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Inherited predisposition to stillbirth: an intergenerational analysis of 26,788 mother-daughter pairs

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Disclosure of interests

The authors report no conflict of interest.

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No inherited predisposition to stillbirth transmitted from mother to daughter found in this study.

Short title:

Inherited predisposition to stillbirth

AJOG at a glance (50 words, max 130)

- **A:** to determine if daughters were at higher risk of stillbirth if their mother had a history of stillbirth
- **B:** There does not appear to be an inherited predisposition to stillbirth transmitted from mother to daughter
- **C:** This is the first observational study to investigate inherited predisposition to stillbirth between mother-daughter pairs

Abstract

Background

Previous evidence suggests that placental dysfunction including pre-eclampsia is inherited from mother to daughter, but heritability of stillbirth has never been investigated.

Objective

To investigate if there is an inherited predisposition to stillbirth transmitted from mother to daughter.

Study Design

We carried out a nested case-control study within the intergenerational cohort held in the Aberdeen Maternity and Neonatal Databank (AMND). All mothers who had at least one daughter in Aberdeen, United Kingdom between 1949 and 2000 were included. Mother – daughter pairs were linked using the Scottish Community Health Index (CHI) number. The main exposure was mother's history of stillbirth. The primary outcome was stillbirth in any of the daughter's pregnancies. A population average model using Generalised Estimating Equations (GEE) with robust standard errors was used to estimate odds of a mother's history of stillbirth in daughters with a stillbirth compared to daughters with only livebirths. This method accounted for clustering of daughters within mothers and multi-adjusted analyses were performed to include confounders at the daughter's pregnancy level.

Results

Among the daughters, 384 had a history of one or more stillbirths (cases) while 26,404 only ever had livebirths (controls). We found no statistically significant

association between mothers' history of stillbirth (adjusted Odds Ratio (aOR) 0.63; 95% CI 0.24-1.63) or miscarriage (aOR 1.01; 95% CI 0.71-1.42) and stillbirth in daughters.

Conclusions

This is the first study to investigate an inherited predisposition to stillbirth. There was no evidence of an inherited predisposition to stillbirth transmitted from mother to daughter.

Keywords

Stillbirth, intrauterine death, mother-daughter pairs, family history, familial, intergenerational

Introduction

In the USA, 23,000 babies were stillborn in 2013 (5.96 per 1000 total births).[1] In 2015 the stillbirth rate per 1000 total births was 4.5 in England and Wales[2] and 18.4 worldwide.[3] Although several risk factors[3-7] have been incriminated, many cases of stillbirth remain unexplained.[7-10] Parents often look for an explanation for this catastrophic life event and are willing to make lifestyle changes to try to improve the outcome of future pregnancies. Women with a history of stillbirth have an increased risk of recurrence of this event[11,12] as well as other obstetric complications in subsequent pregnancies.[13] This suggests that there may be genetic, lifestyle or environmental factors which may have a detrimental and repeated impact on future reproductive outcomes.

Familial predisposition to adverse obstetric outcomes such as preterm birth,[14-16] growth restriction[17-19] and pre-eclampsia[16,20] suggests that disorders of placental function may be inherited. As placental dysfunction, growth restriction and prematurity are all associated with the pathophysiology of stillbirth[3,7] it is possible that there could be an underlying familial predisposition. Previous studies[16,21] have investigated mothers with adverse obstetric outcomes however none have investigated the influence of a mother's history of stillbirth on the risk of a similar event in daughters.

The Aberdeen Maternity and Neonatal Databank (AMND) is a population based database which holds routinely collected obstetric and fertility related data from 1949 to the present day for all deliveries and reproductive outcomes from the only

maternity hospital for the geographical area of Aberdeen City, Scotland, U.K.[22] Data is routinely collected continuously from hospital medical records by a dedicated data management team and entered into the AMND database at the end of each pregnancy.[22] All pregnancy records are automatically included and information entered routinely for all women under the jurisdiction of Aberdeen Maternity Hospital. Therefore, we can be confident that all stillbirth records for this area are recorded within the database. The AMND provides a rare opportunity to study an intergenerational population with a low outmigration rate,[22] enabling us to explore stillbirth in mother-daughter pairs. This cohort has been successfully used in the past to answer a similar question about inherited predisposition to preterm birth.[15] The objective of this study was to determine if a history of stillbirth in mothers was associated with an increased risk of stillbirth in daughters.

Materials and methods

Study design and conduct

This was a case-control study nested within the intergenerational cohort of mother-daughter pairs from the AMND.[22] The population consisted of all mother-daughter pairs who each had pregnancies delivered (livebirths or stillbirths) from 1949 until 2016 at Aberdeen Maternity Hospital, Scotland. Mothers who delivered babies between 1949 and 2000, and daughters who gave birth between 1965 and 2016 were included. Mother-daughter pairs were identified by deterministic matching using unique Scottish Community Health Index (CHI) numbers where available or probabilistic matching on surname (daughters' maiden name), post code and dates of delivery by the AMND data management team at the University of Aberdeen and

an anonymised database was given to researchers for analysis. Only singleton births in both the mothers and daughters were included.

Mothers who gave birth to live born sons but not daughters were excluded. As the risk of stillbirth is 4-fold higher for multiple pregnancies than singleton pregnancies,[23] multiple pregnancies in both mothers and daughters were excluded. The World Health Organisation (WHO) defines stillbirth as a baby born with no signs of life at or after 28 weeks gestation.[24] However in the United Kingdom, including within the AMND, stillbirth is defined as a baby born with no signs of life after the 24th gestational week.[4] Therefore in this study we used intrauterine death from 24 weeks gestation as the definition of stillbirth.

Cases were defined as daughters with a history of at least one stillbirth in any of their pregnancies. Controls were defined as daughters with a history of only ever delivering live born infants, with no history of miscarriage or stillbirth. The exposure was a mother's history of stillbirth, and secondly a mother's history of miscarriage. The pregnancy record for the first stillbirth (cases) or first livebirth (controls) were included in all data analyses.

Potential confounders adjusted for in the multivariate model were: daughter's age at delivery, smoking status (non-, ex- and current smoker), deprivation category[25] (most deprived (4-6) and least deprived (1-3)), body mass index (<20, 20-25, 26-30, >30), pre-eclampsia (yes/no), antepartum haemorrhage (yes/no), gestation at birth (preterm (<37 week gestation and 37+ week gestation), parity (primigravid/ parous).

Age at delivery is routinely collected by the AMND from the hospital medical records.[22] Smoking status is self-reported at the time of antenatal booking and then documented within the hospital record from which it is collected for the AMND. Gestation at delivery is coded according to the due date estimated by first trimester ultrasound where available from hospital records (from 1986 onwards)[22] and otherwise by last menstrual period date recorded at first antenatal booking. Antepartum haemorrhage (APH) is defined in the AMND as vaginal bleeding after 24 weeks gestation and is collected from hospital records. Pre-eclampsia is defined as gestational hypertension and at least one episode of proteinuria (0.3g protein in 24 hours)[26]and is collected from the hospital records. Deprivation category[25] is a Scottish measure of deprivation which categorises socioeconomic deprivation by assessing national information on several parameters including income, employment, health, education and housing. Deprivation category ranks deprivation from 1 to 6, where 1 represents the least and 6 the most deprived area. This is entered for all women at their pregnancy booking appointment according to their home address (using post codes).

Assuming a 1% prevalence of stillbirth in the population, a power calculation using nQuery advisor software (nQuery (2017). Sample Size and Power Calculation. "Statsols" (Statistical Solutions Ltd), Cork, Ireland) showed that there was 94% power to detect a difference in prevalence of stillbirth of 3% in 576 daughters of mothers with at least one stillbirth compared to 1% in 26212 daughters with a mother with all live births, with p=0.05 in a two-sided test. After taking account of the clustered data structure, with large numbers of mothers, small numbers of daughters

per mother, and assuming very small intraclass correlation (ICC)), the power of the study was expected to be at least 80%.

Statistical analysis

All data were stored and analysed using SPSS software (*IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.*). The analyses were carried out under a multilevel framework, using a population average model [29-31] with Generalised Estimating Equations (GEE) to account for the clustering of multiple daughters (level 1) nested within the same mother (level 2). Specifically, the robust standard errors of the regression co-efficients were estimated by specifying a working exchangeable correlation structure which assumes that the risk of stillbirth is the same in any daughter if the mother had history of stillbirth. Unadjusted and adjusted analyses were carried out to determine associations between sociodemographic and pregnancy characteristics and a daughter's history of stillbirth. Odds Ratios (OR) and 95% confidence intervals (95%CI) are presented. P-values of less than 0.05 were considered statistically significant.

Missing values

Where >5% of covariate data were missing, values were aggregated from complete data in another of the same daughter's pregnancies. Aggregated missing data were used for daughter's BMI, smoking status and deprivation category. Complete case analysis was then carried out using the aggregated covariate data. Where there was

more than one pregnancy record available for the same daughter from which to aggregate data:

i. the maximum recorded BMI was used;
ii. maximum recorded deprivation category score was used (highest value representing most deprived)
iii. 'smoker' was accepted over 'ex-smoker' and 'non-smoker';

Ethical considerations

Approval to conduct this study was obtained from the AMND steering committee. The AMND has an overall Research Ethics Committee approval (Reference No.:1/0/58-13-NS-0050 North of Scotland Research Ethics committee) which allows data recorded within AMND to be used for steering committee approved research projects. The study is reported in accordance with the STROBE Statement for observational studies.[27]

Results

An anonymised dataset with 122,870 mother and daughter pregnancies was received from the AMND data management team. Following cleaning and removal of any ineligible and duplicate records, 26,788 unique mother-daughter pairs were eligible for inclusion in this study (Figure 1). Figure 2 shows the rate of stillbirths over the study time period (as a percentage of total births for mothers and daughters within the AMND population sample). Stillbirth ranged from 0.3% and 1.1% of all intrauterine pregnancies during this sample. A total of 384 daughters had a history

of at least one stillbirth while 26,404 only had livebirths. Ten (2.6%) daughters with a history of stillbirth had two stillbirths. For this analysis, only the first stillbirth was considered.

Demographic and pregnancy characteristics were compared between daughters who ever had a stillbirth (n=384, cases) and daughters who only ever had livebirths (n=26404, controls). (Table 1). Women with a stillbirth were over three times more likely to have an APH, more likely to be socioeconomically deprived and twice as likely to smoke in their first stillborn pregnancy compared to daughters with their first live born pregnancy.

We compared reproductive histories in mothers of daughters with and without a history of stillbirth (Table 2). There was no association between a mother's history of stillbirth and stillbirth in the daughter (OR 0.72; 95%CI 0.32-1.62; aOR 0.63; 95%CI 0.24-1.63) after adjustment for potential confounders. Similarly, there was no association between a mother's history of miscarriage (OR 0.88; 95%CI 0.65-1.20; aOR 1.01; 95%CI 0.71–1.42) or two or more recurrent miscarriages (OR 0.77; 95%CI 0.36-1.63; aOR 0.94; 0.42-2.10) and the outcome of stillbirth in the daughter.

Comment

Principal findings

From our analyses, there does not appear to be an increased risk of stillbirth in daughters whose mothers had a history of stillbirth or miscarriage. To the authors' knowledge, this is the first observational study to investigate stillbirth risk transmitted from mother to daughter.

Stillbirths were seventeen times more common prior to 37 weeks gestation. In comparison with those who had only livebirths, daughters who had a history of stillbirth were almost three times more likely to have an antepartum haemorrhage in their first stillbirth. Daughters with a stillbirth were significantly more likely to be socioeconomically deprived and smokers.

Strengths and limitations

Aberdeen has a stable population with a low out-migration rate[22] which means that many mothers and daughters remain in Aberdeen for their pregnancies making this an ideal data source to perform an intergenerational study. There remains a small risk of bias that some mothers and daughters may not have all their pregnancies recorded within the AMND. Standardised coding criteria and regular quality checks means the AMND is a robust and valid data source[22] and allows many covariates to be included in the model because of the detailed clinical information recorded in the database. Using Scottish Community Health Index (CHI) identifiers meant that mothers and daughters could be easily linked within the AMND therefore it was possible to include all eligible women in the study. Deterministic matching should be 100% accurate using CHI numbers and probabilistic matching can be up to 97% accurate. The use of retrospective data will always incur risks of bias, but the risk is

minimised given the low outmigration rate[22] and because the data in the AMND is routinely collected there is no risk of recall bias.

The relative rarity of stillbirth as an outcome meant that a nested case-control approach was the most efficient study design. However, as there were only 384 cases in the sample, we cannot rule out the possibility of a type 2 error.

As each mother and daughter could have several pregnancies, there was clustering of more than one pregnancy within each daughter and daughters nested within each mother. Including individual daughters (first stillbirth (cases) versus first livebirth (controls), as opposed to including each daughter pregnancy, ensured that cases and controls were only included once. This meant that there was no issue of clustering of pregnancies within daughters. To account for clustering of more than one daughter (sisters) within mothers, we used a population average model under a multilevel framework approach.

Stillbirth rates have varied over time in this sample between 0.3% and 1.1% of all intrauterine pregnancies which may reflect temporal variations in reporting. There is a sharp increase from 1995 for mothers which may reflect the change in definition of stillbirths to include up to 24 weeks gestation. A similar increase is seen from 2010 until 2016 in daughters for which there is no clear explanation. This rise could be due to changing population demographics such as increasing obesity or maternal age at conception within daughters Overall, the proportions are generally in keeping with national estimates.[8,28,28,28] Therefore the results are likely to be generalisable to

other areas with similar antenatal care in high-income countries. However, the population in the North East of Scotland is primarily Caucasian and financially affluent[22] which may limit generalisability. A formal analysis of ethnicity however was not possible as this data was not available. It was not possible to study familial predisposition to stillbirth passed via the male line in this study.

By using aggregated values for missing covariate data, we were able to run all of the planned analyses and maximise the power of the study to answer the research questions posed. Given many sociodemographic characteristics are likely to remain the same for a woman's reproductive life, this approach was deemed appropriate. Furthermore, this meant that data were missing for < 10% for all covariates included in the multivariate model. Aggregated data was used for BMI (original missing data = 24%, after aggregation = 6%), smoking (original missing data = 13%, after aggregation = 8%) and deprivation category (original missing data = 14%, after aggregation = 3%). It is possible however that some daughters may have had only one pregnancy recorded and so this method has limitations in cases where that single record has incomplete data.

We were unable to differentiate intrapartum from antepartum stillbirth within the dataset. This is a limitation as there may be different pathophysiological mechanisms involved in the two forms of stillbirth which the results were unable to account for. Earlier stillbirths may be less likely to be caused by placental dysfunction and more likely to be caused by infection or congenital anomaly. Therefore a further analysis was carried out comparing daughter's with a history or preterm (<37 weeks gestation, n=242) and term (≥37 weeks, n=147) stillbirths.

Again, there was no evidence of a familial association with mother's history of stillbirth and term versus preterm stillbirth in the daughter (aOR 1.60 (0.25 – 10.39), adjusted for age at delivery, smoking, deprivation category, BMI, year of delivery, parity, Pre-eclampsia, APH). However due to the small sample size these results should be interpreted with caution. Larger intergenerational datasets should aim to investigate familial predisposition to stillbirth according to gestational age.

Furthermore, we were unable to include relevant maternal medical conditions, such as chronic hypertension, diabetes, connective tissue disorders, thyroid disorders, thrombophilias or substance abuse as confounding factors. These conditions were not all recorded within the database. This is a limitation to the study as these conditions are associated with stillbirth.

Interpretation

This study adds to the body of literature on stillbirth aetiology. Our results do not suggest a need for extra vigilance for women with a maternal history of stillbirth, but more research is needed to confirm or refute our findings in other populations as there may be a possibility that our study is underpowered.

The lack of association is in keeping with the findings of other studies which investigated the inheritability of placental dysfunction. Wikstrom et al[16] found that being born small for gestational age (SGA) led to a higher risk of disorders of placental dysfunction. The findings suggest that there could be a genetically

inherited predisposition to placental dysfunction transmitted from parents. However, in the adjusted analyses in this large population-based cohort study the risk of stillbirth in offspring was not statistically significant (aOR 1.24 (95%CI 0.84 to 1.82)).[16] The results suggest that there is no inherited predisposition to stillbirth if born SGA.[16] Conversely, an animal study found that Rhesus monkey daughters had a higher risk of stillbirth if their mothers were born small for gestational age.[29] A population based study found that mothers of Pakistani descent who lived in Norway were at greater risk of stillbirth and infant death than mothers born of Norwegian descent, suggesting there could be a genetic predisposition, though other socioeconomic or environmental factors could be responsible for this ethnic variation.[21]

The recurrence risk of stillbirth[11] supports the theory that some women may possess a predisposition to stillbirth, however this may not be an inherited familial predisposition. It is possible that daughters with a maternal or family history of stillbirth may be more aware of modifiable risk factors for stillbirth and may be more vigilant to seek obstetric care for example with reduced fetal movements. This could potentially lead to a reduction in the risk of stillbirth in daughters. However, there was no statistically significant association found in our study.

Future research

This paper sets a model for the same research question to be answered with larger datasets and where possible using national datasets in different populations. National intergenerational datasets with enough longevity to capture the reproductive

379 history of mothers and daughters should be used to confirm or refute our findings.
380 The outmigration rate should also be quantified in future research to minimise bias
381 from attrition when mothers and daughters have pregnancies recorded in different
382 geographical areas and hospitals. Placental abruption was independently
383 associated with a history of stillbirth in daughters in this study. An intergenerational
384 study[16] found placental abruption was more common in women who were born SGA.
385 This suggests an association with placental dysfunction and risk of abruption. More
386 research is needed to determine if there is a familial predisposition to antepartum
387 haemorrhage and specifically placental abruption. If a familial predisposition to
388 placental abruption was found this could be associated with consequent higher risk
389 of stillbirth in these women.

390 Stillbirth can cause significant psychological stress in a subsequent pregnancy[30] as
391 well as an increased risk of future adverse obstetric outcomes.[13] This emphasises
392 the need to improve our ability to identify women at risk of stillbirth as well as to
393 develop prevention. Although this study presents no evidence of a familial
394 predisposition to stillbirth, more research is needed to identify potential genetic or
395 epigenetic factors associated with disorders of placental dysfunction including
396 stillbirth.

397

398 ***Conclusion***

399 There does not appear to be an inherited predisposition to stillbirth transmitted from
400 mother to daughter. More research is needed to understand the aetiology of
401 stillbirth.

402

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Contribution to authorship

AW wrote the first and subsequent drafts, each of which were reviewed by SohB, SB, PD and EAR. The final draft of the paper was edited by all authors. AW, SohB, SB conceived the idea for the study and designed the study. PD was involved in initial planning and provided clinical input. AW, SB, SohB and EAR were involved in planning methodology. AW and EAR performed the statistical analyses.

Table / Figure Caption List

Figure 1 **Flowchart of selection of mother-daughter pairs**

Figure 2 **Stillbirths over time for study mothers and daughters from 1949 until 2016**

Table 1 **Comparison of demographic and pregnancy characteristics for daughters with and without a history of stillbirth**

Table 2 **Comparison of mother's reproductive history for daughters with and without a history of stillbirth**

Table 1 Comparison of demographic and pregnancy characteristics for daughters with and without a history of stillbirth (N = 26788)

Daughter's pregnancy characteristic	Daughters with history of stillbirth n (%), (N=384)	Daughters with only livebirths n (%), (N=26404)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value
Age at delivery in years					
≤20	88 (22.9)	7461 (28.3)	0.97 (0.74 – 1.26)	0.76 (0.55- 1.06)	<0.001*
21-25	127 (33.1)	8726 (33.0)	1.00	1.00	
26-30	93 (24.2)	6678 (25.3)	0.99 (0.75 – 1.29)	1.36 (0.98 – 1.88)	
31-35	59 (15.4)	2900 (11.0)	1.41 (1.02 – 1.93)	2.22 (1.51 – 3.27)	
36-40	15 (3.9)	598 (2.3)	1.19 (0.62 – 2.29)	2.02 (1.09 – 3.77)	
>40	2 (0.5)	41 (0.2)	3.48 (0.83 – 14.60)	2.77 (0.54 – 14.20)	
Smoking status					
Non smoker	135 (37.8)	13154 (54.0)	1.00	1.00	<0.001*
Current Smoker	200 (56.0)	8671 (35.6)	1.97 (1.57 – 2.47)	1.93 (1.46 – 2.56)	
Ex-smoker	22 (6.2)	2540 (10.4)	1.81 (1.29 – 2.52)	1.01 (0.61 – 1.66)	
Missing	27 (7.0)	2039 (7.7)			
Deprivation category					
Least deprived (1-3)	160 (42.7)	13364 (52.4))	1.00	1.00	0.004
Most deprived (4-6)	215 (56.0)	12161 (47.6)	1.49 (1.22 – 1.84)	1.48 (1.14 – 1.93)	
Missing	9 (2.3)	879 (3.3)			
Body mass index					
<20	5 (1.4)	57 (1.2)	0.78 (0.32 – 1.95)	0.68 (0.27 – 1.72)	<0.001*
20-25	72 (20.0)	1066 (21.5)	1.00	1.00	
26-30	140 (38.9)	2065 (41.7)	1.15 (0.87 – 1.53)	1.40 (1.00 – 1.96)	
>30	143 (39.7)	1760 (35.6)	1.40 (1.05 - 1.86)	2.06 (1.48 – 2.86)	
Missing	24 (6.3)	1639 (6.2)			
Pre-eclampsia					
No	342 (89.1)	24564 (93.6)	1.00	1.00	0.560
Yes	42 (10.9)	1693 (6.4)	1.42 (0.99 – 2.02)	0.89 (0.61 – 1.31)	
APH					
No	237 (61.7)	23501 (89.0)	1.00	1.00	<0.001*

Yes	147 (38.3)	2903 (11.0)	4.10 (3.30 – 5.08)	2.82 (2.16 – 3.69)	
Preterm birth					
Term (≥37 weeks)	134 (35.4)	24524 (93.1)	1.00	1.00	<0.001*
Preterm (<37 weeks)	244 (64.6)	1818 (6.9)	24.55 (19.78 – 30.48)	17.58 (13.75 – 22.48)	

*denotes statistically significant.
Multi-adjusted models adjusted for age at delivery, smoking, deprivation, BMI, year of delivery, parity, gestation, pre-eclampsia, antepartum haemorrhage, and exposure of mother's history of stillbirth
Missing covariates where possible aggregated from other pregnancy records from same daughter for BMI, smoking and deprivation; thereafter complete case analysis carried out with aggregated values for covariates included. Missing data was not included when calculating proportions.

Table 2 Comparison of mother's reproductive history for daughters with and without a history of stillbirth (N = 26788)

Mother's reproductive history	Stillbirths, n (%) (N=384)	Livebirths n (%) (N=26404)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value
Mother's history of stillbirth					
No	378 (98.4)	25834 (97.8)	1.00	1.00	0.341
Yes	6 (1.6)	570 (2.2)	0.72 (0.32 -1.62)	0.63 (0.24 – 1.63)	
Mother's history of miscarriage					
No	338 (88.0)	22878 (86.6)	1.00	1.00	0.979
Yes	46 (12.0)	3526 (13.4)	0.88 (0.65 – 1.20)	1.01 (0.71 – 1.42)	
Mother's history of recurrent miscarriage					
None or 1	377 (98.2)	25782 (97.6)	1.00	1.00	0.884
2 or more	7 (1.8)	622 (2.4)	0.77 (0.36 – 1.63)	0.94 (0.42 – 2.10)	
Mother's history of any pregnancy loss					
No	334 (87.0)	22421 (84.9)	1.00	1.00	0.589
Yes	50 (13.0)	3983(15.1)	0.84 (0.62 – 1.14)	0.91 (0.65 – 1.28)	

*denotes statistically significant.
Multi-adjusted models adjusted for age at delivery, smoking, deprivation, BMI, year of delivery, parity, gestation, pre-eclampsia, antepartum haemorrhage, and mother's reproductive history
Missing covariates where possible aggregated from other pregnancy records from same daughter for BMI, smoking and deprivation; thereafter complete case analysis carried out with aggregated values for covariates included.
Missing data was not included when calculating proportions.

Figure 1 Flowchart of selection of mother-daughter pairs

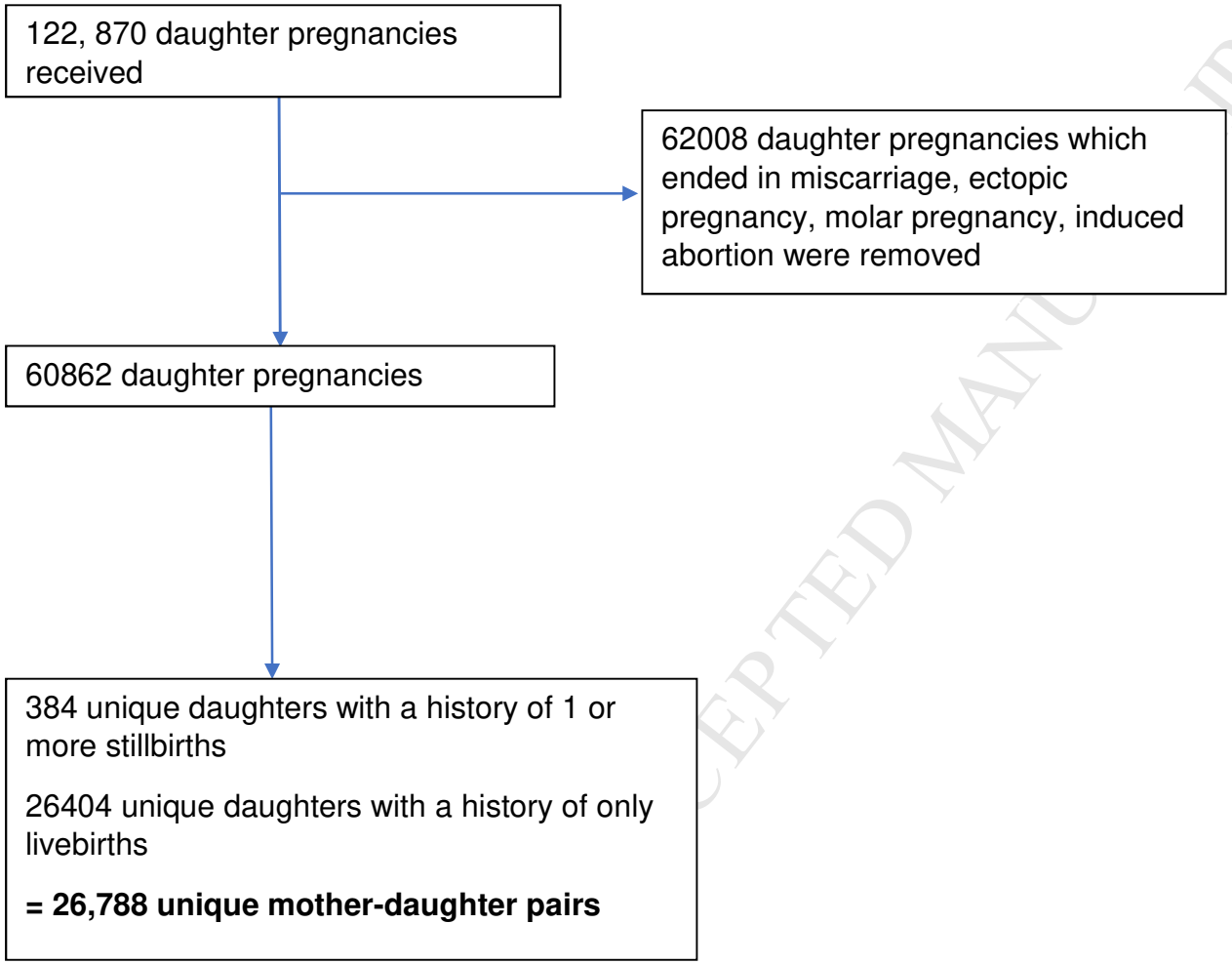

Figure 2 **Stillbirths over time for study mothers and daughters from 1949 until 2016 (percentage of total births including stillbirths and livebirths)**