Supplementary Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eAppendix. Details on the seven national administrative databases

The *Maternal and Child Health Database* collects administrative data that can correctly identify the parents of an offspring and contains 99.78% of all parent-child pairs in Taiwan with their unique identifiers.\(^1\) The *Artificial Reproductive Data* registry is a compulsory national database.\(^2\) It was established based on legal requirements regulating that each assisted reproduction institution in Taiwan reports for all cases the information on assisted reproductive technology (ART) treatment, such as ART methods, causes of infertility, types of embryos, and clinical pregnancy.\(^3\)

The databases of the *Registry for Beneficiaries* and *Ambulatory Care Expenditures by Visits* are claims databases of the National Health Insurance (NHI) program, which is a compulsory social insurance that covers 99.6% of Taiwan’s residents.\(^4\) These databases manage information such as household income basis (NT$), medical diagnoses coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before 30 September 2015 and ICD-10-CM afterwards, as well as the date of diagnosis. The validity of the diagnosis codes has modest-to-high sensitivity and positive predictive values.\(^5\)

The *Birth Certificate Application* registry is regulated by the Protection of Children and Youth Welfare and Rights Act ensuring that medical facilities report relevant birth information within seven days of birth. Therefore, it contains data on all births and includes information on the date of birth, sex of the child, gestational age, birth weight, parent’s original nationality, parent’s age, mother’s residential township at delivery, parity, multiple gestations, and pregnancy risk behaviors (including tobacco, drinking, and substance addiction).\(^6\) The obstetric records in the Birth Certificate Application have been evaluated as valid and complete.\(^7\)

The *Taiwan Cancer Registry Data* registry contains data on all incident cases of cancers, such as the age at diagnosis and the morphology and topography codes according to the International Classification of Diseases for Oncology (ICD-O). Hospitals are required to report cancer information based on the Cancer Control Act 2003. The completeness of this database (97%) and its data quality
make it an excellent resource. The *Cause of Death Data* registry records all deaths for Taiwanese citizens including the age at death, and its accuracy and completeness have been documented.

Before requesting access to these national administrative databases, researchers must receive approval from the IRB. Additionally, peer experts review and approve the use of these databases to ensure the appropriateness of their use. All national administrative databases are managed and stored by the Health and Welfare Data Centre, Ministry of Health and Welfare. The names of the included individuals are encrypted and anonymized using unique identifiers. To protect personal information, researchers are required to conduct on-site analyses at the Health and Welfare Data Center. All data intended to be brought out from this center must be reviewed to prevent the possibility of disclosing an individual’s identity.
eFigure 1. The process of linking the seven national administrative databases

Note. All individuals were assigned a unique personal identification (ID) number in the national administrative databases. This enables linkage to other national administrative databases. The unique ID numbers in the Maternal and Child Health Database allow the identification of an individual’s parents and siblings. Therefore, the ID number of the Maternal and Child Health Database was used to link the following six national administrative databases: Artificial Reproductive Data, Registry for Beneficiaries, Ambulatory Care Expenditures by Visits, Birth Certificate Application, Taiwan Cancer Registry Data, and Cause of Death Data. The Artificial Reproductive Data database did not have a child’s ID. Hence, to identify which child in a household was born after ART, we required that the offspring’s birth date be within 290 days following the date of transfer, after using the parents’ ID to link to the Registry for Beneficiaries database. Then, because the Birth Certificate Application database only contains mothers’ IDs, it cannot identify birth data if a mother gave birth twice in the same year or had multiple gestations.

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Therefore, the Birth Certificate Application database was divided into three datasets: (1) all singletons and no siblings born in the same year, (2) siblings born in the same year, and (3) multiple gestations. The variables for the linkage between the first dataset—(all singletons and no siblings born in the same year) and the merged Maternal and Child Health Database were mothers’ ID, children’s birth year, and sex. As for the other two datasets, siblings born in the same year and multiple gestations, an additional linkage variable, i.e., a unique sequential number generated for each mother’s birth data based on birth year and birth order, was used. After linking the seven national administrative databases, 95.97% of the parents-child pairs (n=2,553,583) were matched successfully. There were 4.03% of parents-child pairs (n=107,260) who failed to be linked to the Birth Certificate Application records, and most of them lacked all birth data.
eFigure 2. Criteria for children who were conceived through ART

Abbreviations: ART, assisted reproductive technology; LMP, last menstrual period; EDD, estimated delivery date.

To minimize possible misclassifications, children conceived through ART were defined as those for whom one of the parents had an infertility diagnosis, a clinical pregnancy was recorded after ART, and the birth date was within 290 days after the transfer date. The 290 days were derived by subtracting from 308 days (44 weeks of gestational age) 14 days (the duration between LMP and retrievals), subtracting another 7 days (to account for 3–7 days in embryo culture), and adding 3 days of errors. A previous study indicated that the mean difference in gestational age was 0.9–2.1 days between the methods using the last menstrual period, crown-rump length, and biparietal diameter; therefore, an error of 3 days was used.10
Figure 3. Flow diagram of study participants

2,553,583 Parents-child triads in Taiwan during 2004-2017

245,567 (9.62%) Excluded
- 66,204 Parents had a history of cancer
- 156,216 Parents were foreign nationals
- 22,249 Parents were younger than 20 years
- 2,141 Siblings were born in the same year
- 3,329 Use of sperm or oocyte donations
- 1,689 Mothers had a record of addiction to alcohol/tobacco/drugs during pregnancy

2,308,016 Parents-offspring triads included for analyses
### eTable 1. Classification table from the ICCC-311

| Cancers groups                                      | ICD-O-3 morphology                                                                 | ICD-O-3 topography |
|-----------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|
| **I. Leukemias**                                    |                                                                                     |                    |
| (a) Lymphoid leukemias                              | 9820, 9823, 9826, 9827, 9831-9837, 9940, 9948                                      | C000-C809          |
| (b) Acute myeloid leukemias                         | 9840, 9861, 9866, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931                    | C000-C809          |
| (c) Chronic myeloproliferative diseases              | 9863, 9875, 9876, 9950, 9960-9964                                                  | C000-C809          |
| (d) Myelodysplastic syndrome and other myeloproliferative diseases | 9945, 9946, 9975, 9980, 9982-9987, 9989 | C000-C809          |
| (e) Unspecified and other specified leukemias       | 9800, 9801, 9805, 9860, 9930                                                      | C000-C809          |
| **II. Lymphomas and reticuloendothelial neoplasms** |                                                                                     |                    |
| (a) Hodgkin lymphomas                               | 9650-9655, 9659, 9661-9665, 9667                                                  | C000-C809          |
| (b) Non-Hodgkin lymphomas (except Burkitt lymphoma) | 9591, 9670, 9671, 9673, 9675, 9678-9680, 9684, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9731-9734, 9760-9762, 9764-9769, 9970 | C000-C809          |
| (c) Burkitt lymphoma                                 | 9687                                                                                | C000-C809          |
| (d) Miscellaneous lymphoreticular neoplasms         | 9740-9742, 9750, 9754-9758                                                         | C000-C809          |
| (e) Unspecified lymphomas                           | 9590, 9596                                                                          | C000-C809          |
| **III. CNS and miscellaneous intracranial and intraspinal neoplasms** |                                                                                     |                    |
| (a) Ependymomas                                     | 9383, 9390-9394                                                                    | C000-C809          |
| (b) Astrocytomas                                    | 9380                                                                                | C723               |
|                                                     | 9384, 9400-9411, 9420, 9421-9424, 9440-9442                                        | C000-C809          |
| (c) Intracranial and intraspinal embryonal tumors   | 9470-9474, 9480, 9508                                                               | C000-C809          |
|                                                     | 9501-9504                                                                          | C700-C729          |
| (d) Other gliomas                                   | 9380                                                                                | C700-C722, C724-C729, C751, C753       |
|                                                     | 9381, 9382, 9430, 9444, 9450, 9451, 9460                                           | C000-C809          |
| (e) Other specified intracranial and intraspinal neoplasms | 8270-8281, 8300, 9350-9352, 9360-9362, 9412, 9413, 9492, 9493, 9505-9507, 9530-9539, 9582 | C000-C809 |
| (f) Unspecified intracranial and intraspinal neoplasms | 8000-8005 | C700-C729, C751-C753 |

**IV. Neuroblastoma and other peripheral nervous cell tumors**

| (a) Neuroblastoma and ganglioneuroblastoma | 9490, 9500 | C000-C809 |
| (b) Other peripheral nervous cell tumors | 8680-8683, 8690-8693, 8700, 9520-9523 | C000-C809 |
| | 9501-9504 | C000-C699, C739-C768, C809 |

**V. Retinoblastoma**

| 9510-9514 | C000-C809 |

**VI. Renal tumors**

| (a) Nephroblastoma and other nonepithelial renal tumors | 8959, 8960, 8964-8967 | C000-C809 |
| | 8963, 9364 | C649 |
| (b) Renal carcinomas | 8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231, 8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576 | C649 |
| | 8311, 8312, 8316-8319, 8361 | C000-C809 |
| (c) Unspecified malignant renal tumors | 8000-8005 | C649 |

**VII. Hepatic tumors**

| (a) Hepatoblastoma | 8970 | C000-C809 |
| (b) Hepatic carcinomas | 8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260- | C220, C221 |
### VIII. Malignant bone tumors

(a) Osteosarcomas  
8910-8917, 8919-8920  
C400-C419, C760-C768, C809

(b) Chondrosarcomas  
8920, 8922, 8924  
C400-C419, C760-C768, C809

(c) Ewing tumor and related sarcomas of bone  
8926  
C400-C419, C760-C768, C809

(d) Other specified malignant bone tumors  
8810, 8811, 8823, 8830  
C400-C419

(e) Unspecified malignant bone tumors  
8000-8005, 8800, 8801, 8803-8805  
C400-C419

### IX. Soft tissue and other extraosseous sarcomas

(a) Rhabdomyosarcomas  
8900-8905, 8910, 8912, 8920, 8991  
C000-C809

(b) Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms  
8810, 8811, 8813-8815, 8821, 8823, 8834-8835  
C000-C399, C440-C768, C809

(c) Kaposi sarcoma  
9140  
C000-C809
| Category                                                                 | Codes                                                                 | ICDCodes       |
|-------------------------------------------------------------------------|----------------------------------------------------------------------|----------------|
| (d) Other specified soft tissue sarcomas                                | 8587, 8710-8713, 8806, 8831-8833, 8836, 8840-8842, 8850-8858, 8860-8862, 8870, 8880, 8881, 8890-8898, 8921, 8982, 8990, 9040-9044, 9120-9125, 9130-9133, 9135, 9136, 9141, 9142, 9161, 9170-9175, 9231, 9251, 9252, 9373, 9581 | C000-C809       |
|                                                                         | 8830                                                                | C000-C399, C440-C768, C809 |
|                                                                         | 8963                                                                | C000-C639, C659-C699, C739-C768, C809 |
|                                                                         | 9180, 9210, 9220, 9240                                               | C490-C499      |
|                                                                         | 9260                                                                | C000-C399, C470-C759 |
|                                                                         | 9364                                                                | C000-C399, C470-C639, C659-C699, C739-C768, C809 |
|                                                                         | 9365                                                                | C000-C399, C470-C639, C659-C768, C809 |
| (e) Unspecified soft tissue sarcomas                                     | 8800-8805                                                           | C000-C399, C440-C768, C809 |
| (e) Unspecified malignant bone tumors                                   | 8000-8005, 8800, 8801, 8803-8805                                     | C400-C419      |
| X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads     |                                                                      |                |
| (a) Intracranial and intraspinal germ cell tumors                       | 9060-9065, 9070-9072, 9080-9085, 9100, 9101                         | C700-C729, C751-C753 |
| (b) Malignant extracranial and extragonadal germ cell tumors           | 9060-9065, 9070-9072, 9080-9085, 9100-9105                          | C000-C559, C570-C619, C630-C699, C739-C750, |
| (c) Malignant gonadal germ cell tumors | 9060-9065, 9070-9073, 9080-9085, 9090, 9091, 9100, 9101 | C754-C768, C809 |
| (d) Gonadal carcinomas | 8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8313, 8320, 8323, 8380-8384, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573, 8900, 9014, 9015 | C569, C620-C629 |
| (e) Other and unspecified malignant gonadal tumors | 8590-8671 | C000-C809 |

**XI. Other malignant epithelial neoplasms and malignant melanomas**

| (a) Adrenocortical carcinomas | 8370-8375 | C000-C809 |
| (b) Thyroid carcinomas | 8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560-8573 | C739 |
| (c) Nasopharyngeal carcinomas | 8010-8041, 8050-8075, 8082, 8083, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576 | C110-C119 |
| (d) Malignant melanomas | 8720-8780, 8790 | C000-C809 |
| (e) Skin carcinomas | 8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941 | C440-C449 |
| (f) Other and unspecified carcinomas | 8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030 | C000-C109, C129-C218, C239-C399, C480-C488, C500-C559, C580-C589, C600-C609 |
### eTable 2. Association between childhood cancers and mode of conception stratified by the source of infertility and embryo type

| Variables          | All childhood cancers | Leukemias | Hepatic tumors |
|--------------------|-----------------------|-----------|----------------|
|                    | No. of cases          | Adjusted HR (95% CI)ᵃ | Adjusted HR (95% CI)ᵃ | No. of cases | Adjusted HR (95% CI)ᵃ | Adjusted HR (95% CI)ᵃ | No. of cases | Adjusted HR (95% CI)ᵃ | Adjusted HR (95% CI)ᵃ |
| Natural conception | 1,417                 | NA        | 348            | 96           | 1 [Reference]         | NA                  | 96            | 1 [Reference]         | NA                  |
| Non-ART conception | 416                   | 1 [Reference] | 104            | 30           | NA                    | 1 [Reference]       | 30            | NA                    | 1 [Reference]       |
| ART conception     |                       |           |                |              |                       |                     |               |                       |                     |
| Source of infertility |                     |           |                |              |                       |                     |               |                       |                     |
| Paternal infertility | NR                   | 3.36 (0.47 to 23.89) | 2.99 (0.42 to 21.35) | 0             | NA                    | NA                  | 0             | NA                    | NA                  |
| Maternal infertility | 34                   | 1.71 (0.99 to 2.42) | 1.59 (0.98 to 2.28) | 6             | 1.43 (0.63 to 3.25)  | 1.35 (0.58 to 3.13) | NR            | 3.16 (0.86 to 7.45)  | 2.82 (0.97 to 7.12) |
| Both               | NR                    | 1.19 (0.67 to 2.11) | 1.07 (0.60 to 1.92) | 7             | 3.32 (0.76 to 7.08)  | 3.17 (0.75 to 6.94) | NR            | 1.90 (0.46 to 7.86)  | 1.69 (0.39 to 7.31) |
| Type of embryo     |                       |           |                |              |                       |                     |               |                       |                     |
| Fresh              | 40                    | 1.60 (1.20 to 2.27) | 1.47 (1.06 to 2.05) | NR            | 1.99 (1.00 to 3.67)  | 1.79 (0.94 to 3.39) | 8             | 2.71 (1.28 to 5.73)  | 2.41 (1.05 to 5.52) |
| Frozen             | 7                     | 1.17 (0.55 to 2.47) | 1.15 (0.54 to 2.46) | NR            | 2.42 (0.60 to 9.87)  | 2.30 (0.55 to 9.59) | 0             | NA                    | NA                  |

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable; NR, not reported due to the number being smaller than three to protect patient confidentiality under the Taiwan Data Protection Law.

ᵃ Adjusted hazard ratios and 95% confidence intervals were estimated from a Cox proportional hazard model adjusted for maternal age, paternal age, child’s birth year, child’s sex, parity, socioeconomic status, residential urbanization level, and abortion history.
**Table 3. Risk of childhood cancers by mode of conception for boys and girls**

| Types of childhood cancers | Number of cases | HR (95% CI)<sup>a</sup> | HR (95% CI)<sup>a</sup> |
|----------------------------|-----------------|--------------------------|--------------------------|
|                            | Natural conception | Non-ART conception | ART conception | Natural conception | Non-ART conception | ART conception |
| Boys                       |                 |                         |                       |                 |                         |               |
| Any type of cancer         | 806             | 232                      | 25                    | 1 [Reference]   | 1.16 (1.00 to 1.35)    | 1.49 (0.99 to 2.24) |
| Leukemia                   | 205             | 63                       | 6                     | 1 [Reference]   | 1.27 (0.96 to 1.70)    | 1.67 (0.73 to 3.80) |
| Hepatic tumors             | 65              | 19                       | 4                     | 1 [Reference]   | 1.08 (0.64 to 1.81)    | 2.18 (0.77 to 6.17) |
| Girls                      |                 |                         |                       |                 |                         |               |
| Any type of cancer         | 611             | 184                      | 22                    | 1 [Reference]   | 1.11 (0.94 to 1.31)    | 1.68 (0.98 to 2.60) |
| Leukemia                   | 143             | 41                       | 7                     | 1 [Reference]   | 1.09 (0.76 to 1.54)    | 2.75 (1.00 to 5.79) |
| Hepatic tumors             | 31              | 11                       | 4                     | 1 [Reference]   | 1.13 (0.56 to 2.26)    | 3.63 (0.99 to 10.78) |

Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable due to no case or too few cases to estimate.

<sup>a</sup> Adjusted hazard ratios and 95% confidence intervals were estimated from a Cox proportional hazard model adjusted for maternal age, paternal age, child’s birth year, child’s sex, parity, socioeconomic status, residential urbanization level, and abortion history.
### eTable 4. Models for mediators and mode of conception as independent variables

| Variables                      | Gestational age < 37 weeks\(^a\) | Gestational age > 42 weeks\(^a\) | Birth weight <2500g\(^b\) | Birth weight >4200g\(^b\) |
|-------------------------------|-----------------------------------|-----------------------------------|----------------------------|----------------------------|
|                               | HR (95% CI)\(^d\)                | HR (95% CI)\(^d\)                | HR (95% CI)\(^d\)          | HR (95% CI)\(^d\)          |
| Natural conception            | 1 [Reference]                    | 1 [Reference]                    | 1 [Reference]              | 1 [Reference]              |
| Subfertility and non-ART conception | 1.23 (1.22 to 1.25)         | 0.66 (0.40 to 1.09)             | 1.22 (1.21 to 1.24)        | 1.04 (0.99 to 1.09)        |
| ART conception                | 4.59 (4.49 to 4.69)             | NA                               | 5.36 (5.25 to 5.48)        | 0.47 (0.38 to 0.57)        |

Abbreviation: ART, assisted reproductive technology; HR, hazard ratios; CI, confidence interval; NA, not applicable due to no case.

\(^a\) Reference group: 36-42 weeks of gestational age

\(^b\) Reference group: 2500-4200 g of birth weight

\(^c\) Reference group: singleton

\(^d\) Adjusted for maternal age, paternal age, child’s birth year, child’s sex, parity, socioeconomic status, residential urbanization level, and abortion history.
### eTable 5. Models for mediators and ART conception as independent variables compared with subfertility and non-ART conception

| Variables                        | Gestational age < 37 weeks<sup>a</sup> | Gestational age > 42 weeks<sup>a</sup> | Birth weight <2500g<sup>b</sup> | Birth weight >4200g<sup>b</sup> |
|----------------------------------|----------------------------------------|----------------------------------------|---------------------------------|---------------------------------|
|                                  | HR (95% CI)<sup>d</sup>               | HR (95% CI)<sup>d</sup>               | HR (95% CI)<sup>d</sup>         | HR (95% CI)<sup>d</sup>         |
| Subfertility and non-ART conception | 1 [Reference]                        | 1 [Reference]                        | 1 [Reference]                  | 1 [Reference]                  |
| ART conception                   | 3.68 (3.59 to 3.77)                   | NA                                    | 4.32 (4.22 to 4.42)            | 0.46 (0.37 to 0.57)            |

Abbreviation: ART, assisted reproductive technology; HR, hazard ratios; CI, confidence interval; NA, not applicable due to no case.

<sup>a</sup> Reference group: 36-42 weeks of gestational age

<sup>b</sup> Reference group: 2500-4200 g of birth weight

<sup>d</sup> Reference group: singleton

<sup>d</sup> Adjusted for maternal age, paternal age, child’s birth year, child’s sex, parity, socioeconomic status, residential urbanization level, and abortion history.
## eTable 6. Models for childhood cancers and mediators as independent variables

| Potential mediators | Any type of childhood cancer | Leukemias | Hepatic tumors |
|---------------------|-----------------------------|-----------|---------------|
|                     | No. of children | No. of events | HR (95% CI)<sup>a</sup> | No. of events | HR (95% CI)<sup>a</sup> | No. of events | HR (95% CI)<sup>a</sup> |
| Gestational age     |                |             |                   |                |                   |                |                   |
| < 37 weeks          | 188,231        | 210         | 1.31 (1.13 to 1.52)| 51             | 1.29 (0.96 to 1.74)| 24             | 1.83 (1.14 to 2.95)|
| 37-42               | 1,967,502      | 1656        | 1 [Reference]     | 412            | 1 [Reference]     | 109            | 1 [Reference]     |
| > 42 weeks          | 142            | 0           | NA                | 0              | NA                | 0              | NA                |
| Birth weight        |                |             |                   |                |                   |                |                   |
| < 2500 g            | 170,312        | 178         | 1.23 (1.05 to 1.45)| 38             | 1.10 (0.78 to 1.55)| 2.20 (1.36 to 3.55)|
| 2500-4200 g         | 1,974,629      | 1672        | 1 [Reference]     | 419            | 1 [Reference]     | 108            | 1 [Reference]     |
| > 4200 g            | 10,934         | 16          | 1.58 (0.97 to 2.60)| 6              | 2.26 (1.01 to 5.06)| 1.40 (0.20 to 10.05)|

Abbreviation: ART, assisted reproductive technology; HR, hazard ratios; CI, confidence interval; NA, not applicable due to no case.

<sup>a</sup> Adjusted for mode of conception, maternal age, paternal age, child’s birth year, child’s sex, parity, socioeconomic status, residential urbanization level, and abortion history.
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