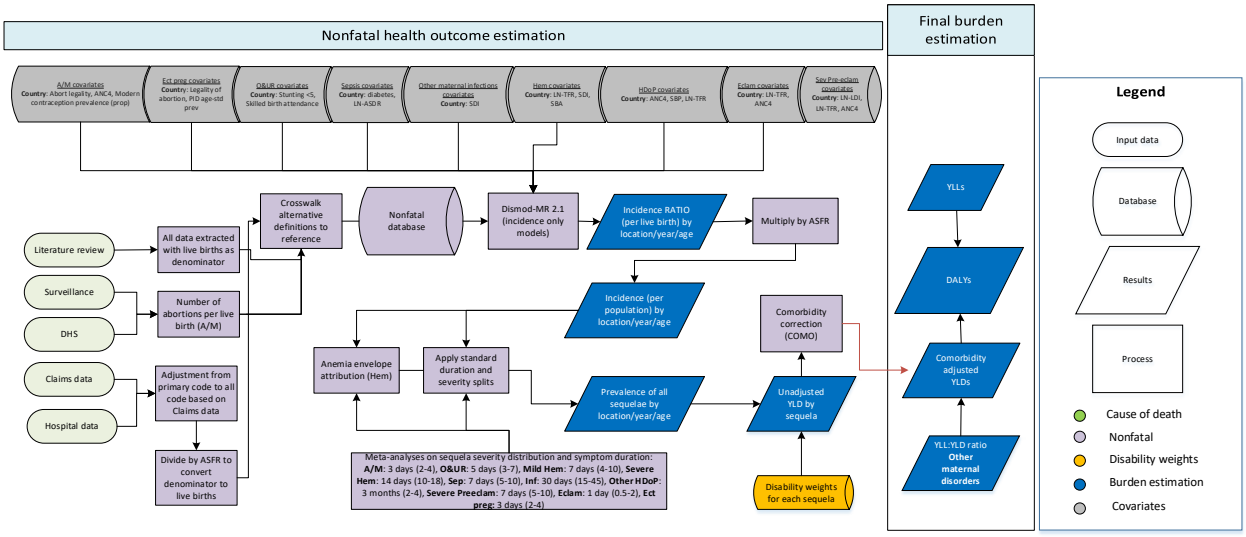
Maternal disorders

Maternal disorders non-fatal burden estimation includes estimation of disability due to seven direct obstetric complications: 1) Abortion and miscarriage; 2) Ectopic pregnancy; 3) Obstructed labour and uterine rupture; 4) Maternal haemorrhage; 5) Maternal sepsis and other maternal infections; 6) Maternal hypertensive disorders; and 7) Other [direct] maternal disorders. These correspond to seven of nine subcauses of maternal death for which we estimate fatal burden. We do not estimate non-fatal burden related to the diseases and injuries underlying indirect maternal deaths and maternal deaths aggravated by HIV/AIDS, based on the premise that non-fatal burden associated with these diseases and injuries is captured in the respective underlying GBD cause.

Flowchart

Maternal disorders: 1) Abortion and miscarriage; 2) Obstructed labor and uterine rupture; 3) Maternal hemorrhage; 4) Maternal sepsis and other maternal infections; 5) Maternal hypertensive disorders; 6) Ectopic pregnancy 7) Other maternal disorders



Abbreviations

A/M: Abortion and miscarriage; Ect Preg: Ectopic pregnancy; O&UR: Obstructed labor and uterine rupture; Hem: Maternal hemorrhage; Sep: Maternal sepsis; Inf: Other maternal infections; HDoP: Maternal hypertensive disorders; Eclam: Eclampsia; Sev pre-eclam: Severe pre-eclampsia; ASFR: Age-specific fertility rate; Stunting <5: Stunting (proportion <2SD height for age, <5 years); MS: Marketscan; ANC4: coverage of 4 visits of antenatal care; SDI: Socio-Demographic Index; lit: Literature data; inpt: Inpatient data; not repr: Not representative; LN: Natural log; TFR: Total fertility rate; LDI: Lag-distributed income per capita; SBA: Skilled birth attendance (proportion), IFD: In facility delivery

Input data and methodological summary

Case definition

Maternal disorders are direct obstetric complications of pregnancy, childbirth, and the postpartum period. These include:

1) Abortion is defined as elective or medically-indicated termination of pregnancy at any gestational age and miscarriage is defined as spontaneous loss of pregnancy before 24 weeks of gestation *with complications requiring medical care*.
2) Ectopic pregnancy defined as any pregnancy occurring outside of the uterus.
3) Obstructed labour and uterine rupture.
    a. Acute event includes failure to progress (no advance of the presenting part of the foetus despite strong uterine contractions), cephalopelvic disproportion (foetal size that is too large for maternal pelvic dimensions), non-vertex foetal positioning during labour (any foetal position besides head down during labour; excludes non-vertex positioning during

antepartum period), and uterine rupture during labour (non-surgical breakdown of uterine wall during labour and delivery). Perineal lacerations without any of the above conditions are excluded from the case definition. (*Estimation of the incidence and short-term disability due to these conditions is described in this appendix section*.)

   b. Fistula is defined as an abnormal connection between either vagina and large intestine (rectovaginal fistula) or between vagina bladder (vesicovaginal fistula). (*The non-fatal burden of fistulas are included in the non-fatal burden of obstructed labour in reporting, but estimation is described in a separate appendix section on "Fistula – impairment."*)

4) Maternal haemorrhage (including placental disorders) – includes both postpartum (>500 ml for vaginal delivery and >1,000 ml for caesarean delivery) and antepartum haemorrhage (vaginal bleeding from any cause at or beyond 20 weeks of gestation and prior to onset of labour). This also includes placental disorders with haemorrhage regardless of blood volume lost or timing of bleeding event. Placental disorders without haemorrhage are included with other [direct] maternal disorders.
5) Maternal sepsis and other maternal infections.
   a. Maternal sepsis is defined as a temperature <36°C or >38°C and clinical signs of shock including systolic blood pressure <90 mm Hg or tachycardia >120 bpm
   b. Other maternal infections are defined as any maternal infections excluding HIV, sexually-transmitted infections, or are not believed to have epidemiological relationship with pregnancy. Examples include urinary tract infections, mastitis, candidiasis, and bacterial vaginosis during pregnancy.
6) Hypertensive disorders of pregnancy – overall category defined as having blood pressure (BP) >140/90 based on multiple measurements in persons who were not hypertensive prior to pregnancy. This category includes several subcategories.
   a. Severe pre-eclampsia is defined by severe hypertension (>160/100), proteinuria (>=0.3 g/l), and additional signs of end-organ damage (liver: low platelets, elevated liver enzymes, coagulation issues; kidney: elevated creatinine; CNS: headaches or visual disturbances). We include here the syndrome of hypertension elevated liver low platelets (HELLP syndrome).
   b. Eclampsia is defined as hypertension and seizures, with or without proteinuria.
   c. Other hypertensive disorders of pregnancy, defined to include gestational hypertension (blood pressure >140/90 based on multiple measurements in persons not hypertensive prior to pregnancy, but without proteinuria or other symptoms) and pre-eclampsia (hypertension [>140/90] and proteinuria without signs of end-organ damage).
7) Other [direct] maternal disorders include a variety of different obstetric complications. The most common of these in ICD-10 coded vital registration sources in terms of number of deaths include O88 (obstetric embolism), O26 (Maternal care for other conditions predominantly related to pregnancy), O90 (Complications of the puerperium, not elsewhere classified), O75 (Other complications of labour and delivery, not elsewhere classified), C58 (Malignant neoplasm of placenta), and O36 (Maternal care for other foetal problems).

Input data

Systematic literature reviews have been completed annually since GBD 2010 and use a consolidated search string for all components of maternal burden estimation. These were updated on May 10, 2019, using the search string below.

(((("Postpartum Hemorrhage" OR "Uterine Hemorrhage") OR (maternal[Title/Abstract] OR pregnan*[Title/Abstract] OR mothers) AND (haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract]) NOT "case report"[All fields]) OR ((

"induced abortion" OR "Therapeutic abortion" OR "legal Abortion" OR "medical abortion" OR "miscarriage" OR "Abortion, Induced"[Mesh] OR "Abortion, Therapeutic"[Mesh] OR "Abortion, Legal"[Mesh] OR "ectopic Pregnancy") NOT ("case report"[Title/Abstract] OR "birth defect"[Title/Abstract] OR congenital[Title/Abstract])) OR ("obstructed labour" OR "obstructed labor" OR "labour dystocia" OR "labor dystocia" OR dystocia OR "cephalopelvic disproportion" OR "cephalo-pelvic disproportion") OR (("obstetric fistula" OR "vesicovaginal fistula") OR "rectovaginal fistula") OR (("Puerperal Infection"[Mesh] OR "Puerperal Infection" OR ((maternal[Title/Abstract] OR pregnan*[Title/Abstract]) AND (Sepsis OR infection[Title/Abstract]))) NOT "case report") OR ((pre-eclampsia[Title/Abstract] OR preeclampsia[Title/Abstract] OR eclampsia[Title/Abstract] OR Pre-Eclampsia[Mesh] OR Eclampsia[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "pregnancy induced hypertension"[Title/Abstract] OR "gestational hypertension"[Title/Abstract] OR "Hypertensive disorders of pregnancy"[Title/Abstract]) NOT ("case report" OR "kidney donor"[Title/Abstract] OR "kidney donors"[Title/Abstract] OR polymorphism*[Title/Abstract] OR endotheli*[Title/Abstract]))) OR((("maternal mortality"[Title/Abstract] OR "maternal death"[Title/Abstract] OR "maternal deaths"[Title/Abstract] OR "MM"[Title/Abstract] OR "confidential enquiry"[Title/Abstract] OR "confidential inquiry"[Title/Abstract] OR ((obstetric[Title/Abstract] OR pregnan*[Title/Abstract]) AND (etiology[Title/Abstract] OR cause[Title/Abstract] OR pattern[Title/Abstract]) AND (death[Title/Abstract] OR mortality[Title/Abstract]))) NOT (fetal[Title/Abstract] OR newborn*[Title/Abstract] OR neonatal[Title/Abstract] OR "case report" [Title/Abstract] OR "case study" [Title/Abstract] OR pathogenesis[Title/Abstract] OR thromboprophylaxis[Title/Abstract])) OR ((("maternal mortality"[Title/Abstract] OR "maternal death"[Title/Abstract] OR "maternal deaths"[Title/Abstract] OR "MMR"[Title/Abstract]) AND ("Afghanistan"[Title/Abstract] OR "Albania"[Title/Abstract] OR "Algeria"[Title/Abstract] OR "Andorra"[Title/Abstract] OR "Angola"[Title/Abstract] OR "Antigua and Barbuda"[Title/Abstract] OR "Argentina"[Title/Abstract] OR "Armenia"[Title/Abstract] OR "Azerbaijan"[Title/Abstract] OR "Bahrain"[Title/Abstract] OR "Bangladesh"[Title/Abstract] OR "Barbados"[Title/Abstract] OR "Belarus"[Title/Abstract] OR "Belize"[Title/Abstract] OR "Benin"[Title/Abstract] OR "Bhutan"[Title/Abstract] OR "Bolivia"[Title/Abstract] OR "Bosnia and Herzegovina"[Title/Abstract] OR "Botswana"[Title/Abstract] OR "Brazil"[Title/Abstract] OR "Brunei"[Title/Abstract] OR "Bulgaria"[Title/Abstract] OR "Burkina Faso"[Title/Abstract] OR "Burundi"[Title/Abstract] OR "Cambodia"[Title/Abstract] OR "Cameroon"[Title/Abstract] OR "Cape Verde"[Title/Abstract] OR "Central African Republic"[Title/Abstract] OR "Chad"[Title/Abstract] OR "China"[Title/Abstract] OR "Colombia"[Title/Abstract] OR "Comoros"[Title/Abstract] OR "Congo"[Title/Abstract] OR "Costa Rica"[Title/Abstract] OR "Croatia"[Title/Abstract] OR "Cuba"[Title/Abstract] OR "Cyprus"[Title/Abstract] OR "Côte d'Ivoire"[Title/Abstract] OR "Democratic Republic of the Congo"[Title/Abstract] OR "Djibouti"[Title/Abstract] OR "Dominica"[Title/Abstract] OR "Dominican Republic"[Title/Abstract] OR "Ecuador"[Title/Abstract] OR "Egypt"[Title/Abstract] OR "El Salvador"[Title/Abstract] OR "Equatorial Guinea"[Title/Abstract] OR "Eritrea"[Title/Abstract] OR "Ethiopia"[Title/Abstract] OR "Federated States of Micronesia"[Title/Abstract] OR "Fiji"[Title/Abstract] OR "Gabon"[Title/Abstract] OR "Georgia"[Title/Abstract] OR "Ghana"[Title/Abstract] OR "Grenada"[Title/Abstract] OR "Guatemala"[Title/Abstract] OR "Guinea"[Title/Abstract] OR "Guinea-Bissau"[Title/Abstract] OR "Guyana"[Title/Abstract] OR "Haiti"[Title/Abstract] OR "Honduras"[Title/Abstract] OR "India"[Title/Abstract] OR "Indonesia"[Title/Abstract] OR "Iran"[Title/Abstract] OR "Iraq"[Title/Abstract] OR "Jamaica"[Title/Abstract] OR "Jordan"[Title/Abstract] OR "Kazakhstan"[Title/Abstract] OR "Kenya"[Title/Abstract] OR "Kiribati"[Title/Abstract] OR "Kuwait"[Title/Abstract] OR "Kyrgyzstan"[Title/Abstract] OR "Laos"[Title/Abstract] OR "Latvia"[Title/Abstract] OR "Lebanon"[Title/Abstract] OR "Lesotho"[Title/Abstract] OR "Liberia"[Title/Abstract] OR "Libya"[Title/Abstract] OR "Lithuania"[Title/Abstract] OR "Macedonia"[Title/Abstract] OR "Madagascar"[Title/Abstract] OR "Malawi"[Title/Abstract] OR "Malaysia"[Title/Abstract] OR "Maldives"[Title/Abstract] OR "Mali"[Title/Abstract] OR "Malta"[Title/Abstract] OR "Marshall Islands"[Title/Abstract] OR "Mauritania"[Title/Abstract] OR "Mauritius"[Title/Abstract] OR "Moldova"[Title/Abstract] OR "Mongolia"[Title/Abstract] OR "Montenegro"[Title/Abstract] OR "Morocco"[Title/Abstract] OR "Mozambique"[Title/Abstract] OR "Myanmar"[Title/Abstract] OR "Namibia"[Title/Abstract] OR "Nepal"[Title/Abstract] 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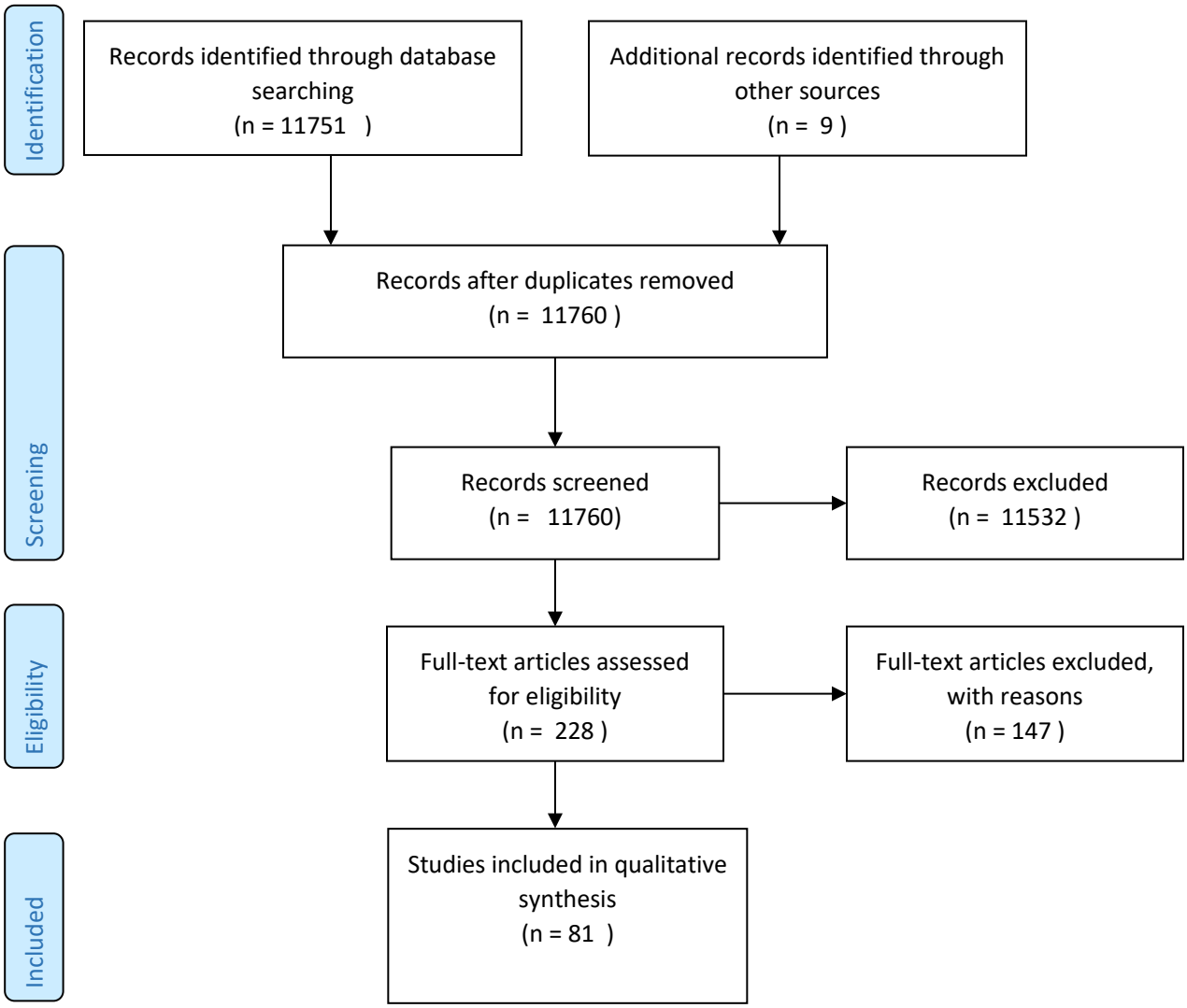
"Swaziland"[Title/Abstract] OR "Syria"[Title/Abstract] OR "São Tomé and Principe"[Title/Abstract] OR "Taiwan"[Title/Abstract] OR "Tajikistan"[Title/Abstract] OR "Tanzania"[Title/Abstract] OR "Thailand"[Title/Abstract] OR "The Bahamas"[Title/Abstract] OR "The Gambia"[Title/Abstract] OR "Timor-Leste"[Title/Abstract] OR "Togo"[Title/Abstract] OR "Tonga"[Title/Abstract] OR "Trinidad and Tobago"[Title/Abstract] OR "Tunisia"[Title/Abstract] OR

"Turkmenistan"[Title/Abstract] OR "Uganda"[Title/Abstract] OR "Ukraine"[Title/Abstract] OR "United Arab Emirates"[Title/Abstract] OR "Uruguay"[Title/Abstract] OR "Uzbekistan"[Title/Abstract] OR "Vanuatu"[Title/Abstract] OR "Venezuela"[Title/Abstract] OR "Vietnam"[Title/Abstract] OR "Yemen"[Title/Abstract] OR "Zambia"[Title/Abstract] OR "Zimbabwe"[Title/Abstract])) NOT ("demographic and health survey"[Title/Abstract] OR "demographic and health surveys "[Title/Abstract] OR DHS[Title/Abstract] OR "reproductive health survey"[Title/Abstract] OR "reproductive health surveys"[Title/Abstract] OR RHS[Title/Abstract])) OR ((HIV[Title/Abstract] OR "Acquired Immunodeficiency Syndrome"[Title/Abstract] OR AIDS[Title/Abstract]) AND (pregnan*[Title/Abstract] OR "postpartum"[Title/Abstract] OR "post partum"[Title/Abstract]) AND ("mortality"[Title/Abstract] OR "death"[Title/Abstract]) NOT "case report")) AND (2017/07/01[PDat] : 3000[PDat]) NOT (animals[MeSH] NOT humans[MeSH]))

PRISMA 2009 Flow Diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



This search produced 117560 hits for title and abstract review. Of these 228 were selected for full-text review and 81 were extracted for inclusion in the models.

In addition, we searched ministry of health websites for pregnancy complication data and used Confidential Enquiry and other sources used in our maternal mortality analyses when they presented data on pregnancy complications. We also performed snowball searches for abortion reporting and surveillance data systems, finding multiple such systems throughout high-income countries and several geographies in Central and Eastern Europe. The table below summarises the number of sources used in each model by cause.

Table 1. Data sources used in estimation of non-fatal pregnancy complications

Cause/Impairment Name	Measure	Total sources	Countries with data
Maternal haemorrhage	All measures	497	88
Maternal haemorrhage	Incidence	497	88
Maternal sepsis and other maternal infections	All measures	422	79
Maternal sepsis and other maternal infections	Incidence	422	79
Maternal hypertensive disorders	All measures	556	105
Maternal hypertensive disorders	Incidence	556	105
Maternal obstructed labour and uterine rupture	All measures	384	76
Maternal obstructed labour and uterine rupture	Prevalence	33	26
Maternal obstructed labour and uterine rupture	Incidence	351	59
Maternal obstructed labour and uterine rupture	Other	14	6
Ectopic pregnancy	All measures	347	59
Ectopic pregnancy	Incidence	347	59
Maternal abortion and miscarriage	All measures	623	59
Maternal abortion and miscarriage	Incidence	623	59

Hospital discharge data were used, as were claims data from Poland and Singapore as well as MarketScan in the United States. These data were extracted and processed as described in the appendix section on claims, inpatient, and outpatient data, including use of primary-to-any inpatient ratio to correct for under-reporting of pregnancy complications in hospital datasets that rely only on primary discharge codes, and inpatient-to-outpatient ratio. Processing of clinical administrative data (ie, hospital and claims) were based on ICD-9 and ICD-10 codes as listed in the table below. We only used inpatient data, corrected for location-year-specific HAQI value for most models, with four exceptions – Hypertensive disorders of pregnancy (total), abortion and miscarriage, ectopic pregnancy, and other maternal infections.

All data were either extracted as incidence ratio (number of events / live birth) or, if data were only available with population as the denominator, they were converted to incidence ratio using GBD 2020 age-specific fertility rate (number of live births / population). The reason is that most literature and surveillance data are expressed in terms of number of events per livebirth rather than per population. Hospital and claims data, which were centrally processed for all GBD 2020 causes to have population as the denominator, were transformed to have livebirths as the denominator by dividing by age-specific fertility rate (ASFR; live births per population).

Table 2. Maternal ICD codes

Non-fatal model	ICD10 code	ICD9 code
Ectopic pregnancy	O00	633
Maternal abortive outcome	N96, O01-O08	630-632, 634-636, 638
Maternal haemorrhage	O20, O43.2, O44-O46, O62.2, O67, O72	640-641, 661.2, 665, 666
Hypertensive disorders of pregnancy	O11-16	642 (excluding 642.0-642.2)
Severe pre-eclampsia	O14.1	642.5
Eclampsia	O15	642.6
Obstructed labour and uterine rupture	O64-O66, O70-O71, O83-O84	652.7, 653, 659.0, 660, 664-665, 669.5
Maternal sepsis	O85	646.5-646.6, 659.3, 670
Other maternal infections	O23, O41.1-O41.9, O86, O91	658.4, 659.2, 672

We also use input data to calculate incidence rate, prevalence and severity of these disorders after completion of the DisMod-MR 2.1 models. We use data for to estimate the proportion of maternal haemorrhage that is mild and severe, the proportion of hypertensive disorders of pregnancy that are long-term sequelae, the proportion of puerperal sepsis cases that continue on to develop secondary infertility. We rely on expert opinion to determine the duration of each of the maternal disorders in order to calculate prevalence.

Data processing

Previously we derived empirical age patterns and performed all crosswalks in DisMod-MR 2.1. Our data processing approach changed for GBD 2019 such that all of this occurred prior to DisMod-MR 2.1 modelling, and we continued with these pre-modelling approaches in GBD 2020.

The first step of data processing was age splitting. For any datum that did not entirely fit within a GBD age group, the observation was split to be multiple age-specific datapoints based on the age pattern predicted by GBD 2019 Decomposition 1 DisMod-MR 2.1 models.

The second step was to develop and apply adjustment factors to correct systematic biases in data collected using non-reference ("alternate") case definitions or collection methods. This process is referred to as 'crosswalking'. In accordance with GBD 2020 principles for data processing, to make data comparable, we began by evaluating the number of observations of each alternate type that matched in year, age, sex and location of the population sampled with a corresponding observation of reference type. We considered within-study matches, where the same source reported both an alternative and reference type, as well as between-study matches, where the alternative and reference type were reported by different sources. For the disorders where we crosswalked based on data source type, we assessed the relative levels of the data and chose the reference data source to be the one with the most plausible values. The ratio of the two observations was then calculated and the standard error of the ratio was calculated using the delta method, and these ratios were modelled in log space using Meta-Regression – Bayesian, Regularised, Trimmed (MR-BRT), a meta-analytic tool developed for GBD 2019. The details of each of the crosswalks are described below by disorder. Across all disorders, all data

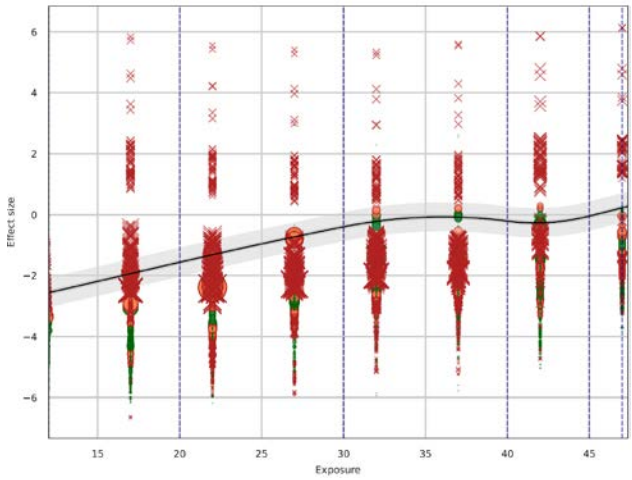
sources that only reported event rates for severe maternal morbidity or “near miss” were excluded as a reliable crosswalk model could not be developed.

The results of the crosswalks are shown in the section below. In each graph, the effect size is the log of the adjustment coefficient estimated by the model, the x-axis is the age, and the points are the input ratios. The X points are trimmed by the model. If the adjustment factor is negative then, the alternative is underestimating the incidence of the specific disorder, relative to the reference, whereas when it is positive, the inverse is true.

Abortion and miscarriage

Surveillance data are the reference category for abortion and miscarriage. US claims data were the only claims data in this dataset and they had similar levels to the US inpatient so we only ran one crosswalk. All clinical data were crosswalked to surveillance data by age.

Figure 1. Clinical to surveillance for abortion and miscarriage

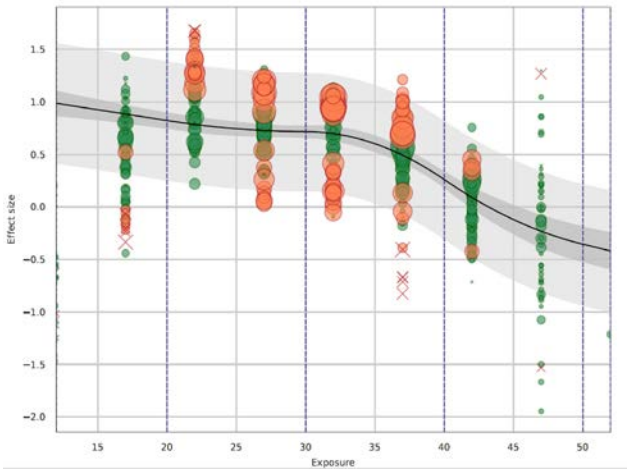


According to this model, clinical data underestimate the number of abortions compared to surveillance until age 45, where the crosswalk changes direction and clinical data overestimate the number of abortion relative to surveillance.

Ectopic pregnancy

We used hospital data adjusted for the inpatient-to-outpatient ratio for ectopic pregnancy. Claims data were the reference category. We crosswalked hospital data to claims by age.

Figure 1. Hospital data to claims data for ectopic pregnancy



According to this model, hospital data overestimated the number of ectopic pregnancies for most of the reproductive age groups. The adjustment factor decreases with age and after age 45, the inverse relationship is true.

Maternal haemorrhage

For maternal haemorrhage, the reference is all cases of maternal haemorrhage including post-partum bleeding ≥ 500ml in vaginal births and ≥ 1000ml in caesarean sections and any amount of bleeding prior to birth. All data sources that reported only on antepartum haemorrhage (APH) or postpartum haemorrhage (PPH) were crosswalked to total haemorrhage by age. We included only within-study matches for this model as many sources provided data for total haemorrhage as well as each subtype. We excluded severe cases of haemorrhage from this analysis due to sparsity of data.

Figure 3. PPH to all haemorrhage

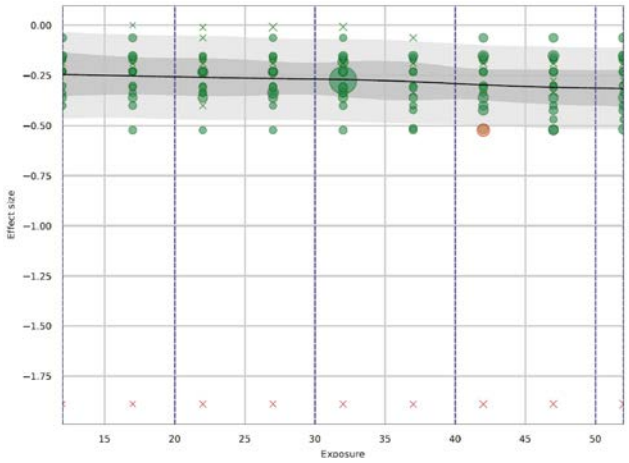
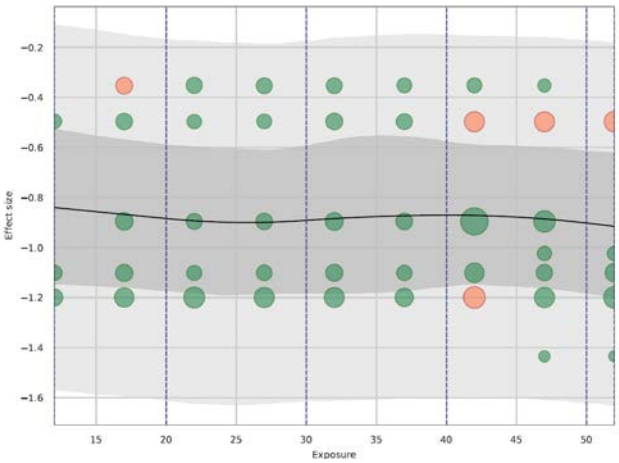


Figure 4. APH to all haemorrhage



The age-specific crosswalk was retained for consistency across all maternal pregnancy complications even though it was not significant in this case. The model shows that there is no difference in the adjustment factor between the different ages.

Puerperal sepsis

Puerperal sepsis cases reported in literature studies that included data collected from a variety of sites and matched our case definition were the reference category. We crosswalked claims data to inpatient

data by age. After this adjustment we crosswalked all of the clinical data to the reference data by age. The age pattern for the claims to inpatient crosswalk was significant with an increase with age until age 40. The age pattern of clinical to literature was slightly decreasing with age.

Figure 5. Claims to inpatient hospital

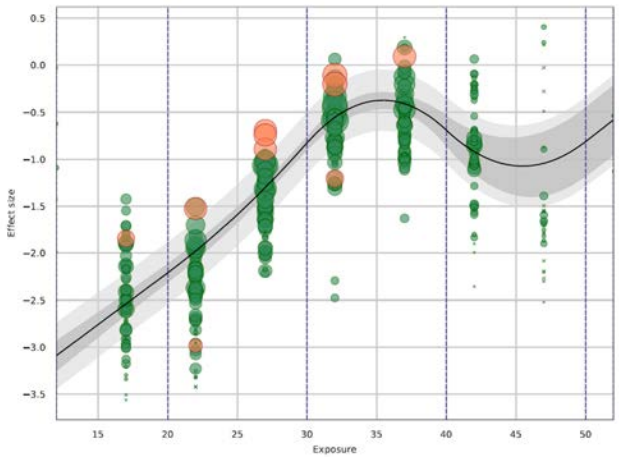
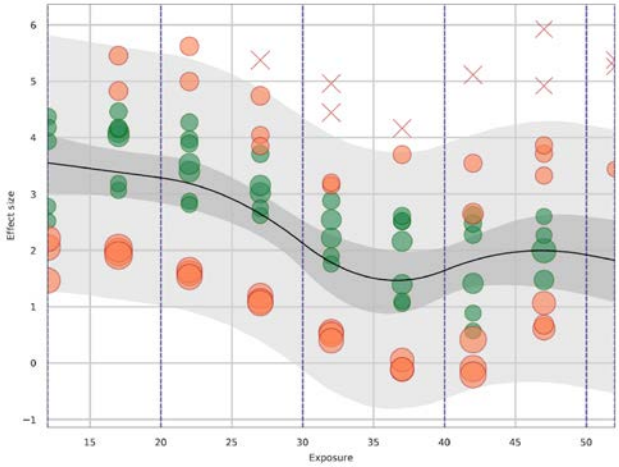


Figure 6. Clinical to lit. for puerperal sepsis

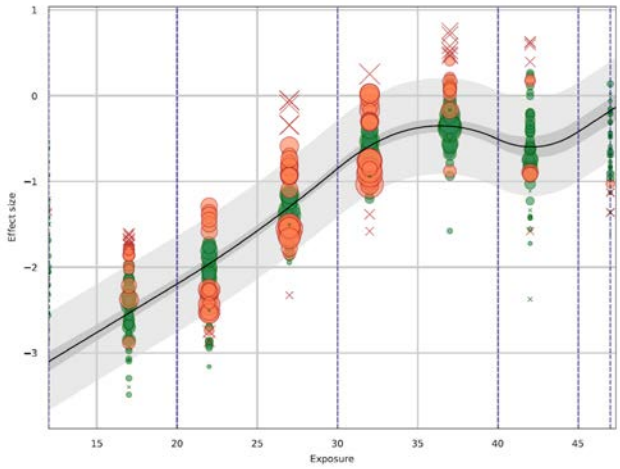


According to the model, claims data underestimated the number of sepsis cases, whereas clinical data overestimated the number of sepsis episodes relative to literature data.

Other maternal infections

Inpatient hospital data were the reference for other maternal infections. We crosswalked claims data to inpatient hospital data by age.

Figure 7. Claims to inpatient hospital data for other maternal infections



The model shows that claims data underestimate cases of maternal infections throughout the different age groups. The age pattern shows a steep increase in the ratio from ages 10 to 35. After age 35 the two data sources have more similar values with the adjustment factor being closer to 0.

Hypertensive disorders of pregnancy

For the overall hypertensive disorders of pregnancy (HDoP), any sources that reported only on pre-eclampsia (PE) or pregnancy induced hypertension (PIH) were crosswalked to total HDoP. We excluded studies reporting chronic hypertension from this process due to insufficient data.

Figure 8. PE to all HDoP

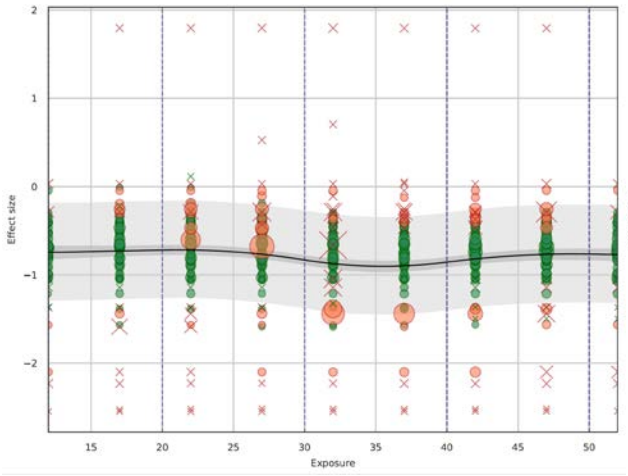
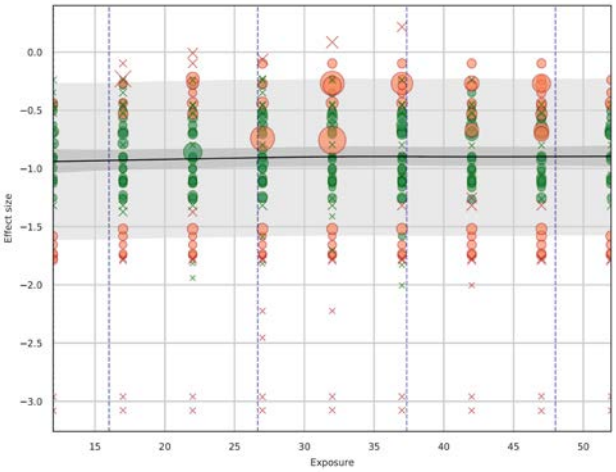


Figure 9. PIH to all HDoP

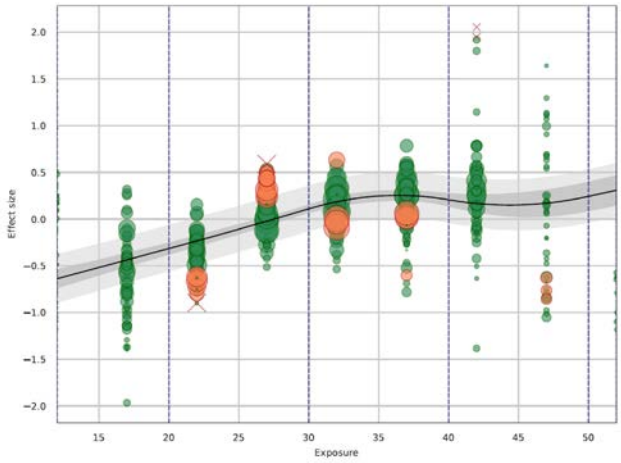


This crosswalk was again completed using only within-study matches and in an age-specific manner, although the age pattern was not significant.

Severe pre-eclampsia

We crosswalked claims data to inpatient hospital data for severe pre-eclampsia.

Figure 10. Claims to inpatient data for severe pre-eclampsia



The crosswalk had a significant age pattern with a slight increase in the ratio of claims to inpatient data with age (mostly from 10 to 35). The model shows that claims underestimate the incidence of severe pre-eclampsia relative to hospital data in ages 10 to 35. After age 35, the two data sources converge in with a slight overestimation of claims data relative to hospital data in the oldest age group.

Eclampsia

For eclampsia we considered the cases reported in literature studies that included data collected from a variety of sites and matched our case definition as the reference. We adjusted claims data to inpatient hospital data and then adjusted all of the clinical data to the reference data. These crosswalks were age-specific.

Figure 11. Claims data to inpatient hospital data

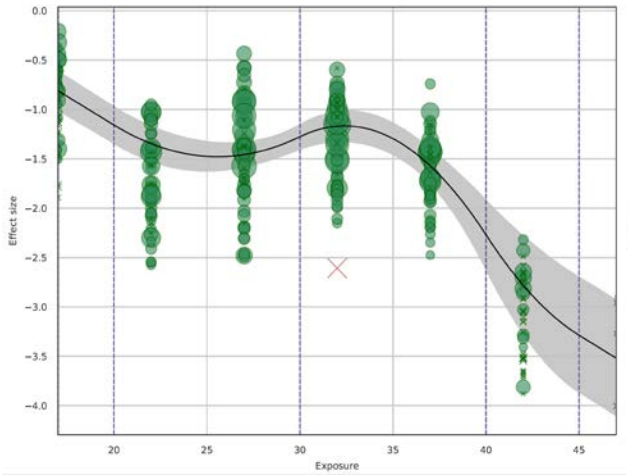
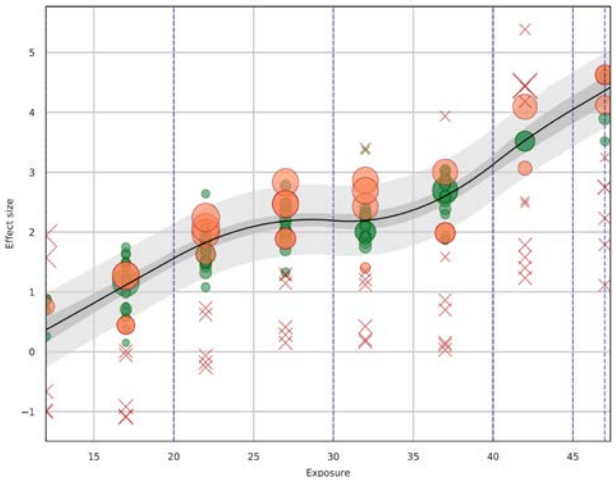


Figure 12. Clinical to lit. data for eclampsia



Both crosswalks had significant and opposite age patterns and directions. The claims to inpatient ratio decreases indicating that claims data underestimated the incidence of eclampsia relative to hospital data, and this underestimation grew larger with age. The clinical to literature crosswalk increases with age, indicating that the clinical data overestimated the incidence of eclampsia and that this difference grew larger with age.

Modelling strategy

Modelling incidence ratios

We used the datasets described above to estimate incidence ratio for each specified pregnancy complication for each year-age-location combination in the GBD 2020 estimation framework using DisMod-MR 2.1. A series of country covariates were chosen to help drive the magnitude of estimates in areas of sparse or absent data. We included the respective log-transformed maternal mortality ratio (MMR) for each maternal disorder that was estimated in GBD 2019 as a predictive covariate for almost every model. Puerperal sepsis and ectopic pregnancy used the log-transformed age-standardised death rate (LN-ASDR) as a covariate, instead of MMR. The coefficients of the covariates in each model are shown below. No specific age or slope priors were used. All models were run with a time window of five years.

Model	Covariate name	Beta value	Exponentiated beta value
Maternal haemorrhage	Skilled Birth Attendance (proportion)	-0.0024 (-0.0061 — -0.00013)	1.00 (0.99 — 1.00)
	Socio-demographic Index	-0.1 (-0.1 — -0.1)	0.90 (0.90 — 0.90)

	MMR due to maternal haemorrhage	1.00 (0.042 — 1.94)	2.72 (1.04 — 6.99)
Maternal hypertensive disorders	Antenatal Care (4 visits) Coverage (proportion)	-0.000033 (-0.00012 — -7.7e-7)	1.00 (1.00 — 1.00)
	MMR due to maternal hypertensive disorders	1.02 (0.057 — 2.00)	2.77 (1.06 — 7.39)
	Age-standardised SEV for High blood pressure	0.000042 (0.0000033 — 0.00016)	1.00 (1.00 — 1.00)
	Age-standardised SEV for High body-mass index	2.00 (2.00 — 2.00)	7.38 (7.38 — 7.38)
Eclampsia	Antenatal Care (4 visits) Coverage (proportion)	-1.84 (-1.86 — -1.81)	0.16 (0.16 — 0.16)
	MMR due to maternal hypertensive disorders	1.00 (0.054 — 1.95)	2.71 (1.06 — 7.01)
	Age-standardised SEV for High body-mass index	2.00 (1.98 — 2.00)	7.36 (7.27 — 7.39)
Obstructed labour	Skilled Birth Attendance (proportion)	-0.0061 (-0.017 — -0.00021)	0.99 (0.98 — 1.00)
	Age-standardised SEV for Child stunting	0.0097 (0.00052 — 0.031)	1.01 (1.00 — 1.03)
	MMR due to obstructed labour	1.01 (0.061 — 1.96)	2.74 (1.06 — 7.11)
Abortion and miscarriage	Legality of Abortion	0.018 (0.017 — 0.019)	1.02 (1.02 — 1.02)
	Contraception (Modern) Prevalence (proportion)	-0.0011 (-0.0027 — -0.000055)	1.00 (1.00 — 1.00)
Ectopic pregnancy	Legality of Abortion	-0.00036 (-0.00085 — -0.000012)	1.00 (1.00 — 1.00)
	Pelvic inflammatory disease age-standardised prevalence	0.50 (0.064 — 0.93)	1.65 (1.07 — 2.53)
Severe pre-eclampsia	Antenatal Care (4 visits) Coverage (proportion)	-0.0068 (-0.021 — -0.00021)	0.99 (0.98 — 1.00)
	MMR due to maternal hypertensive disorders	1.01 (0.059 — 1.96)	2.75 (1.06 — 7.12)
	Age-standardised SEV for High body-mass index	1.99 (1.98 — 2.00)	7.32 (7.21 — 7.39)
Maternal sepsis	Diabetes Age-Standardised Prevalence (proportion)	1.86 (1.55 — 2.00)	6.42 (4.71 — 7.36)
	Maternal sepsis and other maternal infections (lnASDR)	0.058 (0.026 — 0.095)	1.06 (1.03 — 1.10)
Other maternal infections	Socio-demographic Index	-0.011 (-0.032 — -0.00037)	0.99 (0.97 — 1.00)
	Log-transformed age-standardised SEV scalar: HIV	0.021 (0.0034 — 0.039)	1.02 (1.00 — 1.04)
	MMR due to sepsis and other maternal infections	1.00 (0.039 — 1.98)	2.71 (1.04 — 7.28)

If the exponentiated beta coefficient is smaller than 1 then the covariate is negatively associated with the outcome, if it is greater than 1 then the inverse is true.

Estimating incidence rates, prevalence, and YLDs

After completion of DisMod-MR 2.1 models, all age-specific incidence ratios were then converted to incidence rates by multiplying by ASFR and then to prevalence by applying globally assumed durations of disability for each pregnancy complication.

Maternal haemorrhage was split between moderate (500 to <1000 ml blood loss) and severe (≥1000 ml blood loss) on the basis of a meta-analysis of 19 studies[1]. Data on the average duration of acute symptoms were not available so, after consultation with clinician collaborators, we assigned a duration of seven days (+/-3) for moderate haemorrhage and 14 days (+/- 4) for severe haemorrhage. The age-specific anaemia prevalence for maternal haemorrhage was also analysed as part of overall anaemia causal attribution for GBD 2020. The details of the anaemia analysis are described separately in the "Anaemia Impairment" section. Briefly, after estimating total anaemia, a series of counterfactual

distributions are generated based on the age- and sex-specific prevalence of each anaemia-causing condition and the quantitative effect that the condition has on haemoglobin concentration in the blood, a so-called "haemoglobin shift," that was derived by meta-analysing cohort studies, observational studies, or trials comparing the haemotologic status of those with as compared to without the disease. Due to limited data on haemoglobin shift, all were assumed to be invariant over age, sex, location, and year.

For abortion and miscarriage, prevalence was calculated assuming incident cases have acute disability that persist for an average of three days (+/-1). The same was calculated for ectopic pregnancy. Obstructed labour was assigned a duration of five days (+/-2). Again, these determinations were based on clinical expert determination as we could not identify any data to inform this.

Hypertensive disorders of pregnancy (HDoP) was estimated in three models. The duration of severe pre-eclampsia was assigned to be 7 days (+/-2) and other HDoP was assigned a duration of three months (2-4). Eclampsia was a separate model, assigned a duration of one day (+/-1). The disability weight for eclampsia and severe pre-eclampsia is estimated as a combination of the disability weights hypertensive disorders of pregnancy and the respective specific condition. A large number of those with severe pre-eclampsia go on to have long-term sequelae of the condition[2], as do those with eclampsia[3,4]. We estimate these long-term sequelae by using the prevalence results of severe pre-eclampsia and eclampsia as input data for 2 full-compartment DisMod-MR 2.1 models. Sixty-two percent (57% - 67%) of the severe pre-eclampsia cases are estimated to be long-term sequela. For eclampsia we estimate that 6.5% (6.1% - 6.9%) of the cases continue on to long-term sequela in data-rich locations, whereas 11% (10.8% to 12%) in not data-rich. We apply these percentages to the outputs of the severe pre-eclampsia and eclampsia DisMod-MR 2.1 models and use the resulting dataset as the input for the long-term sequelae models.

Maternal sepsis and other maternal infections were also estimated separately. Maternal sepsis was assigned a duration of five days (+/-2) and, based on the same data identified in our review of pelvic inflammatory disease[5] (PID; described separately), 9% (7.7% - 10%) of incident cases of puerperal sepsis were estimated to continue on to have secondary infertility due to maternal sepsis. We apply this proportion to the incidence results of puerperal sepsis and use them as input data for a full-compartment DisMod-MR 2.1 model. Other maternal infections were assigned a wide potential duration of 15 to 45 days (mean 30).

The sequelae, health states, lay descriptions and disability weights for each maternal disorder are listed in table 3. Disability weights in GBD were calculated from two large surveys carried out in 2010 and 2013 as described in the Disability Weight section of the appendix. We assigned abdominopelvic pain of varying severity to approximate the disability from maternal haemorrhage, obstructed labour, ectopic pregnancy, and abortion and miscarriage. We used two health states to estimate the disability weight due to eclampsia (moderate abdominal pain and severe epilepsy). Tension-type headaches and mild motor plus cognitive impairment were used for severe pre-eclampsia. When two or more health states were combined for one sequela we calculated the disability weight as described Disability Weight section of the Diseases and Injuries Appendix.

Table 2: Health states and disability weights for each of the non-fatal maternal disorders

Sequela	Health state name	Health state description	Disability weight
Maternal haemorrhage (< 1L blood lost)	Abdominopelvic problem, moderate	Has pain in the belly and feels nauseous. The person has difficulties with daily activities.	0.114 (0.078-0.159)
Maternal haemorrhage (> 1L blood lost)	Abdominopelvic problem, severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324 (0.22-0.442)
Mild anaemia due to maternal haemorrhage	Anaemia, mild	Feels slightly tired and weak at times, but this does not interfere with normal daily activities.	0.004 (0.001-0.008)
Moderate anaemia due to maternal haemorrhage	Anaemia, moderate	Feels moderate fatigue, weakness, and shortness of breath after exercise, making daily activities more difficult.	0.052 (0.034-0.076)
Severe anaemia due to maternal haemorrhage	Anaemia, severe	Feels very weak, tired and short of breath, and has problems with activities that require physical effort or deep concentration.	0.149 (0.101-0.209)
Severe pre-eclampsia	Moderate abdominal pain, tension-type headaches, mild motor plus cognitive impairment	Has pain in the belly and feels nauseous. The person has difficulties with daily activities. Has a moderate headache that also affects the neck, which causes difficulty in daily activities. Has some difficulty in moving around but is able to walk without help. The person is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.174 (0.120 – 0.239)
Eclampsia	Moderate abdominal pain and severe epilepsy	Has pain in the belly and feels nauseous. The person has difficulties with daily activities. Has sudden seizures with violent muscle contractions and stiffness, loss of consciousness, and loss of urine or bowel control. Between seizures the person has memory loss and difficulty concentrating.	0.602 (0.427 – 0.753)
Long-term sequelae of severe pre-eclampsia	Tension-type headaches, mild motor plus cognitive impairment	Has a moderate headache that also affects the neck, which causes difficulty in daily activities. Has some difficulty in moving around but is able to walk without help. The person is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.067 (0.041 – 0.103)
Long-term sequelae of eclampsia	Tension-type headaches, mild motor plus cognitive impairment	Has a moderate headache that also affects the neck, which causes difficulty in daily activities. Has some difficulty in moving around but is able to walk without help. The person is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.067 (0.041 – 0.103)
Other hypertensive disorders of pregnancy	Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049 (0.031-0.072)
Puerperal sepsis	Infectious disease, acute episode, severe	Has a high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0.133 (0.088-0.19)
Infertility due to puerperal sepsis	Infertility, secondary	Has at least one child, and wants to have more children. The person has a fertile partner, but the couple cannot conceive.	0.005 (0.002-0.011)
Other maternal infections	Infectious disease, acute episode, moderate	Has a fever and aches, and feels weak, which causes some difficulty with daily activities.	0.051 (0.032-0.074)
Obstructed labour, acute event	Abdominopelvic problem, severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324 (0.22-0.442)

Rectovaginal fistula	Rectovaginal fistula	Has an abnormal opening between her vagina and rectum causing flatulence and faeces to escape through the vagina. The person gets infections in her vagina, and has pain when urinating.	0.501 (0.339-0.657)
Vesicovaginal fistula	Vesicovaginal fistula	Has an abnormal opening between the bladder and the vagina, which makes her unable to control urination. The woman is anxious and depressed.	0.342 (0.227-0.478)
Maternal abortive outcome	Abdominopelvic problem, moderate	Has pain in the belly and feels nauseous. The person has difficulties with daily activities.	0.114 (0.078-0.159)
Ectopic Pregnancy	Abdominopelvic problem, moderate	Has pain in the belly and feels nauseous. The person has difficulties with daily activities.	0.114 (0.159-0.078)

Uncertainty and model selection

For all explicitly modelled maternal disorders, uncertainty bounds include uncertainty due to input data, crosswalks of non-reference data, uncertainty in numerical solutions (posteriors) of each DisMod-MR 2.1 model, duration of symptoms, and proportion of all persons with each type of symptom.

In consultation with GBD researchers and collaborators, final models were selected on a combination of qualitative and quantitative goodness of fit to input data, plausibility of geographic and temporal trends, consistency of age pattern, and, when available, comparison with other published studies on the epidemiology of pregnancy complications. Directionality, magnitude, and plausibility of adjustment factors and predictive covariates were also considered in the process of model development. Of note, due to the nature of statistical modelling, final results do not always cover the values reported in input data.

Other direct and indirect maternal causes

We estimated YLDs for other [direct] maternal disorders YLD-to-YLL ratio approach where the ratio of YLD:YLL were pooled for all the causes in the list above and multiplied by the YLL for other [direct] maternal disorders. For other subcauses of maternal disorders, including late maternal death, indirect maternal disorders, and maternal death complicated by HIV/AIDS, we did not estimate any non-fatal burden based on the premise that the associated disability is captured in the respective causes.

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