# Supplemental Online Content

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**eTable 1. List of Cohort Creation Variable, Study Exposure and Outcome Variables, and Model Covariates.**

| Assessment | Timing | Disease, Procedure, or Condition | CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes | OHIP ICD-9 diagnosis or fee codes; or other data source | Hyperlink to a validation study or documentation for related codes |
|---|---|---|---|---|---|
| *Inclusion criteria* | April 1, 2006 – March 31, 2015 | Live birth record in BORN | | BORN | |
| *Exclusion criteria* | Same as above | Gestational age < 24 weeks | | BORN BIS: ga_at_birth_weeks<br><br>NIDAY: gest | |
| | Same as above | Maternal age < 18 or > 55 years | | BORN BIS: matageatstillorlivebirthyears When maternal birthdate was missing in BORN, the birthdate found in RPDB was used instead<br><br>NIDAY: m_bdate | |
| | Same as above | Induction for pregnancy termination | | BORN: ind_for_lbr_induct_prim_id = 1014250 or all_ind_for_lbr_induct_id = 1014250 | |
| | Same as above | Surrogacy pregnancy | | BORN: conception_type_id = 1013170 | |
| | April 1, 2004 – March 31, 2015 | < 2 years of maternal OHIP eligibility prior to birth | | RPDB | |
| | April 1, 2006 – September 30, 2016 | Child death before age 18 months of age | | RPDB | |
| | April 1, 2006 – March 31, 2015 | Pregnancies delivered outside of Ontario | | BORN: lbm_submitted | |
| | Same as above | Pregnancies with no infant record | | BORN BIS: birth_id_enc<br>NIDAY: b_key | |
| | Same as above | Invalid or missing maternal or baby IKN | | BORN: b_valikn | |
| | Same as above | Warning in NIDAY | | BORN NIDAY: warn= B, C, K, O, P, R | |
| | Same as above | Pregnancies with year of birth 1900 | | BORN: b_bdate | |
| | | | | | |
| *Study exposures* | April 1, 2006 – March 31, 2015 | Mode of conception: | | BORN (see below for component codes) | |

| Assessment | Timing | Disease, Procedure, or Condition | CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes | OHIP ICD-9 diagnosis or fee codes; or other data source | Hyperlink to a validation study or documentation for related codes |
|---|---|---|---|---|---|
| | Same as above | Spontaneous conception (unassisted) | | No history of infertility (OHIP ICD-9 = 628), and one of the following:<br><br>BORN BIS: CONCEPTION_TYPE_ID = 1013160, 1013180<br><br>OR<br><br>NIDAY: REPASS = 1,9,0 | |
| | Same as above | Subfertility (infertility without fertility treatment) | | History of infertility (OHIP ICD-9=628), and one of the following:<br><br>BORN BIS: CONCEPTION_TYPE_ID = 1013160, 1013180<br><br>OR<br><br>NIDAY: REPASS = 1,9,0 | |
| | Same as above | Invasive infertility treatment (In-vitro fertilization / intra-cytoplasmic sperm injection) | | BORN BIS: CONCEPTION_TYPE_ID = 1013130, 1013140<br><br>NIDAY: REPASS = 3,4 | |
| | Same as above | Non-invasive infertility treatment (Ovulation induction, intrauterine insemination) | | BORN BIS: CONCEPTION_TYPE_ID = 1013110, 1013120, 1013150, 3000006<br><br>NIDAY: REPASS = 2,5 | |
| | | | | | |
| *Main study outcome* | April 1, 2006 – March 31, 2022 | Autism Spectrum Disorder | ICD-10-CA(DAD): F84 | OHIP ICD-9: 299 | https://doi.org/10.1001/jama.2017.3415<br>https://doi.org/10.1177/1362361312467709 |
| | | | | | |
| *Mediators* | April 1, 2006 – March 31, 2015 | Planned Caesarean delivery | | BORN BIS: cs_type_id = 1013360, 1013370, 1048727<br><br>NIDAY: deltype=2 and cstype=1 | |

| Assessment | Timing | Disease, Procedure, or Condition | CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes | OHIP ICD-9 diagnosis or fee codes; or other data source | Hyperlink to a validation study or documentation for related codes |
|---|---|---|---|---|---|
| | Same as above | Unplanned Caesarean delivery | | BORN BIS: cs_type_id = 1013380<br><br>NIDAY: deltype=2 and cstype=2 | |
| | Same as above | Preterm birth | ICD-10-CA (DAD,SDS): P05, P07, O60 | BORN<br>BORN was the primary source for gestational age. When missing, gestational age was imputed using the algorithm from Margulis et al. | https://doi.org/10.1002/pds.3284 |
| | Same as above | Multiple pregnancy | | BORN BIS: number_of_fetuses >1<br><br>NIDAY: multgest >1 | |

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|---|---|---|---|---|---|
| | April 1, 2005 – March 31, 2019 | Severe neonatal morbidity | ICD-10-CA (DAD): I63, P100-P103, P130, P132, P133, P140, P141, P220, P23, P271, P280, P285, P36, P521, P522, P77, P90, P912, P915, P916, P9181, R56<br><br>CCI (DAD): 1AA52, 1AA87, 1AC87, 1AE87, 1AF87, 1AG87, 1AJ87, 1AK87, 1AN52, 1AN59, 1AN87, 1AP59, 1AP72, 1AP87, 1AW59, 1AW72, 1AW87, 1AX87, 1BA72, 1BA80, 1BA87, 1BB72, 1BB80, 1BB87, 1BD72, 1BD80, 1BD87, 1BF80, 1BG72, 1BG80, 1BG87, 1BK59, 1BM72, 1BM80, 1BM87, 1BN72, 1BN80, 1BN87, 1BP72, 1BP80, 1BP87, 1BQ72, 1BQ80, 1BQ87, 1BS72, 1BS80, 1BS87, 1BT72, 1BT80, 1BT87, 1GA87, 1GA89, 1GB87, 1GB89, 1GD89, 1GE80, 1GE87, 1GE89, 1GE91, 1GH84, 1GJ86, 1GJ87, 1GK87, 1GK89, 1GM80, 1GM86, 1GM87, 1GN92, 1GR87, 1GR89, 1GR91, 1GT78, 1GT87, 1GT89, 1GT91, 1GV87, 1GV89, 1GW87, 1GX80, 1GX86, 1GX87, 1GY70, 1GY72, 1GY86, 1HJ76, 1HJ82, 1HN87, 1HP76, 1HP78, 1HP80, 1HP82, 1HP83, 1HP87, 1HR80, 1HR84, 1HR87, 1HS80 (excl. 1HS80G), | | https://doi.org/10.1007/s10995-016-2047-4 |

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|---|---|---|---|---|---|
| | | | 1HS90, 1HT80 (excl. 1HT80G), 1HT89, 1HT90, 1HU80 (excl. 1HU80G), 1HU90, 1HV80 (excl. 1HV80G), 1HV90, 1HW78, 1HW79, 1HX80, 1HX87, 1HX80, 1HZ87, 1IA76, 1IA80, 1IA87, 1IB76, 1IB79, 1IB80, 1IB82, 1IB87, 1IC76, 1IC80, 1IC82, 1IC87, 1ID76, 1ID80, 1ID82, 1ID86, 1ID87, 1IF83, 1IJ76, 1IJ80, 1IM76, 1IM80, 1IM82, 1IM83, 1IM87, 1IN83, 1IN84, 1IN87, 1JE57 (excl. 1JE57G), 1JE76, 1JE80, 1JE87, 1JJ76, 1JJ80, 1JK76, 1JK80, 1JK87, 1JW51 (excL. 1JW51G), 1JW57, 1JW76, 1LA84, 1LC84, 1LD84, 1NA72, 1NA74, 1NA76, 1NA77, 1NA80, 1NA84, 1NA86, 1NA87, 1NA88, 1NA89, 1NA90, 1NA91, 1NA92, 1NE80, 1NF76, 1NF78, 1NF80, 1NF82, 1NF84, 1NF86, 1NF87 (excl. 1NF87B), 1NF89, 1NF90, 1NF91, 1NF92, 1NK76, 1NK77, 1NK80, 1NK82, 1NK84, 1NK87 (excl. 1NK87B), 1NM74, 1NM76, 1NM77, 1NM80, 1NM82, 1NM87 (excl. 1NM87B), 1NM89, 1NM91, 1NP72, 1NP73, 1NP86, 1NQ74 (excl. 1NQ74B), 1NQ80, | | |

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|---|---|---|---|---|---|
| | | | 1NQ84, 1NQ86, 1NQ87 (excl. 1NQ87B), 1NQ89, 1NQ90, 1NT80, 1NT84, 1NT86, 1NT87, 1NV89, 1OA87, 1OB87, 1OB89, 1OD76, 1OD89, 1OE76, 1OE80, 1OE89, 1OJ76 (excl. 1OJ76B), 1OJ87, 1OJ89, 1OK87, 1OK89, 1OK91, 1OT72, 1OT87, 1OT91, 1PB87, 1PB89, 1PC80, 1PC87 (excl. 1PC87D), 1PC89, 1PC91, 1PE57 (excl. 1PE57BD), 1PE80 (excl. 1PE80D), 1PE82, 1PE87 (excl. 1PE87D), 1PE89 (excl. 1PE89D), 1PG76, 1PG77, 1PG80 (excl. 1PG80D), 1PG86, 1PG89, 1PL74 (excl. 1PL74CD), 1PL80, 1PM79, 1PM86, 1PM87 (excl. 1PM87B), 1PM89, 1PM90, 1PM91, 1PM92, 1QE53, 1QE80, 1QE82, 1QE84, 1QE87, 1QE89, 1QG89, 1QM74, 1QM80, 1QM87, 1QM89, 1QM91, 1QN82, 1QT87, 1QT91, 1RB74, 1RB80, 1RB83, 1RB87, 1RB89,1RD89, 1RF51, 1RF72, 1RF74, 1RF80, 1RF87, 1RF89, 1RM87 (excl. 1RM87B), 1RM89, 1RM91, 1RN87, 1RN89, 1RS74, 1RS80, 1RS86, 1RS87, 1RS89, 1RW87, 1RW88, 1RW91, 1RW92, 1SA74, 1SA75, 1SA80, 1SA89, | | |

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|---|---|---|---|---|---|
| | | | 1SC74, 1SC75, 1SC80, 1SC87, 1SC89, 1SE53, 1SE89 (excl. 1SE89D), 1SF80, 1SF87, 1SF89, 1SG80, 1SG87, 1SH87, 1SM74, 1SM80, 1SM87, 1SN87, 1SN93, 1SQ53, 1SQ74, 1SQ80, 1SQ87, 1SQ91, 1SQ93, 1SW74, 1SY80, 1SY84, 1SY87, 1SZ87, 1VA53, 1VA74, 1VA75, 1VA80, 1VA87, 1VA93, 1VC74, 1VC80, 1VC87, 1VC91, 1VC93, 1VE80, 1VG53, 1VG55, 1VG72, 1VG73, 1VG74, 1VG75, 1VG80, 1VG87, 1VG93, 1VK80, 1VK87, 1VK89, 1VL80, 1VL87, 1VM80, 1VM87, 1VN80, 1VN87, 1VP74, 1VP80, 1VP87, 1VP89, 1VQ74, 1VQ79, 1VQ80, 1VQ82, 1VQ87, 1VQ91, 1VQ93, 1VS72, 1VS80, 1VX87, 1LZ35CAE6, 1LZ35HAC1, 1LZ35HAC5, 1LZ35HAC6, 1LZ35HAC7, 1LZ35HAE6, 1LZ35HAT7, 1LZ35HAT9, 1LZ35HAZ9, 1LZ35HHC1, 1LZ35HHC5, 1LZ35HHC6, 1LZ35HHC7, 1LZ35HHE0, 1LZ35HHE6, 1LZ35HHT7, 1LZ35HHT9, | | |

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|---|---|---|---|---|---|
| | | | 1LZ35HHZ9, 1LZ35HRC5, 1LZ35HRC6, 1LZ35HRC7, 1LZ35HRT9, 1LZ35HRZ9, 1KV53HACH, 1KV53HAFT, 1KV53LAFT, 2IM28GP, 2LZ28GQPL, 2LZ28GRPL, 2LZ28JAPL, 1KX53HACH, 1KX53HAFT, 1KX53 LAFT, 2LZ28GQPL, 2LZ28GRPL, 1GV52DA, 1GV52DATS, 1GV52HA, 1GV52HAHE, 1GV52HATK, 1GV52LA, 1GV52LATS, 1GV52LAXXE, 1GV54JATS, 1GV55JATS, 1HZ30JN, 1HZ30JY, 1GZ30CJ, 1GZ30CJNB, 1GZ30JH, 1LZ19HHU1A, 1LZ19HHU1J, 1LZ19HHU2A, 1LZ19HHU2J, 1LZ19HHU3J, 1LZ19HHU4J, 1LZ19HHU5J, 1LZ19HHU6A, 1LZ19HHU6J, 1LZ19HHU9A, 1LZ19HHU9J, 1LZ19HMU1, 1LZ19HMU2, 1LZ19HMU9, 1LZ35HAC5, 1GZ31CAEP, 1GZ31CAND, 1GZ31CAPK, | | |

| Assessment | Timing | Disease, Procedure, or Condition | CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes | OHIP ICD-9 diagnosis or fee codes; or other data source | Hyperlink to a validation study or documentation for related codes |
|---|---|---|---|---|---|
| | | | 1GZ31CBND, 1GZ31CRND, 1GZ31GPND, 1GZ31JAGX, 1GZ31JAMD, 1GZ31JANC, 1GZ31JAPK | | |
| | April 1, 2006 – March 31, 2015 | Preeclampsia | ICD-10-CA (DAD,SDS,NACRS): O11, O13, O14, O15 | | |
| | | | | | |
| *Covariates* | April 1, 2006 – March 31, 2015 | Maternal age | | RPDB<br>BORN | |
| | Same as above | Gestational age | ICD-10-CA (DAD,SDS): P05, P07, O60 | BORN<br>BORN was the primary source for gestational age. When missing, gestational age was imputed using the algorithm from Margulis et al. | https://doi.org/10.1002/pds.3284 |
| | Same as above | Baby sex | | RPDB | |
| | Same as above | Maternal smoking history | | BORN BIS: mat_smoking_at_adm_for_birth_id = 1017390, 1017400, 1017410, 1017420<br>NIDAY: smoking = 3, 4 | |
| | Same as above | Maternal drug use history | | BORN BIS: expos_drug_and_subst_id = 1020460, 1020470, 1020480, 1020490, 1020500, 1020510, 1020520, 1020530<br>NIDAY: value of 1 in mathp6, mathp7, mathp8, mathp9, mathp10, mathp11, mathp13 | |
| | Same as above | Maternal alcohol history | | BORN BIS: preg_expos_alcohol_id = 1020430, 1020440, 1020442<br>NIDAY: mathp1 = 1 | |

| Assessment | Timing | Disease, Procedure, or Condition | CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes | OHIP ICD-9 diagnosis or fee codes; or other data source | Hyperlink to a validation study or documentation for related codes |
|---|---|---|---|---|---|
| | April 1, 2003 – April 30, 2016 | Maternal mental health diagnosis history | ICD-10-CA (DAD, NACRS):<br>F06-F09, F1-F6, F80, F81 F92-F95, F98 | OHIP:<br>location = O, L, or H, AND<br>spec = 00 or 19, AND<br>ICD-9 295-298, 300-304, 306, 309, 311<br><br>DSM-4 (OMHRS): 291-293, 295-298, 300, 3000-301,0 30113, 3012-3019, 3022-3024, 3026-3029, 303-305, 30651, 307, 3070-3079, 3083, 309, 3090, 3092- 3094, 3099, 310, 31,1 315, 316, 327, 331-333, 347, 394, 395, 403, 648, 652, 780, 799, 967, 995, V15, V40, V61, V62, V65, V70, V71 | https://doi.org/10.1097/00005650-200410000-00004<br>(Steele algorithm where the OHIP codes are from)<br><br>https://www.ices.on.ca/Publications/Atlases-and-Reports/2018/MHASEF<br>(Source for DSM-4 and ICD-10-CA codes, as per concept dictionary) |
| | Same as above | Maternal ASD diagnosis history | ICD-10-CA(DAD): F84 | OHIP dxcode: 299 | |
| | April 1, 2006 – March 31, 2015 | Income quintile | | RPDB | |
| | Same as above | Rurality | | RPDB | |
| | Same as above | Immigrant status | | Immigration Refugees and Citizenship Canada Permanent Resident (IRCC-PR) Database | |
| | Same as above | BMI | | BORN BIS: pre_preg_maternal_weight_kg, maternal_height_cm<br><br>NIDAY: matwgtkg, mathgtm | |
| | Same as above | Obesity | | BORN (BMI > 30)<br>OHIP ICD-9: 278 | |
| | Same as above | Parity | | BORN<br>MOMBABY | |
| | April 1, 1991 – March 31, 2015 | Diabetes | | ODD | https://doi.org/10.1186/s12913-018-3148-0 |

**eTable2. Risk of Autism Spectrum Disorder (ASD) by Mode of Conception.** These analyses are limited to singleton live births.

| Mode of conception | No. with ASD/ No. at risk | Rate of ASD per 1000 person-years | Unadjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI)[a] |
|---|---|---|---|---|
| Analysis among all 1,322,578 singleton live-born children | | | | |
| Unassisted conception | 18,070 / 1,157,027 | 1.91 | 1.00 (ref) | 1.00 (ref) |
| Subfertility | 2668 / 133,090 | 2.48 | 1.29 (1.24-1.35) | 1.20 (1.15-1.25) |
| Ovulation induction or intrauterine insemination | 308 / 16,495 | 2.60 | 1.25 (1.12-1.40) | 1.15 (1.03-1.29) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 266 / 15,966 | 2.46 | 1.14 (1.01-1.29) | 1.03 (0.91-1.17) |
| | | | | |
| Analysis limited to 165,551 singleton live-born children among individuals with infertility | | | | |
| Subfertility | 2668 / 133,090 | 2.48 | 1.00 (Ref.) | 1.00 (Ref.) |
| Ovulation induction or intrauterine insemination | 308 / 16,495 | 2.60 | 0.96 (0.85-1.08) | 0.98 (0.87-1.10) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 266 / 15,966 | 2.46 | 0.88 (0.77-0.99) | 0.84 (0.74-0.96) |
| | | | | |
| Analysis limited to 15,966 live-born children among individuals who underwent *In vitro* fertilization or intracytoplasmic sperm injection | | | | |
| *In vitro* fertilization | 236 / 14,249 | 2.45 | 1.00 (Ref.) | 1.00 (Ref.) |
| Intracytoplasmic sperm injection | 30 / 1717 | 2.60 | 1.06 (0.72-1.54) | 1.09 (0.75-1.59) |

[a] Adjusted for maternal age, parity, income quintile, rurality, immigration status, smoking, obesity, any drug or alcohol use, maternal history of mental illness or ASD, pre-pregnancy diabetes mellitus or chronic hypertension, and infant sex.

**eTable 3. Risk of Autism Spectrum Disorder (ASD) by Mode of Conception.** These analyses are limited to live-born children of mothers aged < 45 years, including by mode of conception.

| Mode of conception | No. with ASD/ No. at risk | Rate of ASD per 1000 person-years | Unadjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI)[a] |
|---|---|---|---|---|
| Analysis among all 1,366,488 live-born children of women aged < 45 years | | | | |
| Unassisted conception | 18,659 / 1,183,508 | 1.93 | 1.00 (Referent) | 1.00 (Referent) |
| Subfertility | 2838 / 140,300 | 2.49 | 1.29 (1.24-1.34) | 1.20 (1.15-1.25) |
| Ovulation induction or intrauterine insemination | 404 / 20,361 | 2.73 | 1.31 (1.19-1.46) | 1.21 (1.09-1.34) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 426 / 22,319 | 2.64 | 1.27 (1.14-1.40) | 1.14 (1.03-1.27) |
| | | | | |
| Analysis limited to 182,980 live-born children of individuals aged < 45 years with infertility | | | | |
| Subfertility | 2838 / 140,300 | 2.49 | 1.00 (Referent) | 1.00 (Referent) |
| Ovulation induction or intrauterine insemination | 404 / 20,361 | 2.73 | 1.01 (0.91-1.13) | 1.02 (0.92-1.14) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 426 / 22,319 | 2.64 | 0.98 (0.88-1.09) | 0.93 (0.83-1.04) |
| | | | | |
| Analysis limited to 22,319 live-born children of individuals aged < 45 years who underwent *In vitro* fertilization or intracytoplasmic sperm injection | | | | |
| *In vitro* fertilization | 378 / 19,882 | 2.63 | 1.00 (Referent) | 1.00 (Referent) |
| Intracytoplasmic sperm injection | 48 / 2437 | 2.76 | 1.04 (0.76-1.42) | 1.06 (0.78-1.45) |

[a] Adjusted for maternal age, income quintile, rurality, immigration status, smoking, obesity, parity, any drug or alcohol use, maternal history of mental illness or ASD, pre-pregnancy diabetes mellitus or chronic hypertension, and infant sex.

**eTable 4. Risk of Autism Spectrum Disorder (ASD) by Mode of Conception.** Analysis additionally adjusted for calendar year.

| Mode of conception | No. with ASD/ No. at risk | Rate of ASD per 1000 person-years | Unadjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI)[a] |
|---|---|---|---|---|
| Analysis among all 1,370,152 singleton live-born children | | | | |
| Unassisted conception | 18,689 / 1,185,024 | 1.93 | 1.00 (Referent) | 1.00 (Referent) |
| Subfertility | 2858 / 141,180 | 2.49 | 1.29 (1.24-1.34) | 1.20 (1.15-1.25) |
| Ovulation induction or intrauterine insemination | 404 / 20,429 | 2.72 | 1.31 (1.18-1.45) | 1.21 (1.09-1.34) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 458 / 23,519 | 2.71 | 1.29 (1.17-1.43) | 1.16 (1.04-1.28) |
| | | | | |
| Analysis limited to 185,128 singleton live-born children of individuals with infertility | | | | |
| Subfertility | 2858 / 141,180 | 2.49 | 1.00 (Referent) | 1.00 (Referent) |
| Ovulation induction or intrauterine insemination | 404 / 20,429 | 2.72 | 1.01 (0.91-1.12) | 1.03 (0.92-1.15) |
| *In vitro* fertilization or intracytoplasmic sperm injection | 458 / 23,519 | 2.71 | 1.00 (0.90-1.11) | 0.95 (0.85-1.05) |
| | | | | |
| Analysis limited to 23,519 live-born children of individuals who underwent i*n vitro* fertilization or intracytoplasmic sperm injection | | | | |
| *In vitro* fertilization | 408 / 20,968 | 2.70 | 1.00 (Referent) | 1.00 (Referent) |
| Intracytoplasmic sperm injection | 50 / 2,551 | 2.77 | 1.01 (0.75-1.37) | 1.05 (0.77-1.42) |

[a] Adjusted for maternal age, parity, income quintile, rurality, immigration status, smoking, obesity, any drug or alcohol use, maternal history of mental illness or ASD, pre-pregnancy diabetes mellitus or chronic hypertension, infant sex, and calendar year

**eTable 5. Mediation Analysis of the Effect of Selected Adverse Pregnancy Outcomes on the Association Between Mode of Conception and Associated Risk of Autism Spectrum Disorder (ASD). Each mode of conception is compared to a birth in a mother with unassisted conception (reference group).** This analysis is restricted to 1,322,578 singleton live births.

| Adverse pregnancy outcome mediator assessed | Mode of conception | Adjusted hazard ratio, total effect (95% CI) | Adjusted hazard ratio[a], natural direct effect (95% CI) | Adjusted hazard ratio[a], natural indirect effect (95% CI) | Proportion mediated (%) |
|---|---|---|---|---|---|
| Preeclampsia | Subfertility | 1.20 (1.16-1.23) | 1.20 (1.17-1.22) | 1.00 (0.98-1.02) | 0.6 |
| | Ovulation induction or intrauterine insemination | 1.15 (1.09-1.22) | 1.15 (1.08-1.22) | 1.00 (0.98-1.02) | 2.8 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.03 (0.97-1.10) | 1.03 (0.97-1.09) | 1.01 (0.99-1.02) | 16.3 |
| | | | | | |
| Caesarean birth | Subfertility | 1.20 (1.16-1.23) | 1.19 (1.16-1.21) | 1.01 (0.99-1.03) | 5.5 |
| | Ovulation induction or intrauterine insemination | 1.15 (1.09-1.23) | 1.15 (1.08-1.21) | 1.01 (0.99-1.03) | 5.5 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.03 (0.96-1.10) | 1.01 (0.95-1.07) | 1.02 (1.00-1.04) | 69.0[b] |
| | | | | | |
| *Planned Caesarean birth*[c] | Subfertility | 1.18 (1.14-1.21) | 1.17 (1.14-1.19) | 1.01 (0.99-1.03) | 5.7 |
| | Ovulation induction or intrauterine insemination | 1.16 (1.08-1.25) | 1.15 (1.08-1.23) | 1.01 (0.99-1.03) | 5.6 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.04 (0.97-1.12) | 1.02 (0.95-1.10) | 1.02 (1.00-1.04) | 49.5 |
| | | | | | |
| *Unplanned Caesarian birth*[d] | Subfertility | 1.20 (1.16-1.24) | 1.19 (1.16-1.22) | 1.00 (0.98-1.03) | 2.7 |
| | Ovulation induction or intrauterine insemination | 1.16 (1.09-1.24) | 1.16 (1.09-1.23) | 1.00 (0.98-1.02) | 2.5 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.01 (0.93-1.08) | 0.99 (0.93-1.07) | 1.01 (0.99-1.03) | N/A[e] |
| | | | | | |
| Preterm birth < 37 weeks | Subfertility | 1.20 (1.16-1.23) | 1.19 (1.16-1.21) | 1.01 (0.99-1.03) | 4.1 |
| | Ovulation induction or intrauterine insemination | 1.15 (1.09-1.23) | 1.15 (1.08-1.21) | 1.01 (0.99-1.03) | 4.4 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.03 (0.97-1.10) | 1.02 (0.96-1.08) | 1.02 (1.00-1.04) | 48.9 |
| | | | | | |
| Neonatal adverse morbidity | Subfertility | 1.20 (1.16-1.23) | 1.19 (1.17-1.22) | 1.00 (0.99-1.02) | 2.7 |
| | Ovulation induction or intrauterine insemination | 1.15 (1.09-1.22) | 1.15 (1.08-1.21) | 1.00 (0.99-1.02) | 3.2 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 1.03 (0.96-1.10) | 1.02 (0.96-1.09) | 1.01 (0.99-1.03) | 28.9 |

[a]Adjusted for maternal age, parity, income quintile, rurality, immigration status, smoking, obesity, any drug or alcohol use, maternal history of mental illness or ASD, pre-pregnancy diabetes mellitus or chronic hypertension, and infant sex.

[b]Statistically significant natural indirect effect at a P-value < 0.05.

[c]Among 135,058 pregnancies.

[d]Among 135,139 pregnancies.

[e]Not applicable, as "the [proportion-mediated measure] is problematic when the natural direct effect and natural indirect effect operate in different directions. One can obtain a proportion mediated much larger than 100%, and the measure is no longer really meaningful. Even more dramatically, if the natural direct and indirect effects are of roughly the same magnitude but of opposite signs, then the total effect will be close to zero and the proportion-mediated measure then takes the natural indirect effect and divides it by a number close to zero which will result in an enormous (and again meaningless) proportion." Source: VanderWeele TJ. Explanation in Causal Inference: Methods for Mediation and Interaction. New York, NY: Oxford University Press, 2015, page 48.

**eTable 6. Mediation Analysis of the Effect of Selected Adverse Pregnancy Outcomes on the Association Between Mode of Conception and Associated Risk of Autism Spectrum Disorder (ASD) Among 1,370,152 Live-Born Children.** Each mode of conception is compared to a birth in a mother with subfertility (reference group).

| Adverse pregnancy outcome mediator assessed | Mode of conception | Adjusted hazard ratio, total effect (95% CI) | Adjusted hazard ratio[a], natural direct effect (95% CI) | Adjusted hazard ratio[a], natural indirect effect (95% CI) | Proportion mediated (%) |
|---|---|---|---|---|---|
| Preeclampsia | Unassisted conception | 0.84 (0.81-0.86) | 0.84 (0.82-0.85) | 1.00 (0.98-1.02) | 0.5 |
| | Ovulation induction or intrauterine insemination | 0.96 (0.90-1.02) | 0.96 (0.90-1.02) | 1.00 (0.98-1.02) | 6.6 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.86 (0.81-0.92) | 0.86 (0.81-0.92) | 1.00 (0.99-1.02) | 2.5 |
| | | | | | |
| Caesarean birth | Unassisted conception | 0.83 (0.81-0.86) | 0.85 (0.83-0.86) | 0.99 (0.97-1.01) | 6.3 |
| | Ovulation induction or intrauterine insemination | 1.01 (0.95-1.07) | 1.00 (0.95-1.06) | 1.01 (0.99-1.03) | 74.3 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.95 (0.90-1.01) | 0.93 (0.89-0.98) | 1.02 (1.01-1.04) | 51.3[b] |
| | | | | | |
| *Planned Caesarean birth*[c] | Unassisted conception | 0.85 (0.82-0.88) | 0.86 (0.84-0.88) | 0.99 (0.97-1.01) | 6.1 |
| | Ovulation induction or intrauterine insemination | 1.01 (0.94-1.07) | 1.00 (0.94-1.06) | 1.01 (0.99-1.03) | N/A[d] |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.95 (0.89-1.02) | 0.93 (0.87-0.99) | 1.03 (1.01-1.05) | 57.1[b] |
| | | | | | |
| *Unplanned Caesarian birth*[e] | Unassisted conception | 0.84 (0.81-0.86) | 0.84 (0.82-0.86) | 0.99 (0.97-1.01) | 3.5 |
| | Ovulation induction or intrauterine insemination | 1.01 (0.95-1.08) | 1.01 (0.95-1.07) | 1.00 (0.98-1.02) | 22.9 |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.93 (0.88-1.00) | 0.92 (0.87-0.98) | 1.02 (1.00-1.04) | 24.5 |
| | | | | | |
| Multiple pregnancy | Unassisted conception | 0.86 (0.83-0.88) | 0.87 (0.84-0.89) | 0.99 (0.97-1.01) | 7.4 |
| | Ovulation induction or intrauterine insemination | 1.03 (0.96-1.09) | 0.98 (0.92-1.03) | 1.05 (1.03-1.07) | N/A[d] |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.98 (0.90 -1.04) | 0.89 (0.84-0.95) | 1.10 (1.06-1.13) | N/A[d] |
| | | | | | |
| Preterm birth < 37 weeks | Unassisted conception | 0.84 (0.82-0.86) | 0.85 (0.83-0.87) | 0.99 (0.97-1.00) | 7.9 |
| | Ovulation induction or intrauterine insemination | 1.00 (0.95-1.06) | 0.98 (0.92-1.03) | 1.03 (1.01-1.05) | N/A[d] |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.98 (0.92-1.03) | 0.92 (0.87-0.97) | 1.06 (1.04-1.08) | N/A[d] |
| | | | | | |
| Neonatal adverse morbidity | Unassisted conception | 0.84 (0.81-0.86) | 0.84 (0.83-0.86) | 0.99 (0.97-1.01) | 4.3 |
| | Ovulation induction or intrauterine insemination | 1.00 (0.95-1.06) | 0.99 (0.94-1.04) | 1.02 (1.00-1.03) | N/A[d] |
| | *In vitro* fertilization or intracytoplasmic sperm injection | 0.97 (0.92-1.02) | 0.95 (0.90-0.99) | 1.03 (1.01-1.05) | 88.4[b] |

[a]Adjusted for maternal age, parity, income quintile, rurality, immigration status, smoking, obesity, any drug or alcohol use, maternal history of mental illness or ASD, pre-pregnancy diabetes mellitus or chronic hypertension, and infant sex.

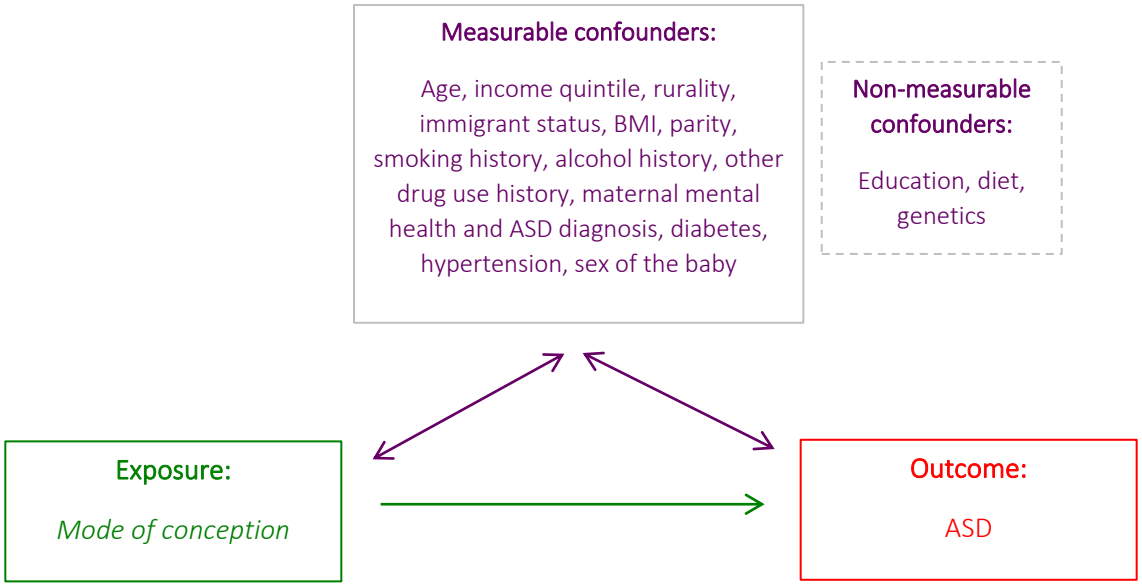
[b]Statistically significant natural indirect effect at a P-value < 0.05.

[c]Among 1,176,963 pregnancies.

[e]Not applicable, as "the [proportion-mediated measure] is problematic when the natural direct effect and natural indirect effect operate in different directions. One can obtain a proportion mediated much larger than 100%, and the measure is no longer really meaningful. Even more dramatically, if the natural direct and indirect effects are of roughly the same magnitude but of opposite signs, then the total effect will be close to zero and the proportion-mediated measure then takes the natural indirect effect and divides it by a number close to zero which will result in an enormous (and again meaningless) proportion." Source: VanderWeele TJ. Explanation in Causal Inference: Methods for Mediation and Interaction. New York, NY: Oxford University Press, 2015, page 48.

[e]Among 1,159,016 pregnancies.

**eFigure 1. Conventional Model to Examine the Relation Between Mode of Conception and Autism Spectrum Disorder (ASD) in Childhood.**



**eFigure 2. Causal Mediation Analysis of the Relation Between Mode of Conception and Autism Spectrum Disorder (ASD) in Children**