and the risk of childhood cancer. Compared to mothers without exposure to either risk factor, children whose mothers had

TABLE 1 General characteristics of study population in Taiwan, 2004 to 2015.

		Infection during pregnancy[a]		Antibiotic prescription during pregnancy[a]	
	Total	Yes	No	Yes	No
Number	2 292 102	1 552 387	714 799	1 942 047	325 139
Acute lymphoblastic leukemia	798	560	233	703	90
Central nervous system tumors	389	264	123	339	48
Hepatoblastoma	136	100	36	120	16
Medulloblastoma	86	56	30	79	7
Follow-up time (years), median (IQR)	7.96 (6.20)	7.79 (6.18)	8.19 (6.25)	8.06 (6.29)	7.27 (5.60)
Age at cancer diagnosis, cases only (years), n (%)					
0-4	2004 (73.17)	1372 (73.64)	617 (72.5)	1753 (73.29)	236 (73.29)
5-9	587 (21.43)	401 (21.52)	180 (21.15)	508 (21.24)	73 (22.67)
10-14	148 (5.40)	90 (4.83)	54 (6.35)	131 (5.48)	13 (4.04)
Age of cancer diagnosis (years), median (IQR)	2.72 (4.06)	2.69 (3.99)	2.82 (4.22)	2.74 (4.01)	2.62 (4.14)
Birth year, n (%)					
2004-2007	777 057 (33.90)	513 683 (33.09)	253 077 (35.41)	679 544 (34.99)	87 216 (26.82)
2008-2011	708 476 (30.91)	482 785 (31.10)	218 181 (30.52)	589 139 (30.34)	111 827 (34.39)
2012-2015	806 569 (35.19)	555 919 (35.81)	243 541 (34.07)	673 364 (34.67)	126 096 (38.78)
Sex, n (%)					
Male	1 190 872 (51.96)	806 321 (51.94)	371 478 (51.97)	1 012 177 (52.12)	165 622 (50.94)
Female	1 101 230 (48.04)	746 066 (48.06)	343 321 (48.03)	929 870 (47.88)	159 517 (49.06)
Mother's age (years), n (%)					
<30	1 051 675 (45.88)	732 339 (47.18)	307 024 (42.95)	894 288 (46.05)	145 075 (44.62)
30-<40	1 188 291 (51.84)	790 387 (50.91)	389 849 (54.54)	1 005 551 (51.78)	174 685 (53.73)
40 and over	47 901 (2.09)	29 661 (1.91)	17 926 (2.51)	42 208 (2.17)	5379 (1.65)
Missing	4235 (0.18)	—	—	—	—
Mother's age (years), mean (SD)	30.35 (4.84)	30.21 (4.83)	30.70 (4.85)	30.36 (4.87)	30.41 (4.64)
Family income (TWD), n (%)					
<30 759	550 262 (24.01)	367 159 (23.65)	165 012 (23.09)	462 285 (23.80)	69 886 (21.49)
30 759-48 200	547 531 (23.89)	391 347 (25.21)	152 727 (21.37)	475 623 (24.49)	68 451 (21.05)
48 200-73 317	553 224 (24.14)	381 587 (24.58)	169 424 (23.70)	471 106 (24.26)	79 905 (24.58)
≥73 317	550 296 (24.01)	351 074 (22.62)	198 421 (27.76)	454 377 (23.40)	95 118 (29.25)
Missing	90 789 (3.96)	61 220 (3.94)	29 215 (4.09)	78 656 (4.05)	11 779 (3.62)
Family income (TWD), mean (SD)	54 584.00 (36 075.91)	53 724.22 (34 738.74)	57 644.25 (38 512.93)	54 244.65 (35 557.11)	59 205.91 (38 360.35)
Urbanization level of inhabited area, n (%)					
High	1 220 489 (53.25)	805 893 (51.91)	400 731 (56.06)	1 022 627 (52.66)	183 997 (56.59)
Middle	861 047 (37.57)	595 854 (38.38)	256 386 (35.87)	732 517 (37.72)	119 723 (36.82)
Low	209 813 (9.15)	150 089 (9.67)	57 485 (8.04)	186 289 (9.59)	21 285 (6.55)
Missing	753 (0.03)	551 (0.04)	197 (0.03)	614 (0.03)	134 (0.04)

TABLE 1 (Continued)

	Total	Infection during pregnancy[a]		Antibiotic prescription during pregnancy[a]	
		Yes	No	Yes	No
Parity, n (%)					
1	922 928 (40.27)	610 804 (39.35)	296 657 (41.50)	793 062 (40.84)	114 399 (35.18)
2	1 125 093 (49.09)	771 525 (49.70)	345 264 (48.30)	944 665 (48.64)	172 124 (52.94)
3 or more	244 081 (10.65)	170 058 (10.95)	72 878 (10.20)	204 320 (10.52)	38 616 (11.88)

[a]Missing information on medical diagnoses and/or drug prescription (n = 24 916).

TABLE 2 Hazard ratios and 95% confidence intervals for the association between medically diagnosed infection during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015 (N = 2 267 186).

	Number of events	Incidence density rate (per 100 000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Noninfected cohort	233	4.07	Ref	Ref
Infected cohort, any type of infection	560	4.61	1.13 (0.97-1.31)	1.15 (0.99-1.35)
Viral infection	130	4.35	1.06 (0.85-1.31)	1.07 (0.86-1.34)
Bacterial infection	381	4.44	1.08 (0.92-1.27)	1.11 (0.94-1.32)
Respiratory infection	266	4.58	1.11 (0.93-1.33)	1.14 (0.95-1.36)
Enteric infection	23	6.09	1.49 (0.97-2.28)	1.60 (1.04-2.46)
Urinary tract infection	88	4.42	1.07 (0.84-1.36)	1.15 (0.89-1.47)
Central nervous system tumors				
Noninfected cohort	123	2.15	Ref	Ref
Infected cohort, any type of infection	264	2.17	1.01 (0.82-1.25)	0.98 (0.79-1.22)
Viral infection	76	2.54	1.18 (0.89-1.57)	1.13 (0.84-1.52)
Bacterial infection	194	2.26	1.05 (0.84-1.31)	1.01 (0.80-1.28)
Respiratory infection	123	2.12	0.98 (0.76-1.26)	0.94 (0.73-1.22)
Enteric infection	6	1.59	0.74 (0.33-1.67)	0.74 (0.33-1.69)
Urinary tract infection	46	2.31	1.07 (0.76-1.50)	1.02 (0.72-1.46)
Hepatoblastoma				
Noninfected cohort	36	0.63	Ref	Ref
Infected cohort, any type of infection	100	0.82	1.28 (0.88-1.88)	1.34 (0.90-1.98)
Viral infection	28	0.94	1.45 (0.89-2.38)	1.54 (0.92-2.56)
Bacterial infection	65	0.76	1.18 (0.79-1.77)	1.25 (0.82-1.90)
Respiratory infection	42	0.72	1.12 (0.72-1.75)	1.18 (0.74-1.86)
Urinary tract infection	11	0.55	0.84 (0.43-1.65)	0.84 (0.41-1.71)
Medulloblastoma				
Noninfected cohort	30	0.52	Ref	Ref
Infected cohort, any type of infection	56	0.46	0.88 (0.57-1.37)	0.83 (0.53-1.29)
Viral infection	16	0.54	1.02 (0.56-1.87)	0.99 (0.54-1.82)
Bacterial infection	45	0.52	1.00 (0.63-1.59)	0.93 (0.58-1.48)
Respiratory infection	31	0.53	1.01 (0.61-1.68)	0.99 (0.60-1.64)
Urinary tract infection	15	0.75	1.45 (0.78-2.69)	1.28 (0.68-2.43)

Note: Number of hepatoblastoma and medulloblastoma cases exposed to enteric infections were ≤5.

[a]Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low) and parity (1, 2, ≥3).

TABLE 3 Hazard ratios and 95% confidence intervals for the association between antibiotic prescription during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015 (N = 2 267 186).

	Number of events	Incidence density rate (per 100 000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia				
Not prescribed antibiotics	90	3.73	Ref	Ref
Any type of antibiotics	703	4.55	1.25 (1.01-1.56)	1.30 (1.04-1.63)
Tetracyclines	23	7.46	2.09 (1.32-3.30)	2.15 (1.34-3.45)
Amphenicols	13	4.99	1.43 (0.80-2.57)	1.28 (0.67-2.42)
Beta-lactam antibacterials—penicillin	287	3.97	1.09 (0.86-1.38)	1.15 (0.90-1.47)
Other beta-lactam antibacterials	561	4.62	1.27 (1.02-1.59)	1.31 (1.04-1.65)
Sulfonamides and trimethoprim	11	4.68	1.34 (0.72-2.51)	1.42 (0.75-2.69)
Macrolides, lincosamides and streptogramins	79	4.33	1.22 (0.90-1.65)	1.30 (0.95-1.78)
Aminoglycoside antibacterials	178	4.29	1.19 (0.92-1.54)	1.18 (0.91-1.55)
Quinolone antibacterials	15	3.78	1.05 (0.61-1.82)	1.04 (0.59-1.84)
Other antibacterials	16	4.06	1.12 (0.66-1.90)	1.08 (0.61-1.91)
Intestinal anti-infectives	13	4.08	1.15 (0.64-2.06)	1.22 (0.67-2.21)
Central nervous system tumors				
Not prescribed antibiotics	48	1.99	Ref	Ref
Any type of antibiotics	339	2.19	1.12 (0.82-1.51)	1.16 (0.84-1.59)
Tetracyclines	6	1.95	1.04 (0.45-2.43)	0.74 (0.26-2.09)
Amphenicols	6	2.30	1.24 (0.53-2.90)	1.32 (0.55-3.15)
Beta-lactam antibacterials—penicillin	172	2.38	1.22 (0.88-1.67)	1.29 (0.92-1.80)
Other beta-lactam antibacterials	273	2.25	1.14 (0.84-1.55)	1.17 (0.85-1.62)
Sulfonamides and trimethoprim	7	2.98	1.60 (0.72-3.54)	1.43 (0.60-3.43)
Macrolides, lincosamides and streptogramins	33	1.81	0.95 (0.61-1.48)	0.93 (0.58-1.48)
Aminoglycoside antibacterials	95	2.29	1.18 (0.83-1.67)	1.26 (0.87-1.81)
Quinolone antibacterials	11	2.77	1.44 (0.75-2.77)	1.55 (0.79-3.03)
Other antibacterials	8	2.03	1.05 (0.50-2.22)	1.16 (0.54-2.48)
Hepatoblastoma				
Not prescribed antibiotics	16	0.66	Ref	Ref
Any type of antibiotics	120	0.78	1.25 (0.74-2.10)	1.37 (0.79-2.40)
Beta-lactam antibacterials—penicillin	53	0.73	1.17 (0.67-2.05)	1.34 (0.74-2.43)
Other beta-lactam antibacterials	105	0.86	1.38 (0.82-2.34)	1.50 (0.86-2.64)
Macrolides, lincosamides and streptogramins	16	0.88	1.48 (0.74-2.95)	2.03 (0.98-4.20)
Aminoglycoside antibacterials	44	1.06	1.75 (0.99-3.11)	2.05 (1.11-3.80)
Other antibacterials	10	2.54	4.06 (1.84-8.95)	5.26 (2.29-12.12)
Medulloblastoma				
Not prescribed antibiotics	7	0.29	Ref	Ref
Any type of antibiotics	79	0.51	1.77 (0.82-3.84)	1.96 (0.85-4.51)
Beta-lactam antibacterials—penicillin	44	0.61	2.08 (0.94-4.62)	2.28 (0.96-5.38)
Other beta-lactam antibacterials	67	0.55	1.91 (0.88-4.16)	2.10 (0.91-4.85)
Macrolides, lincosamides and streptogramins	10	0.55	1.97 (0.75-5.18)	2.22 (0.80-6.18)
Aminoglycoside antibacterials	25	0.60	2.10 (0.91-4.85)	2.37 (0.96-5.83)

[a]Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low) and parity (1, 2, ≥3). Antibiotic exposures that had a low occurrence of ≤5 cancer cases were excluded.

received an antibiotic prescription only (without infection) were at an increased risk of developing ALL (adjusted HR = 1.53; 95% CI: 1.05-2.23). Similarly, children whose mothers had received both a medically diagnosed infection and an antibiotic prescription during pregnancy were also at increased risk of ALL (adjusted HR = 1.66; 95% CI: 1.16-2.38). However, our data did not allow us to examine

TABLE 4 Hazard ratios and 95% confidence intervals for the association between infection and antibiotic prescription during pregnancy and risk of childhood cancer in Taiwan, 2004 to 2015 (N = 2 267 186).

Infection	Prescribed antibiotics	Number of events	Incidence density rate (per 100 000 person-years)	HR (95% CI)	Adjusted HR (95% CI)[a]
Acute lymphoblastic leukemia					
No	No	36	3.16	Ref	Ref
No	Yes	197	4.29	1.41 (0.99-2.01)	1.53 (1.05-2.23)
Yes	No	54	4.25	1.34 (0.88-2.04)	1.47 (0.95-2.27)
Yes	Yes	506	4.65	1.51 (1.07-2.11)	1.66 (1.16-2.38)
Central nervous system tumors					
No	No	19	16.67	Ref	Ref
No	Yes	104	22.66	1.38 (0.85-2.25)	1.40 (0.85-2.31)
Yes	No	29	22.81	1.37 (0.77-2.44)	1.27 (0.70-2.32)
Yes	Yes	235	21.62	1.31 (0.82-2.09)	1.29 (0.80-2.09)

[a]Adjusted for birth year, sex, maternal age (years), family income (quartile), urbanization level (high, middle, low) and parity (1, 2, ≥3).

associations with other types of cancer (≤5 cases in reference group).

We lacked sufficient evidence to establish a linear relationship between the number of infection episodes during pregnancy and the risk of childhood cancer in offspring. While two to three episodes of infection during pregnancy were associated with an increased risk of ALL (adjusted HR = 1.24; 95% CI: 1.03-1.50), we saw weak to null associations for four or more episodes (adjusted HR = 1.11; 95% CI: 0.89-1.38) or one episode only (adjusted HR = 1.09; 95% CI: 0.90-1.32) compared to children of mothers never infected in pregnancy (Table S3).

4 | DISCUSSION

Maternal infections during pregnancy showed a moderate increase in the risk of childhood hepatoblastoma and a smaller increase in the risk of childhood ALL. Furthermore, having received an antibiotic prescription during pregnancy was associated with an elevated risk of childhood ALL, particularly for tetracyclines. Specific types of antibiotics were also found to be associated with an increased risk of hepatoblastoma. Furthermore, children whose mothers were exposed to an antibiotic prescription (without infection) or both infection and an antibiotic prescription during pregnancy were at higher risk of developing ALL. However, the number of infection episodes during pregnancy did not show a linear association with the risk of childhood cancer.

Interestingly, our findings suggest a relatively strong association with childhood ALL for mothers who were prescribed antibiotics during pregnancy even without having a maternal infection recorded in the medical records. This may suggest a potential direct effect of antibiotic exposure on the risk of ALL in offspring. As we observed that a relatively large proportion of participants (24.8%) had been prescribed antibiotics without a concomitant diagnosis for an infection, this may reflect at least some of these prescriptions having been given as prophylaxis in preparation for birth to prevent infections during the delivery process. This practice aligns with certain guidelines, including the prophylaxis strategy for preventing group B Streptococcus infection during pregnancy.[32-35] Although it is plausible that certain infections were diagnosed solely based on clinical symptoms without laboratory confirmation, the likelihood of prescriptions for antibiotics without clear indications in Taiwan is low. This is due to the fact that prescription practices are regulated by the national insurance system, which maintains stringent auditing standards within the healthcare system.[19] If these prescriptions indeed happened without an indication due to a pregnancy infection, they may suggest an independent direct effect of antibiotics on the risk of offspring ALL. Further studies are needed to investigate this possibility.

Our findings support previous research that found positive associations between common infections during pregnancy and the risk of childhood ALL.[1-3] A previous cohort study in Denmark observed an increased risk of childhood ALL among children born to mothers with infections during pregnancy (adjusted HR = 1.35; 95% CI: 1.04-1.77).[2] In our study, urinary tract infections did not seem to increase risk, but for enteric infections positive associations were suggested. While previous studies in European countries reported positive associations between maternal genitourinary tract infections during pregnancy and childhood ALL (with HR and OR ranging from 1.34 to 1.92),[2,3] a matched case-control study in California which collected data using self-report found no association (OR = 0.70; 95% CI: 0.42-1.17).[36] Variations in effect estimates for specific infection types and ALL may be random observations driven by small sample sizes for these subtypes.

We found a potential association between maternal infection during pregnancy, particularly viral infections, and the risk of childhood hepatoblastoma. This observation aligns with a previous cohort study conducted in Taiwan, which also suggested an association between aternal hepatitis B infection before childbirth and the risk of childhood

hepatoblastoma, although the confidence interval for the effect estimate was very wide (adjusted HR = 1.40; 95% CI: 0.56-3.52).[18] A small matched case-control study conducted in North America did not find a difference in the incidence of common infections (hepatitis, measles, mumps, influenza, chicken pox or infectious mononucleosis) or maternal antibiotic use during pregnancy and childhood cancers.[37]

A possible mechanism by which common infections during pregnancy may contribute to the risk of childhood ALL has proposed by Greaves.[10,38] In the case of hepatoblastoma, it would be plausible that a specific infection such as a viral hepatitis infection may either cause maternal immune dysregulation or infect fetal hepatocytes[39,40] consequently leading to mutations in liver cells as has been shown for adult hepatocellular carcinoma.[41,42]

Our results indicate that prescription of certain antibiotics during pregnancy, particularly tetracyclines, may increase the risk of childhood ALL. This aligns with previous research conducted in Denmark, Sweden and Canada reporting similar associations.[9,43] On the other hand, a study in the United Kingdom found a slightly negative or null association between systemic antibacterial use during pregnancy and childhood ALL (OR = 0.88; 95% CI: 0.72-1.07).[7] This highlights the need for further investigation of the relationship between antibiotic use during pregnancy and the risk of childhood leukemia. Notably, doxycycline, a commonly used drug from the tetracycline group, has been found to increase the average number of megakaryocytes and the periportal leukocytic infiltration in liver cells, as well as causing DNA damage, in a study on rat embryonic development.[44] Furthermore, doxycycline is considered a nitrosatable drug, and maternal prescriptions of nitrosatable drugs have also been associated with childhood ALL.[15]

While our findings should be considered exploratory, they suggest associations between the prescription of beta-lactam antibacterials (excluding penicillin) during pregnancy and the occurrence of childhood hepatoblastoma. In contrast, a cohort study conducted in Denmark and Sweden found no associations between maternal prescriptions of other beta-lactam antibacterials and the risk of childhood cancers (HR = 0.88; 95% CI: 0.50-1.57).[9] Instead, penicillin, particularly pivampicillin, were found to increase the risk of hepatic tumors in offspring (HR = 8.31; 95% CI: 2.88-23.99).[9] Cephalosporins, which are commonly used beta-lactam antibacterials, have long been considered safe for pregnant women.[45-47] To our knowledge, there is no specific evidence available regarding the teratogenic or carcinogenic effects of this group of medicines.

Our utilization of a data-linkage method that relies on comprehensive registries covering the entire population as a part of the national insurance program minimizes the potential for participation bias to occur. Furthermore, the integration of national insurance data enabled us to gather clinical diagnoses for infections and medical prescriptions independently and before the detection of cancer in the offspring. This eliminates any potential for recall bias and ensures a clear temporal relationship between the exposure and the outcome.

Nevertheless, the current study has certain limitations. While clinical diagnoses of infections were typically documented using a standardized coding system, it is likely that many common infections—especially those of viral origin—were diagnosed solely based on clinical presentation without being confirmed through laboratory testing. This may introduce exposure misclassification. However, such misclassification would have occurred regardless of outcome status and would therefore be nondifferential, leading most likely to a bias towards the null for binary exposures.

The presence of uncontrolled confounding is a possibility in our study due to incomplete information on certain factors, such as maternal vaccination and the use of over-the-counter supplements. These factors could potentially be associated with both certain types of cancer and the exposure status under investigation. However, since there are only a limited number of established causes for childhood cancers, the potential for uncontrolled confounding is minimal. It should be noted that vaccination rates among pregnant women in Taiwan appear to vary across diseases, ranging from 20% to 70%.[48-51]

Studies focusing on prenatal exposure and its impact on postnatal outcomes may encounter live birth bias.[52] This bias arises because childhood cancers are only identified in children who were born alive,[52] while certain infections and antibiotic usage during pregnancy have been linked to congenital malformations that are also associated with higher rates of fetal loss and stillbirth.[53,54] This bias may, for example, explain the inverted U-shaped association in our study with an increasing number of infections during pregnancy. Nevertheless, the magnitude of this type of bias may be small.

Additionally, premature death could be an event competing with the risk of a childhood cancer diagnosis. Our primary focus was to investigate risk factors for childhood cancer and using the Cox model assumes independent censoring. However, as child mortality is rare in Taiwan,[55] any bias due to dependent censoring is likely minimal.

Despite the inclusion of a substantial number of mother and child pairs in our cohort, we are investigating rare diseases such that our sample size is nevertheless limited especially for certain cancer types and specific subcategories of exposure. Another limitation of our study is the issue of multiple comparisons. However, it is worth noting that the majority of associations observed in our study align with those previously reported in the existing literature.

5 | CONCLUSION

This large population-based cohort study confirmed that there are some associations between infections and antibiotic exposure during pregnancy and childhood ALL. We also found some associations for specific types of antibiotic prescriptions and hepatoblastoma, but future investigations are required to confirm these results.

AUTHOR CONTRIBUTIONS

Anupong Sirirungreung: Drafted the article; Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. **Pei-Chen Lee:** Designed the study; Took responsibility for data acquisition, the integrity of the data and the accuracy of the data analysis; Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. **Ya-Hui Hu:** Took responsibility for data acquisition, the integrity of

the data and the accuracy of the data analysis; Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. **Zeyan Liew:** Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. **Beate Ritz:** Mentored Anupong Sirirungreung and revised the article; Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. **Julia E. Heck:** Designed the study; Responsible for the analysis plan, result interpretation and critical revision of the article for intellectual content. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Our study is based on deidentified information from Taiwan national health insurance and registries, and permission is required before data access. Further details are available from the corresponding author upon request.

ETHICS STATEMENT

Our study was approved by Office of the Human Research Protection Program, University of California, Los Angeles (IRB#17-000807), and the Institutional Review Board of the Taipei City Hospital, Taipei. Taiwan. (TCHIRB-11103001-E).

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REFERENCES

1. He JR, Ramakrishnan R, Hirst JE, et al. Maternal infection in pregnancy and childhood leukemia: a systematic review and meta-analysis. *J Pediatr*. 2020;217(8):98-109. doi:10.1016/j.jpeds.2019.10.046
2. He JR, Yu Y, Fang F, et al. Evaluation of maternal infection during pregnancy and childhood leukemia among offspring in Denmark. *JAMA Netw Open*. 2023;6(2):e230133. doi:10.1001/JAMANETWORKOPEN.2023.0133
3. He JR, Hirst JE, Tikellis G, et al. Common maternal infections during pregnancy and childhood leukaemia in the offspring: findings from six international birth cohorts. *Int J Epidemiol*. 2022;51(3):769-777. doi:10.1093/ije/dyab199
4. Fear NT, Roman E, Ansell P, Bull D. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control*. 2001;12(5):443-449. doi:10.1023/A:1011201524589
5. Linet MS, Gridley G, Cnattingius S, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control*. 1996;7(4):437-448. doi:10.1007/BF00052670
6. Linos A, Kardara M, Kosmidis H, et al. Reported influenza in pregnancy and childhood tumour. *Eur J Epidemiol*. 1998;14(5):471-475. doi:10.1023/A:1007437200858
7. Bonaventure A, Simpson J, Ansell P, Roman E, Lightfoot T. Prescription drug use during pregnancy and risk of childhood cancer – is there an association? *Cancer Epidemiol*. 2015;39(1):73-78. doi:10.1016/J.CANEP.2014.10.008
8. Kaatsch P, Scheidemann-Wesp U, Schüz J. Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. *Cancer Causes Control*. 2010;21(8):1335-1345. doi:10.1007/S10552-010-9561-2
9. Momen NC, Olsen J, Gissler M, Kieler H, Haglund B, Li J. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiol Drug Saf*. 2015;24(8):821-829. doi:10.1002/PDS.3806
10. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2018;18(8):471-484. doi:10.1038/S41568-018-0015-6
11. Ye X, Monchka BA, Righolt CH, Mahmud SM. Maternal use of antibiotics and cancer incidence risk in offspring: a population-based cohort study in Manitoba, Canada. *Cancer Med*. 2019;8(11):5367-5372. doi:10.1002/CAM4.2412
12. Hjorth S, Pottegård A, Broe A, et al. Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries. *Int J Epidemiol*. 2022;51(3):778-788. doi:10.1093/IJE/DYAB219
13. Garry VF, Nelson RL. Host-mediated transformation: metronidazole. *Mutat Res Lett*. 1987;190(4):289-295. doi:10.1016/0165-7992(87)90011-X
14. Itoh T, Moto M, Takahashi M, Sakai H, Mitsumori K. Liver initiation activity of norfloxacin but not nalidixic acid, pipemidic acid, and ciprofloxacin on in vivo short-term liver initiation assay in rats. *Toxicology*. 2006;222(3):240-246. doi:10.1016/J.TOX.2006.02.019
15. Sirirungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: a matched case-control study in Denmark, 1996-2016. *Pharmacoepidemiol Drug Saf*. 2023;32(4):496-505. doi:10.1002/PDS.5557
16. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control*. 2006;17(10):1267-1274. doi:10.1007/S10552-006-0066-Y/TABLES/3
17. Liu YL, Lo WC, Chiang CJ, et al. Incidence of cancer in children aged 0-14 years in Taiwan, 1996-2010. *Cancer Epidemiol*. 2015;39(1):21-28. doi:10.1016/J.CANEP.2014.11.010
18. Heck JE, Wu CK, Huang X, et al. Cohort study of familial viral hepatitis and risks of paediatric cancers. *Int J Epidemiol*. 2022;51(2):448-457. doi:10.1093/IJE/DYAB262
19. Li CY, Chen LH, Chiou MJ, Liang FW, Lu TH. Set-up and future applications of the Taiwan Maternal and Child Health Database (TMCHD). *Taiwan J Publ Health*. 2016;35(2):209-220. doi:10.6288/TJPH201635104053
20. Mezei G, Sudan M, Izraeli S, Kheifets L. Epidemiology of childhood leukemia in the presence and absence of Down syndrome. *Cancer Epidemiol*. 2014;38(5):479-489. doi:10.1016/j.canep.2014.07.006
21. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*. 2001;30(6):1428-1437. doi:10.1093/IJE/30.6.1428
22. Atladóttir HO, Thorsen P, Østergaard L, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord*. 2010;40(12):1423-1430. doi:10.1007/s10803-010-1006-y
23. Chiang CJ, Chen YC, Chen CJ, You SL, Lai MS. Cancer trends in Taiwan. *Jpn J Clin Oncol*. 2010;40(10):897-904. doi:10.1093/JJCO/HYQ057
24. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol*. 2019;34(3):211-219. doi:10.1007/s10654-019-00494-6

25. Orimoloye HT, Qureshi N, Lee PC, et al. Maternal anemia and the risk of childhood cancer: a population-based cohort study in Taiwan. *Pediatr Blood Cancer*. 2023;70(3):e30188. doi:10.1002/PBC.30188
26. Heck JE, Lee PC, Wu CK, et al. Gestational risk factors and childhood cancers: a cohort study in Taiwan. *Int J Cancer*. 2020;147(5):1343-1353. doi:10.1002/IJC.32905
27. Huang X, Hansen J, Lee PC, et al. Maternal diabetes and childhood cancer risks in offspring: two population-based studies. *Br J Cancer*. 2022;127(10):1837-1842. doi:10.1038/S41416-022-01961-W
28. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol*. 2006;35(6):1495-1503. doi:10.1093/IJE/DYL177
29. Domingues A, Moore KJ, Sample J, Kharoud H, Marcotte EL, Spector LG. Parental age and childhood lymphoma and solid tumor risk: a literature review and meta-analysis. *JNCI Cancer Spectr*. 2022;6(3):pkac40. doi:10.1093/JNCICS/PKAC040
30. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: a Danish population-based registry study. *Cancer Epidemiol*. 2017;49(5):202-215. doi:10.1016/j.canep.2017.06.010
31. Li CY, Lin RS, Lin CH. Urbanization and childhood leukaemia in Taiwan. *Int J Epidemiol*. 1998;27(4):587-591. doi:10.1093/IJE/27.4.587
32. Tsai HJ. Antibiotic prophylaxis for cesarean delivery: before skin incision or after umbilical cord clamping? *Taiwan J Obstet Gynecol*. 2011;50(1):129-130. doi:10.1016/J.TJOG.2010.06.004
33. Lee CC, Hsu JF, Prasad Janapatla R, et al. Clinical and microbiological characteristics of group B Streptococcus from pregnant women and diseased infants in intrapartum antibiotic prophylaxis era in Taiwan. *Sci Rep*. 2019;9(1):13525. doi:10.1038/S41598-019-49977-2
34. Wang CH, Kung WJ, Lee CH, et al. High rates of colonization and antimicrobial resistance of group B streptococcus highlight the need for vaccination even after implementation of guidelines for intrapartum antibiotic prophylaxis. *Vaccine*. 2022;40(2):282-287. doi:10.1016/J.VACCINE.2021.11.069
35. Li QY, Wang DY, Li HT, Liu JM. Screening-based and risk-based strategy for the prevention of early-onset group B Streptococcus/non-group B Streptococcus sepsis in the neonate: a systematic review and meta-analysis. *Pediatr Infect Dis J*. 2020;39(8):740-748. doi:10.1097/INF.0000000000002674
36. Kwan ML, Metayer C, Crouse V, Buffler PA. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. *Am J Epidemiol*. 2007;165(1):27-35. doi:10.1093/AJE/KWJ336
37. Buckley JD, Sather H, Ruccione K, et al. A case-control study of risk factors for hepatoblastoma. A report from the Childrens cancer study group. *Cancer*. 1989;64(5):1169-1176. doi:10.1002/1097-0142(19890901)64:53.0.co;2-i
38. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer*. 2006;6(3):193-203. doi:10.1038/nrc1816
39. Lin M, Chen Q, Yang LY, et al. Hepatitis B virus infection and replication in primarily cultured human fetal hepatocytes. *World J Gastroenterol*. 2007;13(7):1027-1031. doi:10.3748/wjg.v13.i7.1027
40. Lázaro CA, Chang M, Tang W, et al. Hepatitis C virus replication in transfected and serum-infected cultured human fetal hepatocytes. *Am J Pathol*. 2007;170(2):478-489. doi:10.2353/ajpath.2007.060789
41. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64(1 Suppl):S84-S101. doi:10.1016/j.jhep.2016.02.021
42. Bousali M, Papatheodoridis G, Paraskevis D, Karamitros T. Hepatitis B virus DNA integration, chronic infections and hepatocellular carcinoma. *Microorganisms*. 2021;9(8):1787. doi:10.3390/microorganisms9081787
43. Shaw AK, Infante-Rivard C, Morrison HI. Use of medication during pregnancy and risk of childhood leukemia (Canada). *Cancer Causes Control*. 2004;15(9):931-937. doi:10.1007/S10552-004-2230-6
44. Abd-Allah ER, Abd El-Rahman HA. Influence of doxycycline administration on rat embryonic development during organogenesis. *J Biochem Mol Toxicol*. 2021;35(1):e22613. doi:10.1002/JBT.22613
45. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med*. 2009;163(11):978-985. doi:10.1001/ARCHPEDIATRICS.2009.188
46. Czeizel AE, Rockenbauer M, Sørensen HT, Olsen J. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. *Am J Obstet Gynecol*. 2001;184(6):1289-1296. doi:10.1067/MOB.2001.113905
47. Song Q, Yan J, Bu N, Qian Y. Efficacy and safety of broad spectrum penicillin with or without beta-lactamase inhibitors vs first and second generation cephalosporins as prophylactic antibiotics during cesarean section: a systematic review and meta-analysis. *J Obstet Gynaecol*. 2023;43(1):2195946. doi:10.1080/01443615.2023.2195946
48. Chang YW, Chou FH. Acceptance of pertussis vaccination among pregnant women in Taiwan. *J Commun Health Nurs*. 2021;38(2):85-102. doi:10.1080/07370016.2021.1887565
49. Chao A, Huang YC, Chang YL, et al. Seroprevalence of influenza A H1N1 and seroconversion of mothers and infants induced by a single dose of monovalent vaccine. *Taiwan J Obstet Gynecol*. 2013;52(3):356-359. doi:10.1016/J.TJOG.2013.06.002
50. Cheng PJ, Huang SY, Su SY, Peng HH, Chang CL. Increasing postpartum rate of vaccination with tetanus, diphtheria, and acellular pertussis vaccine by incorporating pertussis cocooning information into prenatal education for group B Streptococcus prevention. *Vaccine*. 2015;33(51):7225-7231. doi:10.1016/J.VACCINE.2015.10.121
51. Wu CH, Hsu TY, Kung FT, ChangChien CC, Tsai CC, Lu SN. Changes in the prevalence of HBsAg and HBeAg: a study of 8696 parturients in a well vaccinated area. *Sci Rep*. 2017;7(1):1212. doi:10.1038/S41598-017-01234-0
52. Liew Z, Olsen J, Cui X, Ritz B, Arah OA. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *Int J Epidemiol*. 2015;44(1):345-354. doi:10.1093/ije/dyu249
53. Keskin-Arslan E, Erol H, Uysal N, Karadas B, Temiz T, Kaplan YC. Pregnancy outcomes following maternal macrolide use: a systematic review and meta-analysis. *Reprod Toxicol*. 2023;115:124-146. doi:10.1016/J.REPROTOX.2022.12.003
54. Sheehy O, Santos F, Ferreira E, Bérard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf*. 2015;10(2):170-179. doi:10.2174/1574886310021505151245 48
55. Abbafati C, Machado DB, Cislaghi B, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1160-1203. doi:10.1016/S0140-6736(20)30977-6

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