厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）

周産期関連の医療データベースのリンケージの研究

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研究代表者　森　臨太郎

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Ⅰ.総括研究報告書

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総括研究報告書

周産期関連の医療データベースのリンケージの研究

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研究要旨

本研究は、周産期に関連する各種データベースとの連結可能性を試行することで将来の有効的な活用を促すこと、また、他データベースとの連結を通して各データベースの妥当性を測ることを目的としている。

研究２年目である本年度は、i）各分担の先生方と産婦人科医・小児科医・疫学者の協調を促し、周産期に関連する各種のデータベースを連結したデータベースの解析を行い単一のデータベースからは産出不可能であったエビデンスを産出する、ii）諸外国における人口動態統計のリンケージ手法を参考に、日本の人口動態統計をより高精度に連結する方法を検討する、iii)他の大規模データベースを連結するための整備を行う、ことを目的として、これを実践した。

A．研究目的

本研究では成育医療分野における各種統計や医学団体所有データベースを過去に活用し、また周産期医療関係の各種データベースをリンケージする手法に関する研究を行ってきたという経験を生かして、成育医療分野のデータベースを連結することで拡充し、さらに多くの臨床研究に活用する。また、公的統計の妥当性検証やデータベース同士の自動連結手法を確立するこ

とで今後の研究基盤を作成することが目的である。

これにより、医療計画の「５疾病５事業」に含まれ、その医療体制整備は極めて重要である小児医療および周産期医療において、関連学会が積極的に作成してきたレジストリや政府が行ってきた政府統計をいまよりも更に有用に活用する方法が広がると考えられる。

本研究での今年度の主な研究成果としては、

-人口動態統計の出生票および死産票に記載されている児の母の情報と、女性の死亡票を高精度にリンケージすることで、妊娠後の女性の死亡を把握するための方法を検討した。

-DPC データのおける診断（ICD-10）コードにより小児の慢性疾患を 12 に分類する Pediatric complex chronic conditions classification system version 2（以下 CCC）の自動分類法と、診療情報に記載された主治医診断名との妥当性を評価した。

-周産期関連の全国データベースや、これら同士を連結することで得られたデータベースを多角的に解析することで、妊婦および出生児の長期予後について、成育医療分野に有用なエビデンスを提供した。

B．研究方法

本研究は、複数のデータベースを相互に利活用しながら研究を行っていくという性質上、各分担研究班の分担研究者および研究協力者同士がお互いの研究を補助するという緻密な連携を取りながら行った。また、本研究を実施するにあたり、医療データベースのリンケージに関する倫理的・法的側面の妥当性についても、研究分担者である倫理専門家の監督のもとで行った。

C．研究結果

①小児慢性特定疾患データベースのリンケージと解析に関する研究

（分担：森臨太郎）

統括班の役割も果たす本分担班では、各分担班同士の情報共有を促し、各種データのリンケージ及び利活用を推進し、各種団体が所有するデータベースのリンケージを可能とするための整備を行っている。特に他データベースとのリンケージの実現可能性が高い二つの年間 10 万件を超える登録のある世界最大級の小児疾病登録データベース、そして早産児の長期予後に影響を与える社会的および医学的因子を把握するために、現在遂行中の早産児コホート（INTACT データベース）について、他データベースとリンケージすることの実現可能性を評価している。

本年度は、小慢登録ＤＢを他のデータベースとリンケージするに当たり、小慢登録ＤＢ内の登録データに大きな偏りが存在するとリンケージ結果にも影響を与えることから、まず小慢登録ＤＢの悉皆性について評価するために、本データベースの特性に

ついて明らかにするために、経済学で用いられている相対的な格差指標を用いて、小慢登録データが申請された自治体ごとに大きく偏りがないかどうか、定量的に評価を行い、小慢登録データが全国データとしての代表性を持ち得るかについて検討を行った。

その結果、小児慢性特定疾病のデータ登録状況に地域間格差がないかを検討したところ、全般的に登録格差が少なく、慢性的に経過する内科的疾病では全般的に登録格差が少なかった。外科系疾患ではやや Theil index 値が高い傾向があり、育成医療等の他の施策の影響が示唆される、という結果が得られた。

②DPC データにおける診断名による小児慢性疾病診断名の代替性検証

（分担：康永秀生）

Pediatric complex chronic conditions classification system version 2（以下 CCC）は、診断（ICD-10）コードと、Procedure コードを組み合わせて、小児の慢性疾患を 12 に分類する手法である。CCC 分類は DPC データにおける診断情報（ICD-10 コード、Procedure 情報）により本データに適応させることが可能であり、慢性疾患を複数有する患児の病院受診の傾向や、医療費のトレンド、ER 受診の傾向などの把握、入院や死亡の予測などに役立てられており、医療データベース研究に非常に有用な手法である。

このため、本年度は、国立成育医療研究センターにて死亡退院した患者を対象とし、約 6 年間の死亡退院患者を電子カルテを用いて、医師記載の診断名と DPC データから産出された CCC コードを比較し、DPC データにおける CCC の妥当性を検証した。

その結果、新生児疾患以外の慢性疾患の特異度は 90%以上で非常に高いこと、感度は、悪性腫瘍、新生児疾患、代謝疾患で高かった。消化器疾患、神経疾患では感度は低いが 60%近くは保たれていること、一方デバイス依存の感度は 12%と非常に低かったことが判明した。CCC 自動分類は DPC データ上でも非常に高い特異度と比較的高い感度を持って小児の慢性疾患を分類できることが示された。移植患者の分類に関しては現状の CCC 自動分類プログラムには問題があり、修正が必要であることが分かった。

③小児死因統計の臨床的死因との合致性に影響する要因に関する研究

（分担：溝口史剛）

昨年度、乳児死亡事例を対象に、統計上の死因と臨床上の死因の合致性、および記載された死因と実際の死因との合致性につきさらなる検証を行い、死亡診断書/死体検案書の記載内容から正確な死因統計を取ることは実質不可能であり、死後に包括的な情報を集約したうえで、死因の検証を行う体制（チャイルド・デス・レビュー：CDR）の整備が望まれるとの研究結果を得た。

そこで本年度は、CDR を実施する上で、現在の各種法制度の下で収集された既存情報をどのように利活用できるのかにつき検

討した。

その結果、現行法の下では統計３３条に基づき人口動態統計の死亡小票をもとにした全数把握は可能であるが、これらの死亡小票内容をもとに個人を特定し、各症例について他のデータベースから詳細情報を抽出するということを行うことはできない。

このため、人口動態統計の死亡小票からCDRを行うべき対象群をスクリーニングするということを行うには、別の法令根拠が求められると考察された。

また、情報のリンケージを進めるためには、先にも述べたように、チャイルドデスレビューという文言がその目的とともに具体的に法令に記載され、リンケージすべき情報とその利活用についても明確化される必要があることが分かった。

④周産期臨床データベースとDPCデータを用いた、産科合併症に関する研究

（分担：永田知映）

本年度は、昨年度より調査票情報の提供を受けた人口動態調査（出生票・死亡票・死産票）を用いて、生殖可能年齢の女性の死亡票と、出生票・死産票をリンクすることで、出産あるいは死産から一定期間内に起こった死亡を網羅し、妊産婦死亡統計データの信頼性および母体死因に関する検討を行った。

2013年1月1日から2015年12月31日の出生・死産データベースと連結される症例（産後1年未満の死亡）、単一死因分類により妊産婦死亡とされていた症例、妊娠関連語句が死因の記載に含まれた症例を抽出することにより、妊娠中および出産して1年未満に死亡した女性のデータを作成した。さらに、これら全例について、死因のレビューを行い、死因別に集計した。その結果、自殺例、単一死因分類では妊産婦死亡とされていなかったが死因が妊娠と関連している可能性があると判断された例など、同年（2014-2015）の公式統計には含まれていない死亡例が見つかった。

この結果、人口動態調査に係る調査票にレコードリンケージ手法を適用して産後1年未満の死亡を同定する方法は実施可能であり、産後1年未満の死亡について、妊娠との関連を問わず、その多くを抽出することが可能と考えられた。一方で、氏名や住所地が変更された場合は死亡票と出生・死産票がリンケージされないなど、この方法の限界も認識された。妊産婦死亡統計には含まれていない産後1年未満の女性の死亡の中にも、妊娠に関連する死亡が存在する可能性が示唆された。

しかし、これら研究結果を厚生労働省担当各課と共有したところ、人口動態調査のデータ処理に関する情報提供を受け、リンケージに用いる情報の選択により、より正確なリンケージが可能であることが判明した。また、当初解析対象としていなかった電子化されていない個票データについても提供が受けられることとなった。上記を踏まえ、より完全なデータを用いて、平成30年度に再度解析を行うこととした。

また、現在の妊産婦死亡統計データおよ

び日本産婦人科医会妊産婦死亡症例検討委員会のデータベースと比較検討することにより、データ間での解離の有無と妊産婦死亡に関連する因子を検討するために、日本産婦人科医会の担当部署との調節を行った。

⑤産褥婦の自殺にかかる状況及び社会的背景に関する研究

（分担：大田えりか）

妊産婦死亡のデータは、妊娠・出産に関連した原因によるものと定義されており、出産後、うつ病の悪化等により自殺に至った死亡は含まれておらず、これらの全国的な症例数は把握されていない。

このため本年度は、本研究班において別途、統計法第３３条に基づき、人口動態調査出生票及び死亡票の調査票情報の提供を厚生労働省に申請し、入手した人口動態調査出生票（2013 年、2014 年、2015 年）、人口動態調査死亡票（2014 年、2015 年）（女性（12 歳～60 歳））をリンケージし、児の出生から１年未満に死亡した女性を抽出、作成されたデータセットを利用した。データセットから、自殺に関連する ICD コードを含む死亡例を抽出した。また、出産後１年未満に産褥婦が自殺した症例について、その属性や自殺時期、地域、両親の社会背景などについて二次解析を行った。

これら研究結果を厚生労働省担当各課と共有したところ、人口動態調査のデータ処理に関する情報提供を受け、リンケージに用いる情報の選択により、より正確なリンケージが可能であることが判明した。また、当初解析対象としていなかった電子化されていない個票データについても提供が受けられることとなった。上記を踏まえ、より完全なデータを用いて、平成 30 年度に再度解析を行うこととした。

⑥各種厚生労働省統計と周産期関連学会データベースのリンケージと解析

（分担：森崎菜穂）

本分担研究においては、①人口動態統計の出生票、死産票、および死亡票をリンケージする複数の手法を比較検討することで、もっとも正確にこれらをリンケージできる手法を提案し、自動的にリンケージするプログラムを作成すること、そして、②各種の周産期関連データベースをリンケージしたデータベースの利用を促進し、その解析を通して単一のデータベースからは産出不可能であった医学的なエビデンスを複数提示すること、を目的としている。

そこで本年度は、①永田班と大田班の解析に用いる児の出生から１年未満に死亡した女性のデータセットを用いるために、出生票とその母の死亡票を高精度にリンケージする手法を検討し、②日本産科婦人科学会周産期登録データベース、新生児医療ネットワーク登録データベース、出生票、死産票、乳児死亡票、出生/死産が起きた時点での市町村の平均給与情報を連結したデータベースを様々な角度から解析し、妊婦および児の予後に関係する医学的・社会的因子について、産科医・小児科医・疫学者とともに複数のエビデンスを発表した。

行う予定である。

D．考察

本年度は研究の２年目として、DPC データベースや小児慢性特定疾病データベースなどの大規模データベースを他のデータとリンケージして活用する際に重要となる妥当性評価を行うとともに、平成 15 年より導入された人口動態統計オンライン報告システムに含まれている個人識別符号を利用して出生票とその母の死亡票を高精度にリンケージするなど、新たなリンケージ手法を検討した。

また、引き続き、得られたデータベースの解析から、妊婦および児の予後に関係する医学的・社会的因子について、産科医・小児科医・疫学者とともに複数のエビデンスを発表した。そして研究成果を関係者で共有することを通して、現在よりも更に正確なリンケージが可能であることが判明するなど、リンケージ手法についても知見を得ることが出来た。

E．結論

研究２年目である本年度は、各種データのリンケージ及び利活用の推進を行った。

最終年度となる平成 30 年度来年度は、更にデータ・リンケージを行い解析できるデータの質および量を増やし、またこれらデータの解析を通じて更に知見を増やすとともに、研究班としての３年間の経験から、今後疫学研究・臨床研究においてデータ・リンケージを用いる際に演じる実務的な問題およびこれらの対処法についての考察を

Ⅱ.分担研究報告書

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

小児慢性特定疾患データベースのリンケージと解析に関する研究

研究要旨

慢性疾病を抱える児童等に対する国の医療費助成等の支援施策である小児慢性特定疾病対策は、年間 10 万件を超える登録のある世界最大級の小児疾病登録データベースである。一方で小児期には類似の医療費支援施策が並列しており、全ての対象者が登録されている訳では無く、小児慢性特定疾病登録データの悉皆性の評価は課題となっていた。

本研究では相対的格差指標である Theil index を用いて、小児慢性特定疾病のデータ登録状況に地域間格差がないかを検討したところ、全般的に登録格差が少なく、慢性的に経過する内科的疾病では全般的に登録格差が少なかった。外科系疾患ではやや Theil index 値が高い傾向があり、育成医療等の他の施策の影響が示唆された。

研究分担者　森 臨太郎（国立成育医療研究センター 政策科学研究部 部長）

研究協力者：

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A. 研究目的

慢性疾患を抱える児童等に対する国の医療費助成等の支援施策である小児慢性特定疾病対策は、申請時に疾病情報を医師が記載した医療意見書を提出する必要がある。医療意見書の項目は電子化され集められ、登録データベースとして疾病研究に利用可能となっている。当該施策が対象とする疾病は、出生直後から発症する者から小児期～青年期にかけて発症するものまで幅広くカバーしており、年間 10 万件を超える世界最大級の小児疾病登録データベースとなっている。しかしながら乳幼児期や小児期には小児慢性特定疾病対策の他に、乳幼児医療費助成制度等の市町村事業として行われる子どもに対する類似の医療費助成施策が併存しており、小児慢性特定疾病に該当する症例の全てについて登録が行われている訳ではない。

この様な背景がある中で、以前より小児慢性特定疾病登録データベース（以下、小慢登録ＤＢ）については、その悉皆性が課題とされてきた。小慢登録ＤＢを他のデータベースとリンケージするに当たり、小慢登録ＤＢ内の登録データに大きな偏りが存在するとリンケージ結果にも影響を与えることから、まず小慢登録ＤＢの特性について明らかにする必要があると考えられた。しかしながら、対象疾病について、わが国における発症率や罹患率が正確に把握できている疾患はほとんど無いことから、小慢登録ＤＢへの登録者数を患者数と比較した絶対的な評価をすることは難しい。そこで本研究では、経済学で用いられている相対的な格差指標を用いて、小慢登録データが申請された自治体ごとに大きく偏りがないかどうか、定量的

に評価を行い、小慢登録データが全国データとしての代表性を持ち得るかについて検討を行った。

B. 研究方法

小児慢性特定疾病対策は、都道府県・指定市・中核市ごとに運用されている施策であり、運用主体の自治体を実施主体とよぶ。医療費助成の財源は国と実施主体が1/2ずつ支出することで運用されている。本研究は、登録状況が実施主体間に差異があるかを経済学で用いられている相対的格差指標であるTheil indexを用いて検証を行った。利用データは電子化が完了している2011年度から2013年度までの小児慢性特定疾患治療研究事業における登録データ（以下、旧小慢登録データ）を用いて行った。

相対的格差を測定するために、以下の計算式で導出されるTheil indexを利用した。

$$T = \sum_{i=1}^{n} p_i r_i \ln(r_i)$$

Theil indexは各群の人口で重み付けらえた健康状態の格差を示す。各群間の格差が全くない状態ではTheil indexは0となり、数値が大きくなるほど、群間の格差が大きいことを示す。

統計学的分析は、STATA version 14.2 (StataCorp LP, College Station, Texas, USA) を用いて行った。

（倫理面の配慮）

本調査は、研究利用について同意がなされている小児慢性特定疾病登録データを用いて行われており、国立成育医療研究センター倫理審査委員会による倫理審査（受付番号：1637）による承認を受けた。

C. 研究結果

Theil indexは他の研究にて既に発症率が推計され、小児慢性特定疾病登録状況が比較的良好であると推定されている１型糖尿病の結果が基準値として見なせると考えた。

2011-13年における小慢対象年齢全体(0-19歳)の１型糖尿病のTheil indexは、平均0.358 [95%CI 0.273-0.443] であった。

対象疾患群ごとに代表的な疾病についてTheil indexの評価を行ったところ、急性リンパ性白血病 0.427 [0.350-0.503]、急性骨髄性白血病0.380 [0.347-0.414]、ネフローゼ症候群 0.350 [0.269-0.430]、IgA腎症 0.314 [0.247-0.381]、慢性肺疾患 0.492 [0.406-0.578]、ファロー四徴症 0.563 [0.466-0.660]、単心室症 0.417 [0.366-0.468]、成長ホルモン分泌不全性低身長症 0.376 [0.349-0.404]、甲状腺機能低下症 0.270 [0.223-0.318]、若年性特発性関節炎 0.312 [0.285-0.340]、２型糖尿病 0.309 [0.197-0.421]、フェニルケトン尿症 0.380 [0.362-0.397]、血友病A 0.403 [0.396-0.410]、免疫性血小板減少性紫斑病 0.390 [0.301-0.478]、ウエスト症候群 0.361 [0.318-0.404]、レノックス・ガストー症候群 0.714 [0.602-0.826]、先天性胆道拡張症 0.261 [0.226-0.296]、胆道閉鎖症 0.440 [0.409-0.472] という結果であった。

このうち１型糖尿病とTheil indexの平均値に差が統計学的に認められなかったものは、急性骨髄性白血病、ネフローゼ症候群、IgA腎症、成長ホルモン分泌不全性低身長症、若年性特発性関節炎、２型糖尿病、フェニルケトン尿症、血友病A、免疫性血小板減少性紫斑病、ウエスト症候群であり、１型糖尿病よりもTheil indexが低値であったものは、甲状腺機能低下症、先天性胆道拡張症であった。

D. 考察

小児慢性特定疾病の対象疾患群の中で代表的な疾病について３年間のTheil indexの平均値を計算し、基準とした１型糖尿病の値との比較を行った。全般的にはTheil indexの値は小さく、登録格差は概ね少ないと考えられた。

Theil indexが高値となる傾向のあった疾病は、外科系疾病で多く、一方内科的疾患で慢性的に経過するものは１型糖尿病と同様の数値となる傾向にあった。外科系疾病で登録格差が大きい理由としては、外科系疾患は育成医療制度を用いることが多く、登録者に偏りが生じることが考えられた。

E. 結論

小児慢性特定疾病の登録データは概ね実施主体間の登録格差は少なく、わが国を代表していると考えられた。

F. 研究発表

1. 論文発表

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G. 知的財産権の出願・登録状況（予定を含む。）

1. 特許情報

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

DPC データにおける診断名による小児慢性疾病診断名の代替性検証

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研究要旨
【目的】Pediatric complex chronic conditions classification system version 2（以下CCC）は、診断（ICD-10）コードと、Procedureコードを組み合わせて、小児の慢性疾患を12に分類する手法である。単施設の医療情報を用いDPCデータにおけるCCCの妥当性を検証した。
【方法】約 6 年間の死亡退院患者を電子カルテを用いて 12 の慢性疾患の有無について調べた。このデータをゴールドスタンダードとして、12 慢性疾患の有無に関して、CCC 自動分類の感度特異度を算出した。【結果】新生児疾患以外の慢性疾患の特異度は 90%以上で非常に高かった。感度は、悪性腫瘍、新生児疾患、代謝疾患で高かった。消化器疾患、神経疾患では感度は低いが 60%近くは保たれていた。一方デバイス依存の感度は 12%と非常に低かった。【考察】移植患者の分類は現状の CCC 自動分類では分類できないことが分かった。【結語】CCC 自動分類は DPC データ上でも非常に高い特異度と比較的高い感度を持って小児の慢性疾患を分類できることが示された。移植患者の分類に関しては現状の CCC 自動分類プログラムには問題があり、修正が必要であることが分かった。

A．研究目的

Pediatric complex chronic conditions classification system version 2（以下CCC）は、診断（ICD-10）コードと、Procedureコードを組み合わせて、小児の慢性疾患を12に分類する手法である。CCCは、慢性疾患を複数有する患児の病院受診の傾向や、医療費のトレンド、ER受診の傾向などの把握、入院や死亡の予測などに役立てられており、医療データベース研究に非常に有用な手法である。しかし、英米で慢性疾患の定義が異なることもあり、CCCの妥当性にはさらなる研究が必要とされている。DPCデータにも、ICD-10コード、Procedure情報が含まれており、CCCを適応させることが可能であるが、これまで先行研究はない。このため、DPCデータにおけるCCCの妥当性を示すことが本研究の目的である。

B．研究方法

2012年4月1日から2017年12月31日までの間に、国立成育医療研究センターにて死亡退院した患者を対象とした。電子カルテ情報から、死亡患者の慢性疾患を循環器疾患、呼吸器疾患、神経疾患、腎疾患、消化器疾患、血液・自己免疫疾患、代謝疾患、その他先天奇形、悪性腫瘍、新生児疾患、デバイス依存、移植の12の慢性疾患に分類した（慢性疾患分類が、2つ以上にわたり存在しても良い）。この電子カルテ情報から分類した結果をゴールドスタンダードとし、同じ患者のDPCデータから、DPCデータ用CCC自動分類プログラムにて分類した結果の感度と特異度を評価した。DPCデータ用CCC自動分類プログラムは、DPCデータ様式１情報に含まれる12のICD-10病名を主に元として慢性疾患分類する。また疑い病名に関しては、日本語病名情報を元に除外するプログラムである。

統計ソフトは、StataCorp社 Stata（version 15）を使用した。本研究は、データベース研究であり、研究対象者への直接の身体的･精神的リスクはない。データ保護のために、インターネットの繋がらない端末で解析した。

C．研究結果

5年9か月の調査期間に196名の死亡退院があった。性別は男性が54%、入院時年齢は、中央値11.7か月
（四分位範囲0-7歳）であった。入院期間は中央値19日（四分位範囲5-81.5日）であった。

図１．各慢性疾患の合併割合

全体で、循環器疾患42%、呼吸器疾患8.7%、神経疾患11%、腎疾患2.6%、消化器疾患14%、血液・自己免疫疾患2.6%、代謝疾患4%、その他先天奇形23%、

悪性腫瘍20%、新生児疾患7.1%、デバイス依存8.7%、移植8.2%を認めた（図１）。
それぞれの疾患におけるCCC自動分類の感度・特異度はそれぞれ、循環器疾患70%，97%、呼吸器疾患77%，98%、神経疾患59%，94%、腎疾患80%，98%、消化器疾患63%，99%、血液・自己免疫疾患80%，97%、代謝疾患88%，98%、その他先天奇形60%，99%、悪性腫瘍98%，100%、新生児疾患93%，86%、デバイス依存12%，100%であった。CCC自動分類では移植患者は分類できなかった。また、複数以上の慢性疾患の合併に関しては、感度57%，特異度82%であった（図２,図３）。

図２.感度

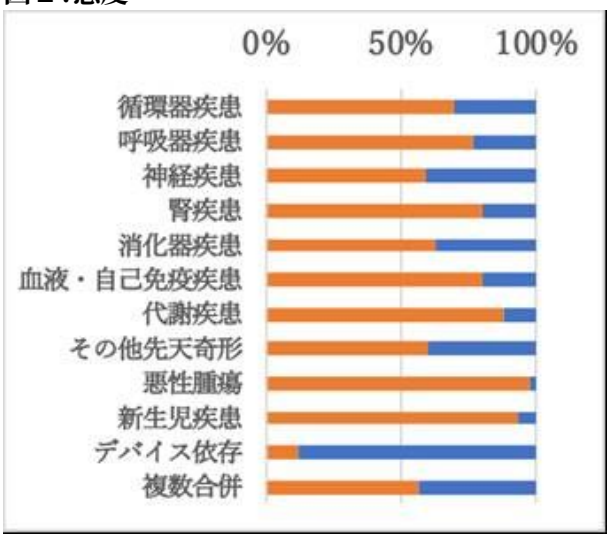
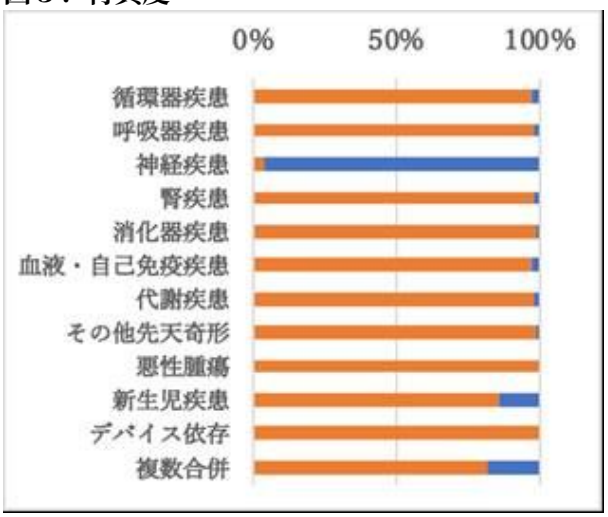


図３．特異度



D．考察
新生児疾患以外の11の慢性疾患の有無の特異度は90%以上で非常に高かった。感度は、悪性腫瘍、新生児疾患、代謝疾患で高かった。消化器疾患、神経疾患では感度は低いが60%近くは保たれていた。一方デバイス依存の感度は12%と非常に低かった。これは、様式１に記載できる病名の数が限られているため、デバイス依存に関連した病名などは入力されないためと考えられた。移植患者の分類は現状のCCC自動分類では分類できないことが分かった。CCC自動分類プログラムの修正が必要と考えられた。しかし、特異度は非常に高く、CCC自動分類の性質を理解して使用すれば大規模データ解析において有用な指標になることが分かった。

E．結論
CCC自動分類はDPCデータ上でも非常に高い特異度と比較的高い感度を持って小児の慢性疾患を分類できることが示された。移植患者の分類に関しては現状のCCC自動分類プログラムには問題があり、修正が必要であることが分かった。

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2. 学会発表　該当なし

G. 知的財産権の出願・登録状況
1. 特許取得・実用新案登録　該当なし

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

産褥婦の自殺にかかる状況及び社会的背景に関する研究

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研究要旨
人口動態統計出生票及び死亡票の連結により抽出された、2014～2015年における産後1年未満の産褥婦の自殺死亡例について、背景や自殺方法などを分析した。全出生と比較し、いくつかの傾向がみられたが、今後、オンライン以外で提出された調査票情報も追加して分析を行う。

A．研究目的

日本では、妊産婦死亡率は3.4（出産10万対、2016年）と大変低く、医療技術の向上等により年々減少傾向にあったが、多くの先進国と同様、近年は微増、微減を繰り返している。一方、公的統計で取り扱う妊産婦死亡のデータは、「妊娠中又は妊娠終了後満42日未満の女性の死亡」であって、妊娠・出産に関連した原因によるものとWHOにて定義されており、出産後、うつ病の悪化等により自殺に至った死亡について、わが国ではこれまで含まれておらず、これらの全国的な症例数は把握されていない。

うつ病等の気分障害が自殺の要因として重要であることが明らかになっており、産褥婦の自殺の状況について、人口動態統計のデータを用いて把握するとともに、当該データを分析することにより、母子保健対策を検討するための基礎資料とすることを目的とする。

B．研究方法

2014～2015年において、産後1年未満の産褥婦の自殺死亡例について、背景や自殺方法などを分析した。

自殺死亡例については、本研究班において別途、統計法第３３条に基づき、人口動態調査出生票及び死亡票の調査票情報の提供を厚生労働省に申請し、入手した人口動態調査出生票（2013年、2014年、2015年）、人口動態調査死亡票（2014年、2015年）（女性（12歳～60歳））をリンケージし、児の出生から１年未満に死亡した女性を抽出、作成されたデータセットを利用した。データセットから、自殺に関連するICDコードを含む死亡例を抽出した。

データの検討にあたっては、生年月日、死因等を含む調査票情報を用いることから、これらの情報を扱うための倫理申請を行った聖路加国際大学大学院において進めた。

C．研究結果

出生票と死亡票のリンケージのデータセットから、2014年～2015年における出産後1年未満（死産後は含まない）の産褥婦の自殺死亡例を抽出することができた。

抽出した自殺死亡例について、年齢や居住地区、出産回数、世帯の職業、死亡時期、原死因、自殺の手段等について、全出生と比較し、いくつかの傾向がみられた。

D．考察

我が国では、2017年度より、新たに産婦健康診査事業が開始された。これは産後うつ等を早期に把握し、必要な支援につなげるため、産婦を対象として、産後2週間、産後1ヶ月などの時期に、母体の身体的機能の回復状況や精神状態等の把握を行うこととしている。

また、死亡診断書の記入において、2017年度より、妊娠又は出産後1年未満の産婦が死亡した場合、産科的原因によるか否かにかかわらず、妊娠又は分娩の事実を記入するように改まったが、これらの情報がどの程度報告されてくるか、医療現場における理解や普及に依ることが大きいことも考えられる。

今回利用した死亡票はオンラインによる提出に限られ、全国カバー率が80~90%であること、出産時と死亡時で氏名が異なるとマッチングできないことから、自殺死亡数は過小評価の可能性がある。

また、今回の調査では、産後1年未満に自殺した症例を抽出しているものであり、妊娠出産やこれらに関連した精神疾患等と自殺の関連については、統計データの元となる死亡診断書に記載される情報が限られているため、ほとんどが不明である。産褥婦の自殺死亡を予防するための対策に結びつけるには情報として不十分であり、各症例についてさらなる詳細な調査が必要と考えられる。

E．結論

出産後１年未満の産褥婦の自殺にかかる状況を把握するため、人口動態調査出生票及び死亡票のリンケージにより抽出された自殺例について検討した。出産後１年未満の自殺死亡例について、いくつかの傾向がみられたが、今後、オンライン以外で提出された調査票情報の提供も申請し、電子的な情報にした上で、これまでのデータに追加して分析を行う。

F．健康危険情報

（分担研究報告書には記入せずに、総括研究報告書にまとめて記入）

G．研究発表

1．　論文発表

なし

2．　学会発表

なし

H．知的財産権の出願・登録状況（予定を含む。）

1．特許取得

なし

2．実用新案登録

なし

3.その他

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

「小児死因統計の臨床的死因との合致性に影響する要因に関する研究」

既存情報を小児死亡検証に既存情報を活用するための可能性と障壁に関する研究

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研究要旨

本分担研究者らは昨年度、小児科学会子どもの死亡登録検証委員会で施行された、2011年の死亡事例検証のパイロットスタディーのうち、登録された乳児死亡事例 214 例のデータを用いて、統計上の死因と臨床上の死因の合致性、および記載された死因と実際の死因との合致性につきさらなる検証を行い、乳児死因簡単分類の変更を要した事例（レッド事例）は 58 例（27%）、乳児死因簡単分類の変更を要さないものの、「Ⅱ欄への追記を含む、何らかの修正が望まれるが、乳児死因簡単分類の変更を伴わない事例」や「死因の明確化のためにはさらなる詳細情報の記載が望まれる事例（Ⅰ欄への追記を要する事例）」と定義づけたイエロー事例が 48 例（22%）存在していたことを報告し、死亡診断書/死体検案書の記載内容から正確な死因統計を取ることは実質不可能であり、死後に包括的な情報を集約したうえで、死因の検証を行う体制（チャイルド・デス・レビュー：CDR）の整備が望まれるとの提言を行った。

本年度は CDR を実施する上で、現在の各種法制度の下で収集された既存情報をどのように利活用できるのかにつき検討した。

現行法の下では死亡小票をもとにした全数把握は可能であるが、死亡小票内容をもとにした詳細に検討すべき事例のスクリーニングは不可能であり、既存情報を生かすためには、別の法令根拠が求められると考察された。また現行法そのままでの弾力的運用には、多くの機関が関与しかつ関係法規とのバッティング（刑事訴訟法、個人情報保護法など）が生じることが容易に想定されるセンシティブ情報を扱うその性質上、「チャイルドデスレビュー」という文言そのものを法令に記載し、根拠を明確にしない限り、既存情報を活用することや、新たに情報を収集したり、他の法令根拠に基づき収集された情報を共有し、子どもの予防可能な死亡を減少させるための知見を具体的に社会に還元させる体制を構築させるには不十分であると思われた。

このような情報のリンケージを進めるためには、先にも述べたように、チャイルドデスレビューという文言がその目的とともに具体的に法令に記載され、リンケージすべき情報とその利活用についても明確化される必要がある。

A．研究目的

本分担研究者らは昨年度、小児科学会子どもの死亡登録検証委員会で施行された、2011 年の死亡事例検証のパイロットスタディーのうち、登録された乳児死亡事例 214 例のデータを用いて、統計上の死因と臨床上の死因の合致性、および記載された死因と実際の死因との合致性につきさらなる検証を行い、乳児死因簡単分類の変更を要した事例（レッド事例）は 58 例（27%）、乳児死因簡単分類の変更を要さないものの、「Ⅱ欄への追記を含む、何らかの修正が望まれるが、乳児死因簡単分類の変更を伴わない事例」や「死因の明確化のためにはさらなる詳細情報の記載が望まれる事例（Ⅰ欄への追記を要する事例）」と定義づけたイエロー事例が 48 例（22%）存在していたことを報告し、死亡診断書/死体検案書の記載内容から正確な死因統計を取ることは実質不可能であり、死後に包括的な情報を集約したうえで、死因の検証を行う体制（チャイルド・デス・レビュー：CDR）の整備が望まれるとの提言を行った。

本年度は CDR を実施する上で、現在の各種制度の下で収集された既存情報をどのように利活用できるのかにつき検討したので報告する。

B．研究方法

CDR は①地域で発生した死亡事例を全数把握し、②予防可能性についてスクリーニングし、③検討を行った時点でその判断を正確にしえない事例や、予防可能性のあったと判断された事例につき、さらなる情報収集を可能な限り行い、そのうえで④再度多面的観点で検証を行い、④必要な場合には死因別に専門家パネルを開催したうえで詳細な検討を行い、⑤予防施策を提言し、⑤その提言がどの程度実施されているのかをトラッキングすることで、可能な限り予防可能な小児期死亡を制度として提言させていくための制度である。

本分担研究では、このうち既存データを CDR の各段階でどの程度利活用できるのかを検討した。

C．研究結果、および D.考察

①死亡事例の全数把握

現在の人口動態調査は新「統計法」（平成 19 年法律第 53 号）に基づく基幹統計調査として実施されている。死亡事例は全例が市区町村に死亡届を提出する必要があり、提出された死亡診断書（死体検案書）をもとに人口動態調査票（死亡票）が作成され、管轄区域の保健所に送付され、死亡票に基づいて死亡小票（死亡票の写し）が作成され、都道府県知事（保健所を設置する市又は特別区の保健所にあっては、市長又は区長を経由）に送付され、厚生労働大臣に送付される。

すなわち死亡診断書（死体検案書）に記載された内容については、市町村及び保健所にデータは保管された状態にある。しかしながら新統計法によって、より利活用されやすい状態となったとはいえ、その二次的利用に関しては現行法の下では、その利活用は大きく制限されており、統計の作成、統計的研究を目的とした調査票の二次利用は、調査を実施した府省自身が利用する場合に限られ（統計法 32 条）ており、調査票情報の提供を受ける場合も公的機関が利用する場合（統計法第 33 条第 1 号）や、公的機関が委託または共同して調査研究を行う場合・公的機関が公募の方法により補助す

る調査研究を行う場合・行政機関などが政策の企画/立案/実施または評価に有用であると認める統計の作成などを行う場合に限られていて（統計法第 33 条第 2 号）、一般の者が利活用可能であるのは公益性があり社会に還元されることなどを条件としたオーダーメード集計（統計法第 34 条）や匿名データ（統計法第 35 条、第 36 条）の提供に限定されている。

つまりは、現行法の下では死亡小票の利用は「統計の作成（その統計調査が本来作成を予定していた統計以外の統計を作成すること）」、「統計的研究（調査票情報を利用して行う統計的手法による研究）」に原則限定されており、既存情報としての死亡小票内の情報を用いて②のスクリーニングを行うことは原則としてできない。

結論としては、①の全数把握をすることのみを目的とした場合には統計法第33条に基づいた既存情報の収集はなしえるが、CDRのための②以降のプロセスを実施するためには、改めて別の法令根拠をもとにした情報収集を行う必要がある。なお英国では2017年10月にCDR実施のための法定ガイドラインが策定されたが、全数報告のために新たにFormAという書式を持ちいて死亡情報を収集することと定めている（報告すべき内容：死亡児の氏名・生年月日・住所・学校/保育園・死亡に至ったエピソードの発生場所、警察通報の有無、死亡診断書/死体検案書の発行状況、予測しえた死亡であったか否か、死亡事実を連絡した関係機関の一覧表、および報告者の氏名/所属機関）。

②予防可能性スクリーニングのための情報把握を可能な限り正確に行うために既存情報を収集するための法令根拠となりうる現行法としては、「児童福祉法」、「母子保健法」、「地域保健法」、「死因身元調査法」が挙げられる。

「児童福祉法」では、「児童及び妊産婦の福祉に関し、実情の把握、情報の提供、相談、調査、指導、関係機関との連絡調整その他の必要な支援を行う」とされているが、対象が児童福祉に関する事項に限定されること、ならびにCDRの結果は児童福祉の向上に資するものの、全小児死亡事例の検証まで同法で包含しうるのかは不明瞭であり、CDRの実施そのものの根拠としうるとは考え難い。

「母子保健法」に関しては、第二十条三項で「国は、乳児及び幼児の障害の予防のための研究その他母性並びに乳児及び幼児の健康の保持及び増進のため必要な調査研究の推進に努めなければならない」とされており、少なくとも乳幼児期に関してはCDRの実施そのものの根拠としうるが、大きな問題点として対象が乳児および幼児に限定されてしまう。第八条三項で、「学校保健安全法・児童福祉法やその他の法令に基づく母性及び児童の保健及び福祉に関する事業との連携及び調和の確保に努める」旨記載されているが、単独でCDRの根拠法とはしえない。また全死亡事例の検証まで同法で包含しうるのかはやはり不明瞭である。

「地域保健法」に関しては乳幼児に限定せずに、保健所に以下に掲げる事項につき、企画、調整、指導及びこれらに必要な事業を行うことと定めている。

・ 人口動態統計その他地域保健に係る統計に関する事項（第 6 条 1 項）

・母性及び乳幼児並びに老人の保健に関する事項（第6条8項）
・その他地域住民の健康の保持及び増進に関する事項（第6条14項）

および必要があるときは、

・地域保健に関する情報を収集し、整理し、及び活用すること（第7条1項）
・地域保健に関する調査及び研究を行うこと（第7条2項）

このうち、CDRの根拠法に転用しうるのは第6条14項、ならびに第7条1項であるが、第6条14項では保健所の業務は企画調整にとどまり情報収集権限は付与されず、第7条1項であれば情報の収集と利活用が可能となるが、全死亡事例の検証まで同項で包含しうるのかは不明瞭である。また「必要があるときは」という条件付けがあるが、何をもって必要があると解釈すればよいのか（予防可能性のあったと判断しうる死亡に限定するのか、小児が死亡したことをもって必要があると判断しうるのか）不明瞭である。

「死因身元調査法」に関しては、正式名称の「警察等が取り扱う死体の死因又は身元の調査等に関する法律」が示す通り、本法律体系をCDRの根拠法とした場合、警察対応となる死亡事例に検証が限定されてしまう。同法には「公衆衛生の向上」につき言明されてはいるものの、法の理念として「市民生活の安全と平穏を確保することを目的」としている。

なお現時点で法案作成され、提出がなされたものの、成立に至ってはいない「死因究明推進基本法（案）」では、その目的を「安全で安心して暮らせる社会の実現」および「生命が尊重され個人の尊厳が保持される社会の実現」に寄与することとしており、第三条2項で、「死因究明の推進は、高齢化の進展等の社会情勢の変化を踏まえつつ、死因究明により得られた知見が疾病の予防及び治療をはじめとする公衆衛生の向上及び増進に資する情報として広く活用されることとなるよう、行われるものとする」と定めており、CDR実施の法令根拠になりうると思われる。ただし「高齢化の進展等の社会情勢の変化を踏まえつつ」との前提記載内容から、即座にこれをもってCDRの実施体制の整備に直結させることは困難である。

結論としては、現行法のままではCDRを実施するためには「法律の弾力的運用」をしなくてはならならない点に変わりはなく、多くの機関が関与し、かつ関係法規とのバッティング（刑事訴訟法、個人情報保護法など）が生じることが容易に想定されるセンシティブ情報を扱うその性質上、「チャイルドデスレビュー」という文言そのものを法令に記載し、根拠を明確にしない限り、既存情報を活用することや、新たに情報を収集したり、他の法令根拠に基づき収集された情報を共有することは、困難である。

なお英国のCDR実施のための法定ガイドラインでは、死亡を把握した機関（実質的にはほとんどが医療機関）にスクリーニングのための情報収集として、各死因別にFormB（新生児[B2]、予期された死亡[B３]、不詳死[B4]、交通外傷/転落[B5]、溺死[B6]、火災[B７]、違法薬物[B8]、その他の事故[B9]、中毒死[B10]、虐待/殺人[B11]、自殺[B12]）という書式を持ちいて死亡情報を報

告することと定めている。

③詳細情報の把握・収集

現行法による、個別具体的な死亡事例調査の根拠法例としては、昨年度の報告で用いた、死因統計上のグルーピング（❶虐待/ネグレクト、殺人、❷自殺、❸その他の外因、❹悪性疾患、❺急性疾患、❻慢性士疾患の増悪、❼染色体/先天異常、❽周産期/新生児、❾感染症、❿不詳死別に、下記のとおりであった。

❶虐待/ネグレクト・殺人

「警察法」「警察官職務執行法」「刑事訴訟法」などが法令根拠となるが、虐待死の行政調査に関しては「虐待防止法第 4 条第 5 項」が根拠となる

❷自殺

「自殺対策基本法第 15 条」が根拠となりうるが、あくまでも公衆衛生学的調査を定めたものと解釈されるものであり、CDR で求められる個別事例検証に関しては、いじめによる自殺であれば、「いじめ防止対策推進法第 28 条第 1 項」が根拠法になるが、いじめ自殺以外の自殺であれば文科省通知「子供の自殺が起きた時の背景調査の指針」があるのみである。

❸その他の外因

保育事故による死亡に関しては、「平成 26 年内閣府令第 39 号」「平成 26 年厚生労働省令第 63 号」「平成 29 年厚生労働省令 123 号」が根拠となる

航空・鉄道・船舶事故死に関しては、「運輸安全委員会設置法」が、
交通事故に関しては「道路交通法第 108 条 14 項」が根拠となる。

なお道路交通法では第 108 条 16 項で「警察署長は、分析センターの求めに応じ、分析センターが事故例調査を行うために必要な限度において、分析センターに対し、交通事故の発生に関する情報その他の必要な情報又は資料で国家公安委員会規則で定めるものを提供することができる」と規定されており、かつ同 24 項では「警察庁及び都道府県警察は、分析センターに対し、国家公安委員会規則で定めるところにより、その事業の円滑な運営が図られるように必要な配慮を加えるものとする」と記載されている。

その他の事故に関しては、「消費者安全法第 23 条」が根拠となりうる。なお消費者安全法では「消費者安全の確保の見地から必要な事故等原因を究明することができると思料する他の行政機関等による調査等の結果を得た場合又は得ることが見込まれる場合においては、この限りでない」とその他の法令根拠に基づく調査により代替しうる旨が明記されており、また同法第 4 条 5 項では「国及び地方公共団体は、消費者安全の確保に関する施策の推進に当たっては、基本理念にのっとり、独立行政法人国民生活センター、消費生活センター、都道府県警察、消防機関、保健所、病院、教育機関、消費生活協力団体及び消費生活協力員、消費者団体その他の関係者の間の緊密な連携が図られるよう配慮しなければならない」旨が明記されている

❹-❽の内因死

医療過誤の可能性がある場合には「医療法第 6 条 11 項」に基づいた調査が根拠法となるが、それ以外では剖検実施に関しての

「死体解剖保存法」以外には、「がん対策基本法」「難病の患者に対する医療等に関する法律」「肝炎対策基本法」「アルコール健康障害対策基本法」「アレルギー疾患対策基本法」など調査研究を推進する各種法が存在するが、個別事例の詳細検討を規定するものではなく、個別死亡事例の検討は臨床病理検討会（CPC）と同様、臨床研修制度や専門医制度でそれを促進する枠組みはあるものの、医療者の専門性向上のための自己研鑽として任意に実施されているものである。

❾感染症

「感染症の予防及び感染症の患者に対する医療に関する法律」、食中毒に関しては「食品衛生法」、検疫に関しては「検疫法」が根拠となる。

❿不詳死

解剖に関しては「死体解剖保存法」が根拠となる。異状死と判断された場合には医師法 21 条に基づき、警察に届け出を行う必要があり、犯罪死の可能性が否定できれば①の根拠をもとに、非犯罪死体と判断された場合でも「死因身元調査法」に基づく調査対象とされる可能性がある。いずれにしろ刑事事件となりうる場合には、刑事訴訟法 47 条「訴訟に関する書類は、公判の開廷前には、これを公にしてはならない。但し、公益上の必要その他の事由があって、相当と認められる場合は、この限りでない」に基づき、CDR に資する情報を警察から得ることは極めて困難である（但し書きの「相当」の範囲が不明瞭であり、実運用はほとんどなされていない）。死因身元調査法に基づく解剖結果に関しては、犯罪捜査の手続に付されていないものに関しては、「検案を行った医師」もしくは「死亡時画像の読影を行った医師」から「解剖等の結果の提供の求めがあった場合」に、「医学研究目的に限り、死者を識別できる方法で第三者に提供することのないことを条件に」提供すべき旨が通達されている（丁捜一発第 117 号）。つまり実際の死亡に対応した臨床医が死体検案を行わなかった場合には、情報は還元されない。なお本通知では「別途の手続が既に確立されている都道府県警察にあっては、その提供方式（含、司法解剖）を継続して差し支えない」との記載や、「司法解剖結果等の提供を求められた場合は、犯罪捜査への支障や刑事訴訟法第 47 条の規定を鑑み、必要に応じて検察庁とも協議を行い可否等について個別に検討する」旨記載されており、一律に司法解剖結果の提供を妨げるものではない。

CDR は、これらの現行の根拠法例をもとにした死亡事例検証にとって代わるものではなく、これらの現行の根拠法例をもとにした死亡事例検証を行いえない事例をカバーするものということもできる。ただ、これらの検証結果は、統合されて一元的に、今後の予防可能死の減少に資するような施策に生かされる必要があり、かつ個人情報を排した状態で、国民がそれをトラッキングできる必要がある。このような情報のリンケージを進めるためには、先にも述べたように、チャイルドデスレビューという文言がその目的とともに具体的に法令に記載され、リンケージすべき情報とその利活用についても明確化される必要があるといえる。

Ｅ．結論

現行法の下では死亡小票をもとにした全数把握は可能であるが、死亡小票内容をもとにした詳細に検討すべき事例のスクリーニングは不可能であり、既存情報を生かすためには、別の法令根拠が求められるが、現行法そのままでの弾力的運用には、多くの機関が関与しかつ関係法規とのバッティング（刑事訴訟法、個人情報保護法など）が生じることが容易に想定されるセンシティブ情報を扱うその性質上、「チャイルドデスレビュー」という文言そのものを法令に記載し、根拠を明確にしない限り、既存情報を活用することや、新たに情報を収集したり、他の法令根拠に基づき収集された情報を共有し、子どもの予防可能な死亡を減少させるための知見を具体的に社会に還元させる体制を構築させるには不十分である。

このような情報のリンケージを進めるためには、先にも述べたように、チャイルドデスレビューという文言がその目的とともに具体的に法令に記載され、リンケージすべき情報とその利活用についても明確化される必要がある。

Ｆ．健康危険情報

該当なし

Ｇ．研究発表

論文発表　なし

学会発表　なし

書籍発刊　なし

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

周産期臨床データベースと DPC データを用いた、産科合併症に関する研究

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研究要旨

平成 29 年度は、平成 28 年度に引き続き、人口動態調査（出生票・死亡票・死産票）のリンケージによる妊産婦死亡統計データの信頼性および母体死因に関する検討を行った。

妊産婦死亡統計において、妊娠に伴う併存疾患の増悪による死亡（間接死亡）は、先進国においても正確な収集が困難であるとされている。我が国の妊産婦死亡率は非常に低いが、間接死亡の報告が少なく、加えてクロスチェックのシステムがないことから、妊産婦死亡統計データの信用性は定かではない。そこで、生殖可能年齢の女性の死亡票と、出生票・死産票をリンケージすることで、出産あるいは死産から一定期間内に起こった死亡を網羅し、現在の妊産婦死亡統計データと比較検討することにより、データ間での解離の有無と妊産婦死亡に関連する因子を検討することとした。

2014 年 1 月 1 日から 2015 年 12 月 31 日の死亡票･死亡個票データベースをリンケージして 12-60 歳女性の死亡データセットを作成した。これらの死亡データベースのうち、2013 年 1 月 1 日から 2015 年 12 月 31 日の出生･死産データベースと連結される症例(産後 1 年未満の死亡)、単一死因分類により妊産婦死亡とされていた症例、妊娠関連語句が死因の記載に含まれた症例を抽出することにより、妊娠中および出産して１年未満に死亡した女性のデータを作成した。これら全例について、死因のレビューを行い、死因別に集計した。その結果、自殺例、単一死因分類では妊産婦死亡とされていなかったが死因が妊娠と関連している可能性があると判断された例など、同年（2014-2015）の公式統計には含まれていない死亡例が見つかった。

人口動態調査に係る調査票にレコードリンケージ手法を適用して産後 1 年未満の死亡を同定する方法は実施可能であり、産後１年未満の死亡について、妊娠との関連を問わず、その多くを抽出することが可能と考えられた。一方で、氏名や住所地が変更された場合は死亡票と出生・死産票がリンケージされないなど、この方法の限界も認識された。妊産婦死亡統計には含まれていない産後 1 年未満の女性の死亡の中にも、妊娠に関連する死亡が存在する可能性が示唆された。

これら研究結果を厚生労働省担当各課と共有したところ、人口動態調査のデータ処理に関する情報提供を受け、リンケージに用いる情報の選択により、より正確なリンケージが可能であることが判明した。また、当初解析対象としていなかった電子化されていない個票データについても提供が受けられることとなった。上記を踏まえ、より完全なデータを用いて、平成 30 年度に再度解析を行うこととした。

平成 29 年度は、平成 28 年度に引き続き、人口動態調査（出生票・死亡票・死産票）のリンケージによる妊産婦死亡統計データの信頼性および母体死因に関する検討を行った。

A. 研究目的

妊産婦死亡統計において、妊娠合併症による死亡（直接死亡）でなく、妊娠に伴う併存疾患の増悪による死亡（間接死亡）は、先進国においても正確な収集が困難であるとされている。我が国の妊産婦死亡率は非常に低く、その周産期医療レベルは世界でも最高水準であると考えられている。一方で、間接死亡の報告が少なく、加えてクロスチェックのシステムがないことから、妊産婦死亡統計データの信用性は定かではない。また、妊娠・出産の高齢化や生殖補助医療の普及により、何らかの疾患を有する妊婦のさらなる増加が見込まれ、間接死亡に関する正確な統計データの重要性が高まっている。そこで、生殖可能年齢の女性の死亡票と、出生票・死産票をリンケージすることで、出産あるいは死産から一定期間内に起こった死亡を網羅し、現在の妊産婦死亡統計データと比較検討することにより、データ間での解離の有無と解離にかかる因子を検討する。

B. 研究方法

生殖可能年齢の女性の死亡票と、出生票・死産票を個票レベルでリンケージし、妊産婦死亡統計データとの合致性を検証した。

【分析に用いた調査票】

- 人口動態調査　死産票　2013～2015 年
- 人口動態調査　出生票　2013～2015 年
- 人口動態調査　死亡票　2014～2015 年
  （ただし 12 歳から 60 歳の女性に限る）

【分析方法】

1. データセットの作成

生殖可能年齢の女性の死亡票および死亡個票のリンケージを、死亡年月日、届け出のあった都道府県・市町村・保健所・支所番号を用いて行った。続いて、出生票/出生個票に関して、先にリンケージした生殖可能年齢の女性の死亡票/死亡個票と、母（女性）の氏名、生年月日によりリンケージした。同様に、死産票/死産個票に関しても、先にリンケージした生殖可能年齢の女性の死亡票/死亡個票と、母（女性）の氏名、住所地、年齢を用いて、リンケージした。

リンケージした生殖可能年齢の女性の死亡票/死亡個票のデータセットより、単一死因分類により妊産婦死亡とされていた症例、妊娠関連語句が死因の記載に含まれた症例、および先のリンケージにより出産・死産より 1 年未満に死亡していた症例を抽出し、妊娠中および出産して 1 年未満に死亡した女性のデータを作成した。

2. 分析

妊娠中および出産して 1 年未満に死亡した全症例について、死亡票/死亡個票の情報に基づき、2 人の産婦人科専門医が独立して死因のレビューを行い、英国で用いられている妊産婦死亡に関する死因分類を用いて、死因別に集計した。（分類が合致していない場合は第三者を交えた討議により解決した。）死因分類別死亡数、死亡率を各年で集計し、これを妊産婦死亡統計データと比較した。

(倫理面への配慮)

本研究は、人を対象とする医学系研究に関する倫理指針（平成 26 年文部科学省・厚生労働省告示第 3 号）を順守して行われる。また、人口動態調査に係る調査票情報の提供については、統計法（平成 19 年法律第 53 号）第 33 条の規定に基づき行われる。本分担研究を含む、全体の研究計画および用いられる手法については、国立成育医療研究センター倫理審査委員会より承認を受けている。

人口動態統計調査に含まれる氏名情報は、暗号化プログラムにより暗号化され、管理される。データの利用場所は限定されており、それ以外への持ち出しは禁止されている。データ利用にかかるコンピュータは ID･パスワードの設定によるアクセス制限、アンチウイルスソフトの導入、最新セキュリティパッチの適用などのセキュリティホール対策の導入、スクリーンロックの導入が図られており、漏洩防止等の措置が講じられている。また、中間生成物は全て外付けのハードディスクに格納し、コンピュータに内蔵される記憶装置には集計情報以外の一切の情報の蓄積を行わない。さらに、これらの情報を利用しないときは、当該外付けのハードディスクをコンピュータから外し、利用場所の施錠可能なキャビネットに施錠の上保管するなど、十分な情報管理を実施している。

C. 研究結果

統計法（平成 19 年法律第 53 号）第 33 条の規定に基づき、人口動態調査に係る調査票情報の提供について申出を行い、調査票情報の提供を受けた。

2014 年 1 月 1 日から 2015 年 12 月 31 日の死亡票・死亡個票データベースをリンケージして 12-60 歳女性の死亡データセットを作成した。これらの死亡データベースのうち､2013 年 1 月 1 日から 2015 年 12 月 31 日の出生・死産データベースと連結される症例（産後 1 年未満の死亡）、単一死因分類により妊産婦死亡とされていた症例、妊娠関連語句が死因の記載に含まれた症例を抽出した。これら全例について、死因のレビューを行い、死因別に

集計した。その結果、自殺例、単一死因分類では妊産婦死亡とされていなかったが死因が妊娠と関連している可能性があると判断された例など、同年（2014-2015）の公式統計には含まれていない死亡例が見つかった。

D. 考察・結論

前述の研究結果を厚生労働省担当各課と共有したところ、人口動態調査の情報処理に関する情報提供を受け、リンケージに用いる情報の選択により、より正確なリンケージが可能であることが判明した。また、当初解析対象としていなかった電子化されていない個票データについても提供が受けられることとなった。上記を踏まえ、より完全なデータを用いて、平成 30 年度に再度解析を行うこととした。

- 人口動態調査に係る調査票にレコードリンケージ手法を適用して産後 1 年未満の死亡を同定する方法は実施可能であった。
- この方法により、産後１年未満の死亡について、妊娠との関連を問わず、その多くを抽出することが可能と考えられた。
- 一方で、氏名や住所地が変更された場合は死亡票と出生・死産票がリンケージされない、妊娠中に死亡した症例は抽出されないなど、この方法の限界も認識された。
- 妊産婦死亡統計には含まれていない産後 1 年未満の女性の死亡の中にも、妊娠に関連する死亡が存在する可能性が示唆された。

E. 健康危険情報

該当なし。

F. 研究発表

1. 論文発表

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2. 学会発表

該当なし。

G. 知的財産権の出願・登録状況

1. 特許取得

該当なし。

2. 実用新案登録

該当なし。

3. その他

該当なし。

厚生労働科学研究費補助金
政策科学総合研究事業（臨床研究等 ICT 基盤構築・人工知能実装研究事業）
分担研究報告書

各種厚生労働省統計と周産期関連学会データベースのリンケージと解析

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研究協力者　大久保祐輔　国立成育医療研究センター社会医学研究部　共同研究員
山本 依志子　国立成育医療研究センター政策科学研究部　上級研究員
小川浩平　国立成育医療研究センター産科　医員

研究要旨

本分担研究においては、①人口動態統計の出生票、死産票、および死亡票をリンケージする複数の手法を比較検討することで、もっとも正確にこれらをリンケージできる手法を提案すること、そして、②各種の周産期関連データベースをリンケージしたデータベースの利用を促進し、その解析を通して単一のデータベースからは産出不可能であった医学的なエビデンスを複数提示すること、を目的としている。

２年目である本年度は、①2013-2015 年度に出生した児の出生票と母の死亡票を高精度にリンケージするための方法を検討し、③2003-2011 年度の出生児について日本産科婦人科学会周産期登録データベース、新生児医療ネットワーク登録データベース、出生票、死産票、乳児死亡票を連結したデータベースを様々な角度から解析し、妊婦および児の予後に関係する医学的・社会的因子について、複数のエビデンスを発表した。

A．研究目的

本分担班では、昨年度は人口動態統計の出生票と乳児死亡票を連結する手段を模索した。しかし、その際、氏名情報などの特異度が高い情報が欠落しているデータベース同士では、連結の不確実性がどうしても高いことが明らかになった。

出生、死亡、などの人口動態調査については、自治体から厚生労働省に送付される調査票の OCR シートを読み込む方法のほかに、自治体において調査票の電子データをオンラインで送信する人口動態統計オンライン報告システムが平成 15 年より導入され、各市町村に順次導入されている。平成 26 年度時点において、全出生の約 90%が本報告システムを用いて報告されている。

そこで、本年度の本分担研究班における研究目的は、①出生票とその母の死亡票を高精度にリンケージする手法を提案すること、②各種の周産期関連データベースをリンケージしたデータベースの解析を通して複数の医学的に有用なエビデンスを提示すること、である。

B．研究方法

①出生票とその母の死亡票を高精度にリンケージする手法の検討

現在、出産後の女性の死亡が妊娠に関係

する死であったかどうかを判定するための材料は、死亡票に記載されている死因情報のみに依存している。しかし、この方法だけでは、出産後時間の経った症例では特に見落としが起きる可能性がある。

このため、妊婦死亡の把握（永田班）および妊婦自殺の把握（大田班）の解析データセットを作成するために、妊娠可能年齢の女性の死亡票・個票を、その妊娠の結果出生あるいは死産となった児の出生票・出生個票あるいは死産票・死産個票と連結するための手法の検討を行った。

②2003-2011 年度出生において、日本産科婦人科学会周産期登録データベース、新生児医療ネットワーク登録データベース、出生票、死産票、乳児死亡票を連結したデータベースを、複数の研究者で解析した。

（倫理面への配慮）

本研究は二次的に得られる情報で行う研究であり、情報収集については特別の倫理的配慮は必要としなかった。しかし、個人情報を多く含む情報の解析であるため、国立成育医療研究センターの倫理委員会において研究計画の承認を得た後に行い、情報漏えいリスクを最小限にとどめるために外部ネットワークから遮断された環境において解析を行い、また結果公表に際しても５例以下のセルについては報告を行わないことで少数例庇護の措置を行った。

C．研究結果

①<u>出生票とその母の死亡票を高精度にリンケージする手法の検討</u>

現在、日本の人口動態統計は市町村が厚生労働省に各種出生・死亡などの情報を個票という形で報告し、これを厚生労働省がクリーニングしたのち、氏名情報や病院名情報を削除し、死因コードを ICD 分類に基づき付与した結果のデータを公式統計に用いている。また、市町村から厚生労働省に提出される情報は約９割がオンライン報告となっている。

このため、個票のみに氏名情報や死因の詳細情報が載っており、その代わり、誤った情報が記載されていることも多く、また日本全体の 10%の症例については情報がないという状態にある。親子のリンケージを行うためには死亡個票や出生個票のみに含まれる母親の氏名情報も、死亡票のみに記載されている死因の ICD 分類も必要であるため、本リンケージは２段階で実施した。

統計法（平成 19 年法律第 53 号）第 33 条の規定に基づき、人口動態調査に係る調査票情報の提供について申出を行い、調査票情報の提供を受けた。

まずは市町村からオンラインで報告されるデータ（○○個票）およびこれを厚生労働省がクリーニングおよびコーディングした結果のデータ（○○票）を、出生、死産、死亡のそれぞれにおいて作成した。

このリンケージには、届け出のあった都道府県・市町村・保健所・支所番号・事件簿番号および（出生・死亡・死産の）年月日、を用いて、年月日および事件簿番号に書き間違いがあった可能性を 1%と仮定して、確率的リンケージ(Probabilistic Linkage)により連結することで作成した。確率的リンケージについては Fellegi and Sunter らによって提唱された理論を用いて、誤字や入力ミスについては編集距離(Lebenstein 距離)を用いて２値の一致度を評価した。

下記の図 1-図 3 に出生、死亡、死産の

それぞれについて、リンケージ結果を示す。なお、m-probability (変数に書き間違いがない確率)を 99%から上下 2%変化させても、リンケージされる確率はほとんど変わらなかった。

図 1 出生票と出生個票のリンケージ

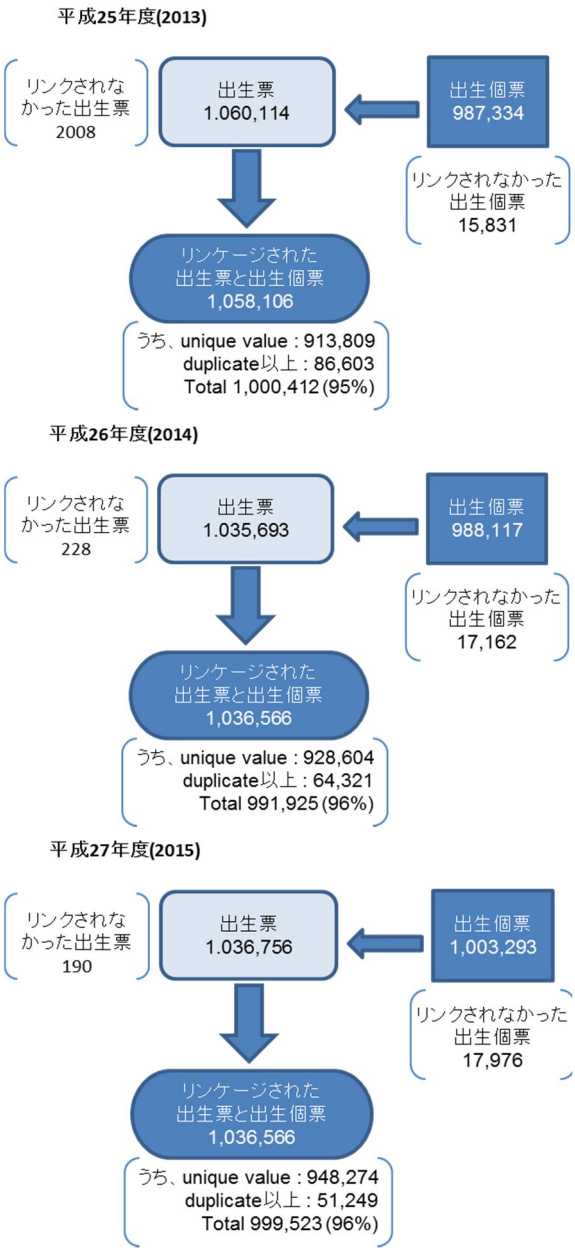


図 2　死亡票と死亡個票のリンケージ

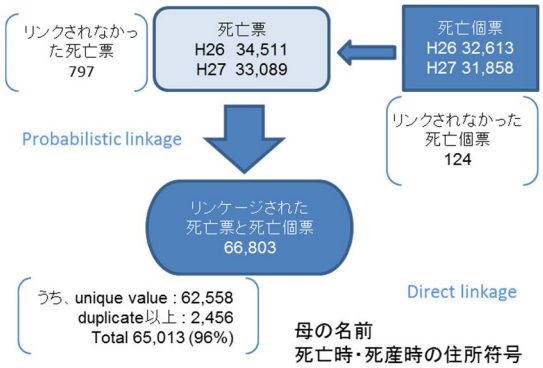
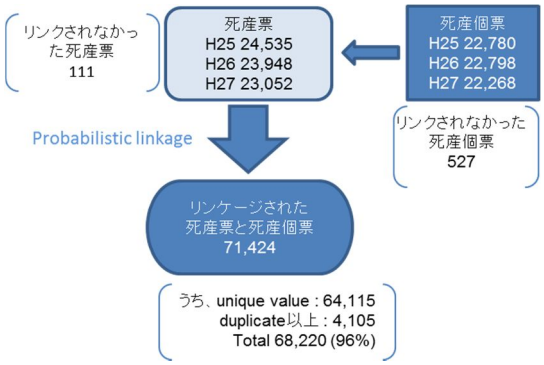


図 2　死亡票と死亡個票のリンケージ



続いて、それぞれリンケージされた死亡票/死亡個票と出生票/出生個票を、母（女性）の氏名および生年月日によりリンケージした。また、それぞれリンケージされた死亡票/死亡個票と死産/死産個票を、母（女性）の氏名および死産時の年齢（+1 あるいは-1 を含める）によりリンケージした。

このリンケージには、Deterministic Linkage つまりは、完全一致していることを条件とした。この方法では結婚あるいは離婚により出産時と死亡時で母の苗字が変わっている場合は捉えられない。しかし、下の名前のみを頼りに連結を試みると、たとえ同じ市町村内での出産・死亡であるという制限をかけたとしても下

の名前も生年月日も同じであるという女性が複数いたため、この方法を用いてのリンケージは現実的ではなかった。

② リンケージされたデータの利活用

本分担研究関係者のみならず、他の分担研究の先生方とともに多角的な解析を積極的に行った。この結果、複数の英語原著論文を出版することが出来、現在も複数を投稿中である。

今年度は論文および学会発表にて、下記の事項を報告した。

-低身長の妊婦が、より身長が高い妊婦よりも早産のリスクが高い理由は、身長が低いほど妊娠高血圧腎症になるリスクが高いことにより説明される。

-日本人の平均身長は 1979 年を境に減少しており、生まれ年別に見ると平均身長はその年の低出生体重児率と逆相関を認める。

-高齢出産は早産や多くの妊娠合併症のリスクとなる。

-日本を含む先進国 34 カ国における早産率と 37-38 週の出生率は高い相関率を示しており、37-38 週での出生を抑えることが早産率減少にも役立つ可能性がある。

-22-24 週の分娩において、児が分娩中の死産あるいは１時間以内の新生児死亡となるリスクは、母の居住市町村の平均年収が低いほど高い。

さらに、なるべく幅広くこのデータベースを有効に活用していただけるように、周産期医療関係者への疫学教育を実施した。

D．考察・結論

本年度は人口動態統計の個票情報に含まれる氏名情報などの特異度の高い情報を用いることで、それまでこれらの情報が含まれていない出生票・死亡票のみでは不可能であった親子を連結する手段を検討し、これが有用である可能性を見出した。

また、事件簿番号が不一致している症例が一定の割合でいる可能性があることやまだ個票のオンライン報告率が１００％ではないなどのいくつかの問題がみつかり、今後はその不一致の理由の探求などが必要であることがわかった。

今までは人口動態統計の連結手段に関しては、匿名化されている人動態統計票の連結が必要であった。これらの情報を高精度に相互連結するためには、母の生年月日や、周産期関連因子など、現在１歳未満の死亡の特記事項として記載されている変数が必要であり、これらの変数がないと出生票と死亡票の正確な連結は難しかった。

今回、氏名情報を用いた家族の連結が可能であることが分かった。この方法を用いて、出産や中絶後の母の死亡のリスク因子の解明に役立つ可能性が高いことが示された。今後兄弟の同定も可能であると思われ、家族のリンケージが進めば、幼児、学童の死亡についても同様の検討が可能になると思われる。

一方で、個人を特定できる可能性が高く“個人識別符号”とされている氏名情報を用いても、結婚や離婚により姓が変わりうる妊婦や褥婦においては、異なるデータベースに含まれる同一人物を完全に特定するのは難しい可能性も示唆された。現在戸籍情報の登録にはマイナンバーは含まれていないが、将来的にはマイナンバーによ

り戸籍情報を含む政府所有の情報を高精度で連結し、公衆衛生学的に有用な研究に活かすことを可能とすることが必要かもしれない。

連結されたデータベースの利活用については、本年度も小児科および産科の先生方とともに周産期データベースの解析を行い、多くの有用な新規発見ができた。しかし、有用なデータベースが作成できても、それを活用し、臨床現場および政策に反映できるような成果を産出できる研究者はまだ少ないという問題もまだ依然として残っている。

E. 健康危険情報

該当なし

F. 研究発表

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G. 知的財産権の出願・登録状況

1. **特許取得**
   該当なし。

2. **実用新案登録**
   該当なし。

3. **その他**
   該当なし。

Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Title 低出生体重児出生率と平均成人身長との関係

Authors: 森崎菜穂[1]、浦山ケビン[1,2]、吉井啓介[3]、SV Subramanian[4]、横谷進[3]

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Abstract
背景：現在、日本の平均寿命は世界で最も長い。また、健康指標と相関を認める平均成人身長も、過去100年で顕著に伸びた。一方、1970年台より低出生体重児率が倍増している。
方法：人口動態統計(1969-2014)から全出生(n=64,115,249)の母児背景の年次推移を、そして全国79の全国あるいは地域コホート(n=3,145,521)に含まれる1969-1996年に生まれた18歳以上の成人後身長の平均の年次推移を調べた。
結果：低出生体重児出生率はU字カーブを描き、1978-1979 (5.5%)に最低値をとった後は増加していた。一方で、平均成人身長は1978-79年［男性 171.5cm, 女性 158.5cm］をピークに以後20年間低下していた。低出生体重児率はその年に生まれた児の平均成人身長と強い逆相関を示した(男性 r=-0.98; 女性 r=-0.88)。出生情報と経済指標を基にした成人身長の予測モデルでは、平均身長は今後も低下し続け、2014年生まれの平均身長は男性では170.0cm (95%信頼区間 169.6, 170.3)、女性では157.9cm (95%信頼区間 157.5, 158.3)となることが予測された。
結論：1980年以後に生まれた成人の平均身長はすでに低下し始めており、この要因には低出生体重児増加が影響していると考えられる。身長が低いほど死亡や生活習慣病のリスクが上がることが分かっているため、低出生体重児増加の長期的な影響として成人の健康状態が悪化することが危惧される。

Abstract

Background: Japan, which currently maintains the highest life expectancy in the world and has experienced an impressive gain in adult height over the past century, has suffered a dramatic two-fold increase in low birth weight (LBW) births since the 1970s.

Methods: We observed secular trends in birth characteristics using 64,115,249 live births included the vital statistics (1969-2014), as well as trends in average height among 3,145,521 adults born between 1969-1996 included in 79 surveys conducted among a national, subnational, or community population in Japan.

Results: LBW rates exhibited a U-shaped pattern showing reductions until 1978-1979 (5.5%), after which it increased. Conversely, average adult height peaked for those born during the same period [males, 171.5 cm; females, 158.5 cm], followed by a reduction over the next 20 years. LBW rate and adult height showed a strong inverse correlation (males, r=-0.98; females, r=-0.88). A prediction model based on birth and economical characteristics estimated national average of adult height would continue to decline, to 170.0 (95% CI 169.6, 170.3) cm for males and 157.9 (95% CI 157.5, 158.3) cm for females among those born in 2014.

Conclusions: Adult height in Japan has started to decline for those born after 1980, a trend which may be attributed to increases in LBW births over time. Considering the known association between shorter adult height and adverse health outcomes, evidence of population level decline in adult health due to long-term consequences of increasing LBW births in Japan is anticipated.

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Ecological analysis of secular trends in low birth weight births and adult height in Japan

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ABSTRACT

Background Japan, which currently maintains the highest life expectancy in the world and has experienced an impressive gain in adult height over the past century, has suffered a dramatic twofold increase in low birth weight (LBW) births since the 1970s.

Methods We observed secular trends in birth characteristics using 64 115 249 live births included the vital statistics (1969–2014), as well as trends in average height among 3 145 521 adults born between 1969 and 1996, included in 79 surveys conducted among a national, subnational or community population in Japan.

Results LBW rates exhibited a U-shaped pattern showing reductions until 1978–1979 (5.5%), after which it increased. Conversely, average adult height peaked for those born during the same period (men, 171.5 cm; women, 158.5 cm), followed by a reduction over the next 20 years. LBW rate and adult height showed a strong inverse correlation (men, r=−0.98; women, r=−0.88). A prediction model based on birth and economical characteristics estimated the national average of adult height would continue to decline, to 170.0cm (95% CI 169.6 to 170.3) for men and 157.9cm (95% CI 157.5 to 158.3) for women among those born in 2014.

Conclusions Adult height in Japan has started to decline for those born after 1980, a trend that may be attributed to increases in LBW births over time. Considering the known association between shorter adult height and adverse health outcomes, evidence of population-level decline in adult health due to long-term consequences of increasing LBW births in Japan is anticipated.

INTRODUCTION

Understanding the determinants of adult height is of keen interest, as numerous epidemiological studies have shown robust associations between being shorter and a shorter life expectancy,[1 2] as well as higher risk of various cardiovascular diseases.[3] The link is suggested to be due to a combination of causal effects of adult height altering blood pressure and body mass index,[3] as well as adult height acting as a proxy of early life factors (eg, undernutrition, infection and social factors) that inhibit childhood growth and alter metabolism, which in turn increases the risk of major non-communicable diseases later in life.[4–6]

Globally, adult height has increased in all countries over the past century.[7] Most high-income countries have experienced a monotonic increase before reaching plateau[1 4 7]; economically thriving low-income and middle-income countries are still experiencing a rapid secular growth,[7] while other countries experiencing economic hardships have experienced a recent decrease in average adult height.[7 8] As serial cross-population assessments of height are not affected by genetic factors (unless the population experienced a large influx of migrant populations), such changes have been interpreted to be reflecting the improved nutritional status and sanitation in wealthier countries and its lack of improvement in other parts of the world.[7 8]

Japan, which currently maintains the highest life expectancy in the world,[9] has experienced an impressive 15 cm gain in adult height over the past century.[7 10 11] While previous reports suggested it has plateaued since births in the 1970s,[7] detailed analysis of recent trends has not been conducted. As Japan has experienced a twofold increase in low birth weight (LBW) births since the 1970s,[12] it is possible that such changes in birth characteristics have influenced secular trends in adult height.

Thus, in this study we aimed to observe trends in average adult height by year of birth using nationally representative serial cross-sectional data. We further examined how trends in birth characteristics are associated with trends in adult height.

METHODS

Calculation of average adult height using population-based data in Japan

Trends in mean adult height for those born between 1969 and 1996 were examined using data from 79 surveys conducted among a national, subnational or community population in Japan. The methodology of this large pooled analysis conducted by the non-communicable diseases (NCD) Risk Factor Collaboration, a network of health scientists around the world, has been previously reported in detail.[7] In brief, multiple routes for identifying and accessing data, including a systematic review, were used to identify all available population-based measurement studies of human anthropometry, after which summary statistics (sample mean and SE by age and sex) were obtained from all relevant studies. Studies were strictly limited to those collected using a probabilistic sampling method with a defined sampling frame and were representative of the general population. All data sources on population subgroups whose anthropometric status may have systematically differed from the general population due to health, ethnic or socioeconomic characteristics were excluded, as well as studies with self-reported height instead of measured height. As a result, 1472 data sources, including 79 data

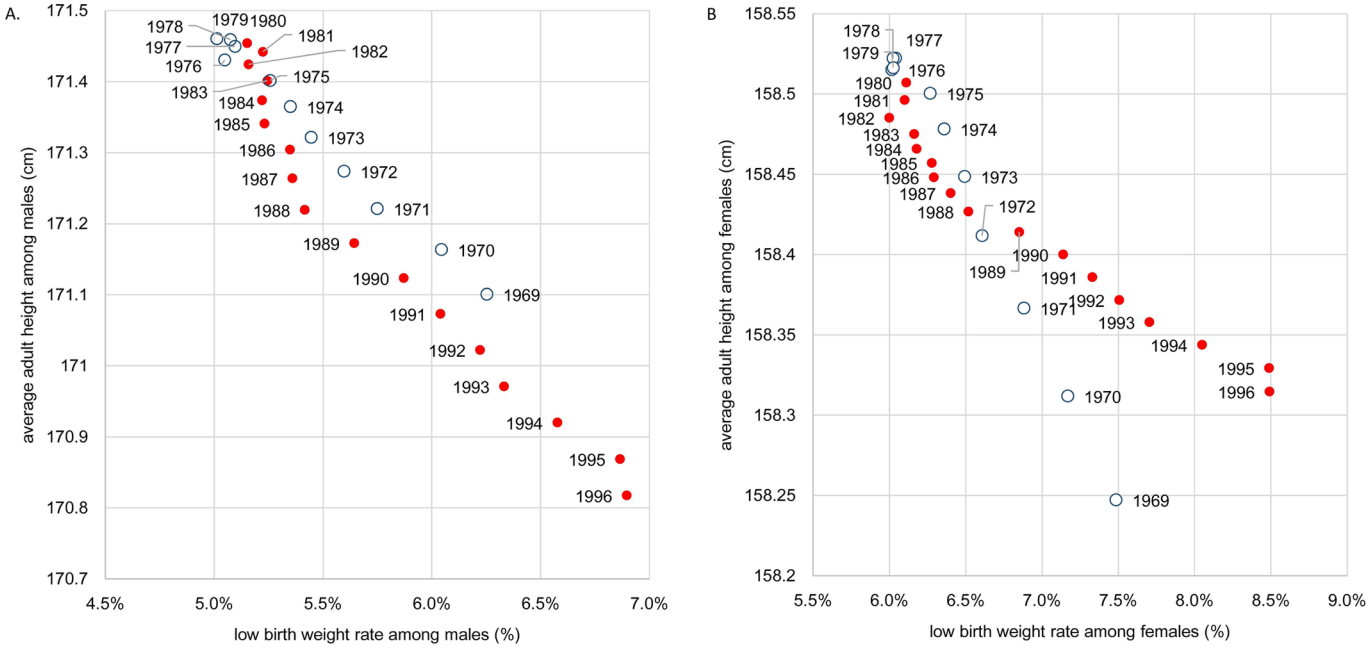

Figure 1 Scatter plot of proportion of low birth weight and average height at adulthood by year of birth (1969–1996) among men (A) and women (B).

sources (39 national-based, 1 subnational-based and 39 community-based) in Japan, were identified, which included 3 242 415 measurements of Japanese adults.

A Bayesian model fitted using the Markov chain Monte Carlo algorithm was used to estimate the mean height and 95% credible intervals (2.5th–97.5th percentiles of the posterior distribution) for each year in men and women separately. This model included a hierarchical structure in which mean height was estimated for each year of birth while accounting for the fact that subnational and community studies may have larger variation and may systematically differ from nationally representative studies. Overall trends in adult height among 200 countries between 1896 and 1996 have been presented previously,[7] with average height among Japanese men and women increasing by 14.5 cm and 16.0 cm over the century, respectively. Mean height and their 95% credible intervals by sex and year of birth as used in this study are available online (http://ncdrisc.org/downloads/height/individual-countries/Japan.csv).

Calculation of birth characteristics using vital statistics

The Japanese national vital statistics database of the Ministry of Health, Labour and Welfare started to collect information on multiplicity and birth weight, as well as maternal characteristics including age, number of previous live births and previous stillbirths, for all registered live births since 1969. For years 1969–1991, birth weight was recorded in categories (every 500 g during 1969–1974; every 100 g during 1975–1991) and since 1992 onwards has been reported in grams. For years 1969–1974, the number of births below 2500 g (exclusive) was not calculable, while the number of births 2500 g or below was calculable. Therefore, we defined LBW as birth weight 2500 g or less (inclusive). We defined primiparous women as those in their first pregnancy, teenage women as maternal age less than 20 at delivery, and advanced maternal age as 35 years and older at delivery. After excluding 277 083 (0.4%) with unknown sex and birth weight, we calculated annual rates of LBW, as well as rates of teenage pregnancies, advanced age pregnancies and primiparous pregnancies, among 64 115 249 births (32 967 335 men and 31 147 914 women) born between 1969 and 2014 by each year of birth.

Statistical analysis

For each sex, we plotted the average height and LBW rates by year of birth and examined the relationship using the Pearson's correlation coefficient. Next, using aggregate annual data for a total of 28 birth years (1969–1996), we conducted linear regression to model average adult height as a function of various birth characteristics (ie, rates of LBW, multiple births, teenage pregnancies, advanced age pregnancies and primiparous pregnancies) and an economic indicator (gross domestic product (GDP) per capita) of each birth year stratified by sex. Using this model, future adult height was predicted for those born between 1997 and 2014, representing individuals who have not yet turned 18 years of age by the time of data collection. To avoid overfitting, the model was bootstrapped 100 times.

All descriptive and statistical analyses were performed using Stata V.13. Statistical significance was set under 0.05, and all statistical tests were two-tailed. 95% CI for outcome prediction using the prediction model was estimated with error set at 2.110 × (SE) reflecting 17 df of the model.

The protocol for this study was approved by the Institutional Review Board of the National Center for Child Health and Development on 22 December 2016.

RESULTS

For both sexes, the average adult height peaked for births between 1978 and 1979, and a reduction was observed over the next 20 years (figure 1). In contrast, LBW rates reduced monotonically until 1978–1979, after which it increased until 2007 and plateaued at around 9.6%–9.7% for the recent 8 years. The lowest LBW rate and tallest adult height were 5.5% (1979) and 171.5 cm (1979 births) for men, and 6.0% (1978) and 158.5 cm (1978 births) for women, respectively. Correlation

Table 1 Ecological analysis of the association between birth characteristics and average adult height in Japan for those born in 1969–1996

	Among men	Among women
	Effect on height (95% CI) in mm	Effect on height (95% CI) in mm
LBW births† (per +1%)	−2.6 (−2.9 to −2.3)***	−1.5 (−2.19 to −1.0)***
Primiparous births (per +1%)	−0.1 (−0.29 to 0.0)*	0.1 (0.09 to 0.2)*
Multiple births (per +1%)	3.2 (1.79 to 4.8)***	1.1 (−0.69 to 2.8)
Teenage pregnancies (per +1%)	0.4 (−0.59 to 1.3)	−0.9 (−2.19 to 0.3)
Advanced age pregnancies‡(per +1%)	−0.3 (−0.59 to −0.1)***	0.0 (−0.39 to 0.2)
GDP per capita (/US$100 000)	−4.6 (−8.69 to −0.1)*	3.6 (−0.29 to 7.4)

Results have been bootstrapped 100 times.
*p<0.05, **p<0.01, ***p<0.001.
†LBW low birth weight (birth weight 2500 g or less).
‡Maternal age at delivery ≥35.
GDP, gross domestic product; LBW, low birth weight.

between annual LBW rate and average adult height of individuals born in the same year was very strong for both sexes (men: 0.98; women: 0.88), while annual rates of birth characteristics (trends shown in online supplementary appendix 1) and GDP per capita (trends shown in online supplementary appendix 2) were not significantly correlated with average adult height by year of birth. Large changes over time were observed for advanced age pregnancy rate increasing from 4.8% in 1969 to 27.1% in 2014, and GDP per capita increasing from US$1692 in 1969 to US$36 161 in 2014. Teenage pregnancy rate and multiple birth rate increased until the 2000s and then decreased, and primiparous pregnancy has stayed fairly stable over the 45 years.

The prediction model using data from 1969 to 1996 and assuming a linear association between birth characteristics and average adult height showed good fit (model R^2=0.99 for men; R^2=0.96 for women). Association between rates of birth characteristics and average adult height was strongest for LBW and multiple births (table 1), showing a reduction in average adult height of 2.5 mm (95% CI 2.2 to 3.0) in men and 1.5 mm (95% CI 1.0 to 2.1) in women for each 1% increase in LBW; an average increase in adult height of 3.2 mm (95% CI 2.0 to 4.5) in men and 1.1 mm (95% CI −0.6 to 2.8) in women was observed for each 1% increase in multiple births. Using this model to predict average adult height for births 1997–2014 based on annual rates of LBW, multiple births, teenage pregnancies, advanced age pregnancies, primiparous pregnancies and GDP per capita, a continued reduction in adult height is expected, with average height for those born in 2014 estimated to be 170.0 cm (95% CI 169.6 to 170.3) for men and 157.9 cm (95% CI 157.5 to 158.3) for women (figure 2).

DISCUSSION

This is the first study to show that in Japan, after continuous rise in average adult height for over 80 years, secular trend shows a decrease beginning from births that occurred after about 1980. We found average adult height was strongly associated with LBW rates for the corresponding year of birth in both men and women, suggesting that increases in LBW births may have affected the observed decrease in height. According to our estimates, men born in 2014 will be 1.5 cm shorter than those born 40 years ago, and women will be 6 mm shorter. Our findings implicate that Japan may experience increased disease burden among adults, beyond those caused by an ageing population, due to the long-term consequences of increasing LBW birth rates in Japan.

Globally, average height has increased over the century (1896–1996) in all countries, most likely reflecting improved nutritional status and sanitation.[7 8] It was widely understood that changes in average adult height for most Asian and European countries have plateaued after experiencing a monotonic increase over the last century.[7] In contrast, countries experiencing economic hardship such as many of those in Sub-Saharan Africa have experienced a recent deterioration in height. However, careful observation of recent trends for those born in 1980–1996 revealed that average adult height has started to decline (http://ncdrisc.org/), even in some high-income countries such as the USA, Sweden, Norway

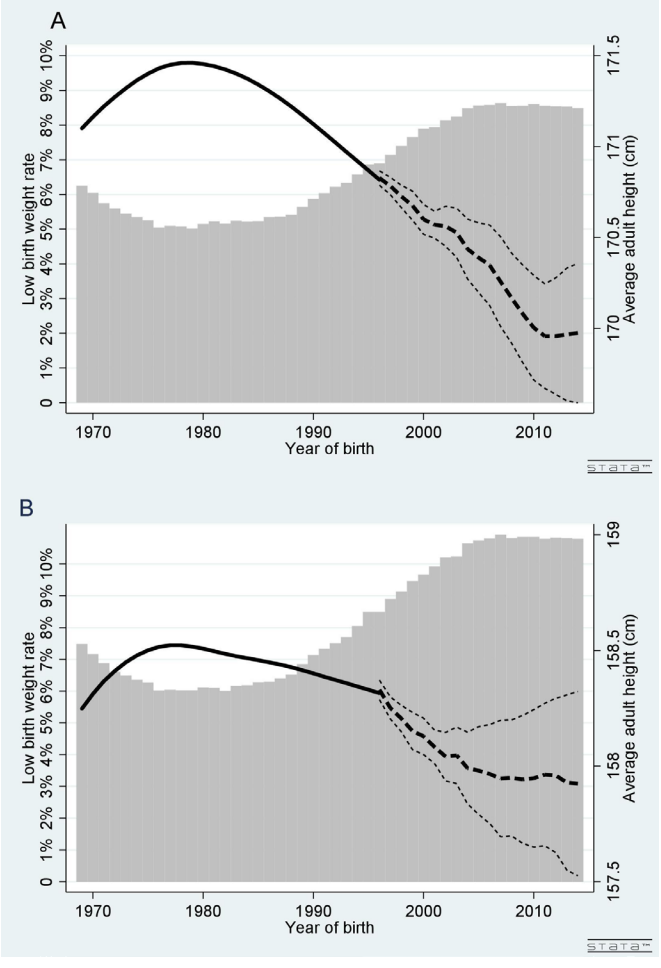

Figure 2 Low birth weight rate (1969–2014, grey bars), average adult height (1969–1996, solid black line) and predicted adult height (1997–2014, dotted black line) by year of birth among men (A) and women (B).

and Japan. While many environmental factors (eg, economical changes, immigration, changes in children's nutritional status) could have contributed to this trend, and the extent of contribution of each factor may differ between countries, the marked patterns observed in our study strongly suggest that the phenomenon is likely attributable to increases in LBW births for Japan. With the current LBW rate (9.6%) nearly twofold higher than that of 1980[12] and among the highest in high-income countries, we estimate that adult height among Japanese is expected to continue to decrease for at least another 10 years.

Japan is uniquely positioned to evaluate population trends in birth characteristics and effects on adult height since it has been experiencing drastic decreases in both gestational length and fetal growth for over 20 years.[13] But recent studies show evidence that other countries as well, such as the USA[14 15] and other regions of the world,[16] are on track to experience similar secular trends into the future regarding reductions in gestational length and fetal growth. Epidemiological studies have repeatedly shown that children born with reduced fetal growth[17] and/or reduced gestational length[18] have shorter height at the individual level. While the majority of infants born small experience catch-up growth, with shorter gestational length, the risk of failing to catch up increases. It has been shown that those who do not catch up by 2–3 years of age tend to have short stature in adulthood.[19 20] Our study not only supports these individual level epidemiological associations, but strikingly for the first time, the results show markedly noticeable population-level effects of changes in LBW rates on adult height. The public health implications of this may potentially be enormous assuming that results from previous studies linking adult height to health status in later life are true. While these findings may be considered a Japan phenomenon for now, it is possible that other countries may experience similar trends in the future.

Numerous reports have shown that adult height is associated with early life experiences and long-term cognitive, educational, economic and health outcomes.[5] Shorter adult height has been associated with increased risk of shorter life expectancy,[1 2] higher risk of various cardiovascular diseases[3] as well as various pregnancy disorders.[21–24] Mendelian randomisation studies[3 25] suggest such associations to be causal, and based on their estimates there will be approximately 3% more cardiovascular disease-related deaths (approximately 6000 cases) among Japanese men born in 2014 as compared with if LBW rates had stayed at the level of 1980. Thus, while long-term adverse effects of LBW reflected through shorter height is yet to be reported (since those born after 1980 are still in an age range not considered to be at high risk of developing chronic diseases or dying) in Japan, our study suggests that the increase in LBW rate is likely to substantially affect population health in the near future. As ecological analyses have shown that gains in mean population height are associated with lower mortality in middle and older ages,[7] this may also affect Japanese life expectancy.

Interestingly, we observed large sex differences in the association between birth characteristics and average height at adulthood. The estimated effect of LBW rate on height was twice as large among men compared with women, and the inverse association between rates of primiparous women and women of advanced age and height was observed only among men. Our findings follow previous reports showing secular change in height to be larger among men compared with women,[7] a finding that is likely explained by larger environmental influences on men compared with women.[26–28] Given the already higher incidence of cardiovascular diseases, strokes and hypertensive disorders and a shorter life expectancy in men, our result of a larger effect of rising LBW rates on height skewed towards this gender implies that we may observe an increase in health discrepancy by gender in the future.

It is important to note the limitations of our study. First, to maximise the number of subjects available for analysis, data from national studies with measurements on adult height were supplemented with estimates from subnational and community studies as well. However, to overcome possible systematic bias and uncertainty of estimates, a statistical model accounting for these uncertainties was applied; estimated 95% credible intervals were narrow (0.5–1.5 mm). Second, while we adjusted for maternal characteristics and other possible confounders reported in previous studies,[18] additional unmeasured factors may have influenced the association between secular trends in LBW and adult height. For example, we were not able to incorporate the effect of changes in foreign resident population, but at most these residents comprised only less than 2% of the Japanese population over time. Additional confidence in our interpretation of these ecological findings is due to the strength of association observed, as well as strong biological plausibility supported by longitudinal studies of both preterm delivery[18] and small for gestational age,[29] the two components of LBW, showing increased risk of shorter adult height. Third, as reporting of gestational length was in months and unreliable until 1979 and birth weight was only reported in crude categories rather than grams until 1992, we were not able to calculate preterm birth rates and small for gestational age rates in all years of interest; thus, we were unable to separately evaluate the effects of these two components of LBW on adult height. While previous studies suggest both decrease in fetal growth (likely due to low maternal nutrition[12 30]) as well as decrease in gestational length (likely due to increased obstetric interventions[13 31]) have contributed to the rise in LBW rates in Japan, future studies are needed to further understand the respective roles of these two mechanisms in affecting adult height.

CONCLUSION

Taking advantage of Japan's chronic pattern of rising LBW rates over the last few decades, our study provides strong evidence of a population-level effect of LBW on decreasing adult height. While understanding causal pathways linking LBW and adult height exceeds the scope of this study, as LBW is a modifiable

What is already known on this subject

- Numerous studies show robust associations between taller height and longer life expectancy. Japan has experienced an impressive gain in adult height over the past century and maintains the highest life expectancy in the world, however has suffered a twofold increase in low birth weight births since the 1970s.

What this study adds

- Adult height in Japan has started to decline significantly for those born after 1980, likely due to the long-term consequences of increasing low birth weight birth rates. Our findings implicate a level of public health urgency for addressing the possible long-term consequences of changes in birth characteristics.

factor, our findings implicate a level of public health urgency for addressing the possible long-term consequences of changes in birth characteristics.

Contributors NM initiated the concept, designed and conducted the study, wrote the initial manuscript and approved the final manuscript as submitted. KY conducted literature review, provided important comments on the interpretation of the results and approved the final manuscript as submitted. SY and KYU oversaw the process and provided important intellectual context to the study design as well as interpretation of results, and approved the final manuscript as submitted. SVS provided important intellectual context to the study design as well as interpretation of the results, and approved the final manuscript as submitted.

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Competing interests None declared.

Ethics approval The protocol for this study was approved by the Institutional Review Board of the National Center for Child Health and Development on 22 December 2016.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Annual rates of birth characteristics (in aggregated form) are available from the authors.

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Ecological analysis of secular trends in low birth weight births and adult height in Japan

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Preeclampsia mediates the association between shorter height and increased risk of preterm delivery

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Abstract

Background: Maternal short stature has been observed to increase the risk of preterm birth; however, the aetiology behind this phenomenon is unknown. We investigated whether preeclampsia, an obstetric complication that often leads to preterm delivery and is reported to have an inverse association with women's height, mediates this association.

Methods: We studied 218 412 women with no underlying diseases before pregnancy, who delivered singletons from 2005 to 2011 and were included in the Japan Society of Obstetrics and Gynecology perinatal database, which is a national multi-centre-based delivery database among tertiary hospitals. We assessed the risk of preterm delivery in relation to height using multivariate analysis, and how the association was mediated by risk of preeclampsia using mediation analysis.

Results: Each 5-cm decrement in height was associated with significantly higher risk of preterm delivery [relative risk 1.20; 95% confidence interval (CI): 1.13, 1.27] and shorter gestational age (−0.30; 95% CI: -0.44, -0.16 weeks). Mediation analysis showed that the effect of shorter height on increased risk of preterm delivery, due to an indirect effect mediated through increased risk of preeclampsia, was substantial for shorter gestational age (48%), as well as risk of preterm delivery (28%). When examining the three subtypes of preterm delivery separately, mediated effect was largest for provider-initiated preterm delivery without premature rupture of membranes (PROM) (34%), compared with spontaneous preterm delivery without PROM (17%) or preterm delivery with PROM (0%).

Conclusions: Preeclampsia partially mediates the association between maternal short stature and preterm delivery.

Key words: Height, preeclampsia, preterm delivery

Key Messages

- Maternal height has been shown to be inversely associated with increased risk of preterm delivery over many populations.
- Preeclampsia is a major cause of preterm delivery, and is reported to be of increased risk among shorter women.
- In this study, we found that preeclampsia partially mediated the association between shorter height and increased risk of preterm delivery.

Introduction

Preterm birth, or birth before 37 completed weeks of gestation, is the leading cause of neonatal mortality, contributing to over one-third of the world's estimated 3 000 000 neonatal deaths per year.[1,2,3] Even after surviving the neonatal period, infants born preterm are at increased risk for delayed childhood development and low economic productivity.[4] Acknowledgment of the large public health impact of preterm birth has led to many initiatives aiming to prevent preterm birth by providing comprehensive antenatal care, childbirth services and emergency obstetric care.[5–7]

Among many identified risk factors of preterm birth, maternal short stature has been widely observed to increase the risk of preterm birth.[8,9] The aetiology behind this association remains unexplained, with the most commonly used suggestion being that short stature may limit the uterine volume for fetal growth.[8,10] However, results from observational studies do not fully support the hypothesis of a tendency for a large infant being delivered early from a shorter mother where the uterus may be disproportionate in size to the infant. For example, paternal height (which is strongly correlated with fetal growth) lacks association with gestational age,[11,12] and maternal short stature is inversely associated with preterm delivery even at the lower gestations when the fetus is still small.[13]

On the other hand, recent studies show that maternal short stature increases the risk of preeclampsia[14–17] as well as placental abruption,[16] two strong indicators of placental ischaemia, a condition known to be the leading cause of medically indicated preterm deliveries.[18–20] Further, several reports showed that short stature also increases the risk of stillbirth,[21,22] whereas earlier delivery when fetal distress is detected is needed to prevent stillbirths. Thus, it is possible that the frequently observed association between shorter height and shorter gestational age may not only be due to physiological 'early filling', but due to increase in earlier deliveries due to higher risk of pregnancy complications among shorter women. However, previous studies[8,9] have not considered the possible role that pregnancy complications may play in the relationship connecting short stature and preterm delivery.

The objective of this study was to examine the extent to which preeclampsia mediates the association between short stature and preterm delivery. To address this objective, we analysed data from the Japan Society of Obstetrics and Gynecology (JSOG) perinatal database, a large national institutional-based obstetrics database in Japan.

Methods

The study population and data collection methods have been previously described in detail.[16,23–25] Briefly, the JSOG perinatal database is an ongoing registry based on a national collaboration of obstetric departments from 149 tertiary hospitals in Japan, collecting individual patient data on all live births and stillbirths delivered at 22 weeks or after, from medical charts using a standardized format. The JSOG Perinatal Committee annually reviews the submitted data for data quality and contacts institutes for correction if a substantial portion contains erroneous or missing data. The data for 2004–11 were recently linked to vital statistics data that verified their accuracy and showed that this registry covers 6.5% of all national births.[23]

There were 280 204 registered women with no medical conditions (respiratory, gastrointestinal, hepatic, renal, haematological, cardiovascular, metabolic, mental disease or hypertension) before pregnancy, who delivered

singletons with no congenital anomaly between April 2005 and December 2011, at 22 weeks of gestation or laer. We excluded 4502 with missing data on either parity, age at delivery, gestational weight gain, infant sex, gestational age or birthweight, or inconsistent combination of birthweight and gestational age (using the method proposed by Alexander *et al.*[26]). Main analysis was based on 218 412 women, further excluding subjects with missing or unreliable [> 4 standard deviations (SD) or < -4 SD of the population] data on height ($n = 44\,780$) and missing or unreliable (> 20 kg considered unreliable) data on pre-pregnancy weight ($n = 12\,510$).

The primary exposure of interest was self-reported maternal height. As only 5% of the database had reported height in millimetres, all measurements were rounded to the nearest centimetre. The primary outcome of interest was preterm birth, defined as less than 37 completed weeks of gestation, based on best obstetric estimates of gestational age estimated from the last menstrual period and corrected by ultrasound measurements during the first trimester. Similarly, we defined early preterm birth as delivery at less than 34 completed weeks of gestation, and late preterm birth as delivery at 34 to 36 completed weeks of gestation. From data of gestational age at delivery, onset of labour and mode of delivery, as well as existence of premature rupture of membranes (PROM), we created three subtypes of preterm delivery[2,27]: (i) preterm delivery with PROM; (ii) provider-initiated preterm delivery with no PROM (defined as preterm delivery by pre-labuor cesarean delivery or labour induction with no PROM); and (iii) spontaneous preterm delivery with no PROM (defined as preterm delivery with spontaneous onset of labour and no PROM). For these classifications, both live births and stillbirths were included; however, as stillbirth is the unfortunate outcome of not being able to deliver when the fetus is under distress, we also observed stillbirth as a secondary outcome.

Our mediator of interest was preeclampsia. Preeclampsia was diagnosed clinically by obstetricians in each hospital using a unified national guideline in line with the International Society for the Study of Hypertension in Pregnancy,[28] defined as systolic blood pressure over 140 mmHg or diastolic blood pressure above 90 mmHg that emerges after 20 weeks' gestation with significant proteinuria $\geq$ 300 mg/day.

Statistical Analysis

First, baseline characteristics were compared by trend analysis using quartiles of height: Quartile 1 (132–155 cm; $n = 54\,603$); Quartile 2 (155–158 cm; $n = 54\,603$); Quartile 3 (158–162 cm; $n = 54\,603$); Quartile 4 (162–183 cm; $n = 54\,603$). In the construction of the quartiles, women with same height at the quartile cutpoints were randomly assigned to the lower or higher quartile, to prevent uneven number of subjects in the categories. Next, we used multivariable Poisson regression to estimate risk ratios (RR) and 95% confidence intervals (CI) for preterm delivery, as well as three preterm delivery subtypes (provider-initiated with no PROM, spontaneous with no PROM, and PROM) and stillbirth, for each quartile of maternal height. Linear regression was used to estimate the effect of maternal height on gestational age.

After confirming the linearity of the association between height and the outcomes through these analyses, we conducted mediation analysis to evaluate the separate direct and indirect (mediated by preeclampsia) effects of each 5-cm increase in height on gestational age and risk of preterm delivery and stillbirth.

All analyses were adjusted by maternal age, parity, smoking status, pre-pregnancy body mass index (BMI) (calculated from self-reported height and self-reported pre-pregnancy weight),[29] and infant sex, which are known risk factors according to previous literature.[30,31] Adjustments were also made for maternal year of birth—to account for an increase in maternal height over the years in Japan[32]—as well as abnormal glucose tolerance (either pre-existing diabetes or gestational diabetes mellitus based on recommendations from the International Association of Diabetes in Pregnancy Study Groups[33]), which has recently been reported to be inversely associated with height.[34] Whereas the main analyses were conducted among women with complete data, we also performed sensitivity analyses that included the 44 780 women with missing height and 12 210 with missing pre-pregnancy weight data after multiple imputation (with 30 imputations) to fill in these values.

Mediation analysis hypothesizes that the total effect of maternal height (X) on an adverse outcome (Y) consists of a direct effect and an indirect effect [i.e. mediated by preeclampsia (M)], and calculates the proportion of the total effect that is indirect (i.e. mediated). Such an analysis enabled us to estimate to what extent the increased risk of preeclampsia among shorter mothers was responsible for increased risks in other outcomes. The original theoretical model proposed by Baron and Kenny[35] had crudely calculated this proportion as 1- c'/c from the following three models: (i) one model estimating the total effect (c) of X on Y; (ii) one model estimating the direct effect (c') of X on Y with M included as a covariate; and (iii) one model estimating the effect of X on M. However, it has been shown that the lack of account of possible exposure-mediator interactions could miscalculate the mediation effect; thus, we used an improved model proposed by VanderWeele

et al.[36,37] As this method cannot accommodate the uncertainty in measures produced by multiple imputation, this analysis was conducted on mothers with complete data.

All descriptive and statistical analyses were performed using STATA version 13 (STATA Corp, College Station, TX), with mediation analysis conducted using the command 'paramed' available in the program. The protocol for this study was approved by the Institutional Review Board of the National Center for Child Health and Development on January 28, 2016 (No. 1102).

Results

Our analysis found that among 218 412 women, 28 323 (13.0%) had preterm delivery, among which 6013 (21%) were provider-initiated preterm deliveries with no PROM, 14 754 (52%) were spontaneous preterm deliveries with no PROM and 7556 (27%) were preterm delivery with PROM; 1317 (0.6%) women delivered a stillbirth, and 5434 (2.5%) women experienced preeclampsia. Women in higher quartiles of height were thinner, older, more likely to be primiparous and smoked less. They also had significantly lower prevalence of all subtypes of preterm delivery, as well as stillbirth delivery, preeclampsia and abnormal glucose tolerance (Table 1). Average gestational ages for the four categories were 38.0 (standard deviation: 2.7) weeks, 38.1 (2.7) weeks, 38.2 (2.6) weeks and 38.3 (2.5) weeks, from shortest to tallest, respectively.

In the adjusted model, we found that quartiles of increasing height was significantly associated with gestational age, and inversely associated with preterm delivery, stillbirth and preeclampsia (Table 2). Women in the lowest

Table 1. Maternal and infant characteristics by quartiles of maternal height among 218 412 women

Maternal and infant characteristics	Quartiles (Q) of height								
	Q1 (n = 54603) 132–155 cm (mean 151.4)		Q2 (*n* = 54603) 155–158 cm (mean 156.4)		Q3 (*n* = 54603) 158–162 cm (mean 159.9)		Q4 (*n* = 54603) 162–183 cm (mean 165.1)		*P*-value
	No.	%	No.	%	No.	%	No.	%	
Maternal age									
< 20 years	1071	2.0	748	1.4	636	1.2	494	0.9	< 0.001
20–35 years	39365	72	38828	71	38302	70	38217	70	
> 35 years	14167	26	15027	28	15665	29	15892	29	
Prepregnancy BMI									
< 18.5 kg/m^2	9143	17	9966	18	10106	19	11620	21	< 0.001
18.5 to 25 kg/m^2	39002	72	39009	71	39060	72	37965	70	
> 25 kg/m^2	6458	12	5628	10	5437	10	5018	9.2	
Parity									
0	26792	49	27296	50	27662	51	28528	52	< 0.001
1< =	27811	51	27307	50	26941	49	26075	48	
Smoking									
Yes	2687	4.9	2592	4.7	2387	4.4	2289	4.2	< 0.001
No	42436	78	42479	78	42552	78	42895	79	
Missing	9480	17	9532	18	9664	18	9419	17	
Infant sex									
male	28167	52	28212	52	27962	51	28103	52	0.456
Female	26436	48	26391	48	26641	49	26500	49	
Pregnancy complications	No.	%	No.	%	No.	%	No.	%	
Preeclampsia	1626	3.0	1372	2.5	1251	2.3	1185	2.2	< 0.001
Preterm delivery	8116	15	7240	13	6752	12	6215	11	< 0.001
- Provider-initiated with no PROM	3323	6.1	3009	5.5	2745	5.0	2453	4.5	
- spontaneous, with no PROM	4793	9.4	4231	8.2	4007	7.7	3762	7.2	
- with PROM	1692	3.1	1540	2.8	1428	2.6	1353	2.5	
Early preterm delivery	4322	7.9	3746	6.9	3532	6.5	3154	5.8	< 0.001
Late preterm delivery[a]	2102	3.8	1954	3.6	1792	3.3	1708	3.1	< 0.001
Stillbirth	355	0.7	288	0.7	361	0.6	313	0.5	0.027
Abnormal glucose tolerance	1938	3.6	1328	3.0	1777	2.9	1565	2.7	< 0.001

P-value calculated for test of trend.

[a]Percentage calculated using births of gestational age 34 weeks or above.

Table 2. Association between maternal height and adverse pregnancy outcomes among 218412 women

	Gestational age [weeks (95% CI)]	Preterm delivery [RR (95% CI)]	Provider-initiated preterm delivery with no PROM [RR (95% CI)]	Spontaneous preterm delivery with no PROM [RR (95% CI)]	Preterm delivery with PROM [RR (95% CI)]
Q1	−0.34 (−0.37, -0.31)	1.29 (1.25, 1.34)	1.24 (1.16, 1.33)	1.31 (1.26, 1.36)	1.23 (1.16, 1.31)
Q2	−0.20 (−0.23, -0.17)	1.16 (1.12, 1.20)	1.14 (1.06, 1.23)	1.17 (1.12, 1.22)	1.15 (1.07, 1.23)
Q3	−0.10 (−0.13, -0.07)	1.09 (1.06, 1.13)	1.05 (0.98, 1.12)	1.11 (1.07, 1.15)	1.06 (1.00, 1.13)
Q4	Reference	Reference	Reference	Reference	Reference

	Early preterm delivery (< 34 weeks of gestation) [RR (95% CI)]	Late preterm delivery (34 to 36 weeks of gestation)[a] [RR (95% CI)]	Stillbirth [RR (95% CI)]
Q1	1.32 (1.26, 1.39)	1.29 (1.25, 1.35)	1.21 (1.04, 1.41)
Q2	1.21 (1.15, 1.28)	1.13 (1.09, 1.19)	1.21 (1.03, 1.41)
Q3	1.12 (1.07, 1.18)	1.08 (1.04, 1.13)	1.10 (0.94, 1.28)
Q4	Reference	Reference	Reference

Quartiles were as follows: Q1 (132–155cm), Q2 (155–158cm), Q3 (158–162cm), Q4 (162–183cm).
Adjusted for maternal year of birth, maternal age, parity, pre-pregnancy body mass index, smoking status, glucose tolerance status and infant sex.
[a]Sample size is 206, = 882 deliveries at 34 weeks or above.

Table 3. Direct effects and indirect (mediated by preeclampsia) effects of each 5-cm decrement in maternal height on gestational age, preterm delivery and stillbirth

	Total effect	Natural direct effect	Natural indirect effect	% mediated
All births ($n = 218412$)				
Gestational age [weeks (95% CI)]	−0.30 (−0.44, −0.16)	−0.16 (−0.19, −0.12)	−0.15 (−0.22, −0.07)	48.3%
Preterm delivery [RR (95% CI)]	1.20 (1.13, 1.27)	1.14 (1.08, 1.19)	1.06 (1.04, 1.07)	28.4%
Provider-initiated with no PROM [RR (95% CI)]	1.15 (1.04, 1.28)	1.10 (1.02, 1.18)	1.05 (1.02, 1.08)	33.5%
Spontaneous, with no PROM, [RR (95% CI)]	1.10 (1.05, 1.15)	1.08 (1.06, 1.10)	1.02 (0.98, 1.06)	16.5%
Spontaneous with PROM, [RR (95% CI)]	1.09 (0.78, 1.53)	1.10 (0.95, 1.27)	1.00 (0.82, 1.21)	0.0%
Early preterm delivery [RR (95% CI)]	1.25 (1.11, 1.40)	1.14 (1.03, 1.26)	1.10 (1.08, 1.11)	39.2%
Stillbirth [RR (95% CI)]	1.22 (0.87, 1.71)	1.16 (0.89, 1.51)	1.06 (1.00, 1.11)	25.6%
Limited to 34 weeks and over ($n = 206882$)				
Gestational age [weeks (95% CI)]	−0.14 (−0.25, −0.04)	−0.09 (−0.11, −0.08)	−0.05 (−0.09, 0.00)	33.5%
Late preterm delivery [RR (95% CI)]	1.20 (1.11, 1.30)	1.13 (1.07, 1.20)	1.06 (1.03, 1.08)	28.9%

Adjusted for maternal year of birth, maternal age, parity, pre-pregnancy body mass index, smoking status, glucose tolerance status and infant sex.

quartile of height had significantly shorter gestational age [-0.34 (95% CI: −0.37, −0.31) weeks], as well as higher risk of preterm delivery [RR 1.29 (95% CI: 1.25, 1.34)] and stillbirth [RR 1.21 (95% CI: 1.04, 1.41)] compared with women in the highest quartile. Results were similar in sensitivity analysis based on all subjects which used imputed values in place of missing or implausible height or weight measures as well as smoking status (see Appendix, available as Supplementary data at *IJE* online).

Next, as shown in Table 3, in the adjusted model accounting for possible mediation by preeclampsia as well as any possible exposure-mediator interactions, the total effect (direct and preeclampsia-mediated indirect effect) of each 5-cm decrement in height was associated with an increased risk of preterm delivery [RR 1.20 (95% CI: 1.13, 1.27) and stillbirth [RR 1.22 (95% CI: 0.87, 1.71)], and decreasing mean weeks in gestational age [-0.30 (95% CI: −0.44, −0.16)]. When evaluating the effect mediated indirectly through preeclampsia, each 5-cm decrement showed an increased risk of preterm delivery [RR 1.06 (95% CI: 1.04, 1.07)] and stillbirth [RR 1.06 (1.00, 1.11)], and decreasing mean weeks in gestational age [-0.15 (95% CI: −0.22, −0.07)]. Among subtypes of preterm delivery, the indirect effect mediated by preeclampsia was largest for risk of provider-initiated preterm delivery with no PROM [RR 1.05 (95% CI: 1.02, 1.08) per 5 cm], followed by risk of spontaneous preterm delivery with no PROM [RR 1.02 (95% CI: 0.98, 1.06) per 5 cm]; an effect on risk of preterm delivery with PROM was undetectable [RR 1.00 (95% CI: 0.82, 1.21) per 5 cm]. The estimated proportion of the effect of height due to an indirect effect mediated through increased risk of preeclampsia was substantial for shorter gestational age (48.3%), preterm delivery (28.4%) and stillbirth (25.6%). Among subtypes of

preterm delivery, mediation was largest for provider-initiated preterm delivery with no PROM (33.5%), followed by spontaneous preterm delivery with no PROM (16.5%) and null for preterm delivery with PROM (0.0%).

Discussion

In a large sample of healthy Japanese women who delivered singletons, we observed that increased risk of preeclampsia partially mediates the association between shorter maternal height and increased risk of preterm birth. The mediated effect was largest for provider-initiated preterm delivery with no PROM, but an effect was also observed for spontaneous preterm delivery with no PROM. No mediation effect was observed for preterm delivery with PROM. Our findings suggest that the robust association between height and preterm delivery, which has been observed among many populations,[8,9] can at least be explained in part by the increased risk of a major obstetric complication, preeclampsia,[14,17] in women of shorter height.

In our study we found a linear association between height and gestational age, as has been observed across diverse populations of numerous ethnicities and among high-, low- and middle-income countries.[8,9] The finding that risk of both early preterm and late preterm birth increases with shorter stature is consistent with recent reports from Sweden, which found similar effects of height on risk of both preterm and very preterm births.[13] Our study also replicates findings on the association between shorter height and increased risk of stillbirth that have been reported from Scotland[21] and Canada.[22]

To our knowledge, this study is the first to suggest that a pathological obstetric complication partially mediates the association between shorter maternal height and increased risk of preterm delivery. As recent studies show that shorter height is associated with increased risk of preeclampsia,[14–17] and preeclampsia plays a key role in preterm delivery,[18–20] such a hypothesis is biologically plausible. The common interpretation of increased risk of preterm delivery and shorter gestation among shorter women has been that a shorter woman would have a smaller uterus subject to 'early filling', but paternal height—which affects fetal growth (most likely genetically) equally as strongly as maternal height[10,38, 39]—has consistently shown no relationship with gestational age.[11,12] Also such 'early filling' would only occur later in pregnancy, and fails to explain why shorter women have increased risk of very preterm and extremely preterm births[13] when the fetus weighs merely approximately 500–1500 g. The hypothesis suggested by our results, that the association is not purely due to anatomical issues related to the woman's uterus or pelvis, but has a pathological component due to pregnancy complications, provides a plausible interpretation that does not conflict with these findings.

We found that the proportion of the effect of height, mediated through preeclampsia, was larger for provider-initiated preterm delivery (33.5%) and spontaneous preterm delivery with no PROM (16.5%), compared with preterm delivery with PROM (0%). Hypertensive disorders in pregnancy are a major determinant of provider-initiated preterm delivery, and intrauterine infections such as chorioamnionitis are considered to be the more common cause of PROM.[27] Thus our results, showing differing magnitudes of mediation that are consistent with the current understanding of hypothesized mechanisms across the preterm subgroups, provide additional confidence in the interpretation that pregnancy complications may partially be responsible for why shorter women have higher risk of preterm delivery.

We also observed the mediated effect of height on preterm delivery to be stronger for early (39.2%) compared with late (28.9%) preterm deliveries. As preeclampsia is a leading indication for delivery, these results suggest that the link between maternal height and preterm delivery is mediated more strongly by preeclampsia with onset at earlier gestations compared with those which occur later. Interestingly, long-term follow-up of women with preeclampsia also showed differences in risk of hypertension and cardiovascular disease (CVD) later in life[40–42] by timing of preeclampsia onset, i.e. risk of future CVD was highest among those whose onset of preeclampsia was early (before 34 weeks of gestation) compared with those with later onset (as well as those with no preeclampsia).[42] These similarities in association, indicating a role for preeclampsia timing, together with the observed inverse association between adult height and both cardiovascular diseases (CVD)[43] and preeclampsia[14–17] risk, suggest a potentially complicated interplay between adult height, the timing of preeclampsia, and ultimately a dual effect on the fetus through preterm delivery and the mother's long-term health risks.

Further investigation is necessary to determine whether this mediated effect is influenced by genetic or environmental factors. Whereas nearly 80% of height is determined genetically, it is thought that 20% is modifiable by early life factors.[44] Thus shorter height may reflect the accumulation of adverse early life exposures (such as fetal, dietary, social and psychological circumstances),[44,45] which are known to be related to hypertension later in life.[43,44,46] On the other hand, a recent Mendelian randomization study using data on genome-wide single nucleotide polymorphisms concluded that the effect of maternal height on gestational age was transmitted through a phenotypic causal mechanism influenced by maternal genetics.[10] Thus the mediation could be due to genetically-driven phenotypes associated with preeclampsia.[47]

Our study has certain limitations. First, height was not measured but self-reported, and hence may not be precise.[48] Non-differential measurement error, as well as overestimation which has been reported to occur particularly among shorter women,[49] may have led to an underestimation of the effect of height on outcomes. Second, our mediation analysis would be subject to unmeasured confounding, due to a confounder that has an effect on both the mediator and outcomes of interest. However, even if we assumed substantial unmeasured confounding (for instance, assuming the effect of unmeasured confounding (U) on gestational age to be four times, and the effect of U on preeclampsia to be three times), the mediating effect would still be substantially large (28.9%). Third, although average height (157.9 cm) and prevalence of pregnancy-induced hypertension (systolic blood pressure over 140 mmHg or diastolic blood pressure above 90 mmHg that emerges after 20 weeks' gestation) in our study (3.9%) were similar to national figures (157.8 cm and 3.5%, respectively), our study was based on a birth registry of tertiary hospitals (which accept referrals from smaller hospitals), and may have included more women with higher social and medical risks compared with the general population.[50,51] Thus, although our study was fairly large, future studies on whether our findings are replicable in other populations should be encouraged.

Our study adds a new piece to the puzzle that may explain the consistently observed association between height and preterm delivery.[8,9] In addition to anatomical restrictions of the smaller pelvis, an increased risk of pathological complications associated with shorter height may explain this association.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

N.M. initiated the concept, designed the study, performed the analysis and wrote the initial manuscript. K.O. gave critical comments on the interpretation of the results and revised the draft. K.Y.U. gave critical comments on the study design, analytical methods, assisted in the interpretation of the results and revised the draft. S.S. and S.S. collected the data and assisted in the interpretation of the results. H.S. assisted in the interpretation of the results and revised the draft. K.Y.U. and Emma Barber have carefully edited the English language.

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Socioeconomic inequity in survival for deliveries at 22–24 weeks of gestation

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ABSTRACT

Objective Guidelines recommend individual decision making on resuscitating infants of 22–24 weeks' gestational age (GA) at birth. When the decision not to resuscitate is made, infants would likely die soon after delivery, and under some circumstances such neonatal deaths may be registered as stillbirths occurring during delivery (intrapartum stillbirth). Thus we assessed whether socioeconomic factors are associated with peridelivery deaths (during or within 1 hour of delivery) of infants delivered at 22–24 weeks' gestation.

Methods We analysed 14 726 singletons of 22–24 weeks' GA using the 2003–2011 Japanese vital statistics, and assessed how maternal characteristics influence risk of peridelivery death as well as intrauterine fetal death (IUFD) and death after 1 hour of age until 40 weeks postmenstrual age.

Results Living in a municipality with low-average income (lowest tertile (risk ratio 1.32, 95% CI 1.20 to 1.44), middle tertile (risk ratio 1.08, 95% CI 0.98 to 1.19)), younger maternal age (age <20 (risk ratio 1.43, 95% CI 1.17 to 1.75), age 20–34 (risk ratio 1.14, 95% CI 1.03 to 1.27)) and having previous live births (risk ratio 1.08, 95% CI 1.01 to 1.17) increased risk of peridelivery deaths, but did not increase risk of IUFD or deaths after 1 hour of age. Peridelivery death was twice as likely to occur in births to multiparous teenage mothers in a low-income municipality, compared with those of older primiparous mothers in a wealthier municipality.

Conclusions Socioeconomic factors substantially influence whether births of 22–24 weeks' GA survive delivery and the first hour of life. Such disparities may reflect the impact of socioeconomic situations on decision making for resuscitation.

What is already known on this topic?

- Institutional factors influence decision making for the resuscitation of extremely low-gestational-age infants at delivery.
- However, it has not been reported how parental social factors play a role.

What this study adds?

- Japanese vital statistics showed socioeconomic factors influenced whether singleton births at 22–24 weeks of gestation survive delivery and the first hour of life.
- However the same factors did not increase mortality in utero or after the first hour.
- The results imply a potential socioeconomic discrepancy in decision making on whether to resuscitate periviable births.

INTRODUCTION

Perinatal care of preterm deliveries at the periviable gestation of 22–24 weeks requires a multidisciplinary approach by an experienced perinatal team including obstetricians, neonatologists, midwives, nursing staff and the parents, as the discussion would focus on intensive care requirements and on whether intensive care should be provided in the first place. While there is a general consensus to provide active care or resuscitation for infants at ≥25 weeks' gestational age, large variation exists in guidelines both internationally and within countries regarding whether to provide active care to more premature infants at 22–24 weeks' gestational age,[1] acknowledging that their mortality and severe impairment rate are high compared with higher gestations. Multiple guidelines recommended 'individualized care', where the provision of active care or the withholding of life-saving treatment would be justified based on the best interests of the unborn infants in shared decision making by the parents and clinicians.[2 3] If an antenatal decision not to provide resuscitation is made, fetuses and infants at 22–24 weeks' gestation would likely die shortly after birth or even during delivery, as obstetric management would not aim to ensure fetal survival. Furthermore, as infants who die shortly after birth are live births by definition, some of these deaths could be registered as stillbirths (intrapartum deaths), especially if they have a gestational age of borderline viability.[4–6] Antenatal decision making before delivery is a major factor affecting peridelivery mortality during delivery or shortly after the birth of fetuses and infants at 22–24 weeks' gestation.[4 7]

The decision-making process to provide or not provide care to maximise odds of survival to births at borderline viability, including both obstetric interventions (antenatal corticosteroids, antenatal transfer and caesarean section for fetal indication) and neonatal interventions (active resuscitation at birth), often requires extensive discussion between parents and clinicians, taking into account various clinical prognostic factors (such as gestational age, estimated fetal weight, multiplicity and any underlying diseases of the mother or child).[8] Parents are often informed that their infants have a high risk of in-hospital death, and that even if they do survive there is a large possibility that the infant may have

severe impairment and chronic diseases later in life. In light of this depressing prospect, socioeconomic factors may play a major role in such decision making because they are related to the family's perception about whether their economical and societal circumstances would allow them to raise a child who needs continuous medical support, or the parents' wish to have a child despite any disability. Thus it is likely that mortality occurring in the few hours before and after birth is more caregiver-driven than clinically driven compared with mortality later in life.

Although many previous studies have investigated clinical[8 9] and institutional[10 11] factors related to resuscitation practices and mortality at the extremely low gestational ages, few studies have investigated the influence of parental social factors on such.[4] Thus, we investigated which parental factors were associated with death in the peridelivery period (from the onset of delivery to 1 hour after delivery) at 22–24 weeks' gestation using a large national database with complete stillbirth registration. Intrapartum stillbirths were included in the outcome, as live birth infants who died shortly after birth due to an antenatal decision not to resuscitate may be registered as intrapartum fetal deaths, although they should be registered as live births.[4–6 12]

METHODS

We used data on stillbirths and live births (linked to infant mortality data) from the period 2003–2011 registered in the Japanese national vital statistics database provided by the Ministry of Health, Labour and Welfare. Using unique identifiers, we linked these data with average annual income figures calculated by municipal (town, city or village) tax data from year of birth collected by the Ministry of Internal Affairs and Communications.

Japan obligates registration of all live births, stillbirths and termination of pregnancies above 12 weeks. Termination of pregnancies above the limit of viability (defined to be 22 completed weeks of gestation since 1990) for any reason has been prohibited with strict regulations that make it extremely difficult to procure an illegal abortion. Thus, under-reporting of stillbirths and termination of pregnancies are considered minimal.

In our database, maternal age, marital status, number of previous live births and stillbirths, place of birth (hospital, birth centre, home, other) and multiplicity, best clinical estimate of gestational age and birth weight were available for both live birth and stillbirths. Time of stillbirth (categorised as termination of pregnancy, intrauterine fetal death (IUFD), intrapartum fetal death (IPFD)) was available for stillbirths. Time from delivery to death (in days if the infant survived more than 24 hours, and hours and minutes if the infant died within 24 hours) was available for all infant deaths. We categorised municipal annual income into tertiles: highest (3.3–6.5 million yen), middle (2.9–3.3 million yen) and lowest (1.9–2.9 million yen). Maternal age was categorised into three categories: under 20 years, 20–34 years, and 35 years and above. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for infants of the same gestational age, parity and sex according to the Japanese birth weight reference.[13] This study considered younger maternal age (especially teenage pregnancy), maternal marital status, income tertile and having had previous live births (likely having a child) as social factors that may have a potential effect on decision making for providing resuscitation.

To assess the impact of parental social factors on the decision not to resuscitate extremely preterm infants, this study defined the primary outcome as mortality at the peridelivery period (from the onset of delivery to 1 hour after delivery). The upper limit of 1 hour of age was used because infants at 22–24 weeks' gestational age are likely to die shortly after birth without resuscitation.[14] We included intrapartum deaths (deaths during delivery) in the primary outcome as the distinction between intrapartum deaths and deaths shortly after live births at perivable gestation (22–24 weeks) can be artificial depending on the birth and death registration practices of the physicians or institutions involved.[4–6 12] This study also assessed IUFD before onset of delivery and neonatal deaths after 1 hour of age (until 40 weeks' corrected age) as secondary outcomes. These secondary outcomes were included in order to investigate whether the effect of social factors as well as biological factors on the primary outcome differed from those of the secondary outcomes.

Analysis was limited to singletons born at 22–24 completed weeks of gestation delivered at hospitals and with complete data on maternal characteristics; after excluding 166 deliveries at home or birth centres, 31 withmissing birth weight information and 1 with missing maternal age. Marital status, number of previous live births and stillbirths, place of birth and municipal annual income were available for all births (as all births were successfully linked to their municipal data). We used Poisson regression with robust error variance including all social and biological factors as covariates to estimate risk ratios (RR) of maternal and infant characteristics on mortality at three intervals: IUFD, peridelivery death and death after 1 hour of age. For the latter two intervals, the analyses excluded infants who already died at previous time intervals. For example, the analyses for peridelivery deaths excluded IUFD cases. All analyses were conducted using Stata V.13 SE. This study was approved by the ethical committee of the National Center for Child Health and Development in Tokyo, Japan.

RESULTS

Among 14 726 deliveries at 22–24 weeks' gestation (8159 stillbirths and 6567 live births), there were 6616 IUFDs (45% of all deliveries), 1797 peridelivery deaths (22% of infants alive at onset of delivery) and 1964 deaths after 1 hour of age until 40 weeks' corrected gestational age (31% among infants alive at 1 hour of age).

Table 1 shows mortality in three periods by maternal and infant characteristics. After adjusting for biological factors, all social factors assessed were significantly associated with the risk of the primary outcome (peridelivery deaths) (table 2). Younger maternal age (teenage pregnancy (RR 1.43, 95% CI 1.17 to 1.75), age 20–25 years (RR 1.14, 95% CI 1.03 to 1.27)), lower municipal average income (lowest tertile (RR 1.32, 95% CI 1.20 to 1.44), middle tertile (RR 1.08, 95% CI 0.98 to 1.19)), being unmarried (RR 1.49, 95% CI 1.33 to 1.67) and having a previous live birth (RR 1.08, 95% CI 1.01 to 1.17) significantly increased risk of peridelivery death. In contrast, none of the social factors were significantly associated with deaths after 1 hour of age. Although unmarried status and maternal age of 20–34 years (compared with 35 years or older) were associated with increased risk of IUFD, lower annual income and having a previous live birth had rather negative associations, and teenage pregnancy was not associated with IUFD.

For biological risk factors, maternal history of stillbirth was a risk factor for peridelivery death (RR 2.48, 95% CI 2.26 to 2.73) and IUFD (RR 1.43, 95% CI 1.37 to 1.50) but was not associated with later survival. Infant male sex had a significant risk of mortality after 1 hour of age (RR 1.11, 95% CI 1.04 to 1.18) but was unrelated to peridelivery death or IUFD. Lower gestational age and SGA were strongly associated with death at

Table 1 Mortality rates in three periods for 14 726 births delivered at 22–24 weeks of gestation, by social and infant characteristics

	Intrauterine fetal deaths (n=6616)		Peridelivery deaths (n=1797)		Deaths after 1 hour of age (n=1964)	
	n	%*	n	%†	n	%‡
Social factors						
Municipal annual income						
Lowest	2122	43	738	27	629	29
Middle	2133	45	566	21	664	30
Highest	2359	47	492	19	670	30
Maternal age						
<20	186	45	74	33	47	30
20–34	5261	45	1433	23	1521	30
≥35	1169	43	290	19	396	30
Marital status						
Not married	706	54	241	40	130	33
Married	5910	44	1556	21	1834	30
Previous live births						
Yes	3061	41	1041	23	1074	30
No	3555	49	756	21	890	30
Biological factors						
Previous stillbirths						
Yes	889	68	271	64	51	32
No	5727	43	1526	20	1913	30
Gestational age						
22 weeks	2425	57	949	53	534	55
23 weeks	2197	44	594	21	760	33
24 weeks	1994	36	254	7	670	20
Infant sex						
Male	3245	43	960	22	1095	32
Female	2869	43	816	22	869	28
Small for gestational age						
Yes	3377	79	239	27	309	45
No	3239	31	1558	22	1655	28

Peridelivery deaths defined as antepartum stillbirths and neonatal deaths occurring within 1 hour from birth.
The percentages in the tables show the mortality rates of fetuses or infants in three periods: before delivery (intrauterine deaths), from onset of delivery to 1 hour of age (peridelivery deaths) and after 1 hour of age.
*Among all deliveries.
†Among all fetuses alive at onset of delivery (excluding intrauterine fetal death).
‡Among births alive at 1 hour of age.

all stages; however, the effect of gestational age was strongest for peridelivery death, while the effect of SGA was smallest for peridelivery death (RR 1.24, 95% CI 1.11 to 1.39).

DISCUSSION

This study found maternal social background was strongly associated with peridelivery deaths (from onset of delivery to 1 hour of age) of fetuses and infants at 22–24 weeks' gestation. Mothers of younger age (especially teenage pregnancies) with experience of a previous live birth (likely to have a child) or with lower income were more likely to experience a peridelivery death for births at 22–24 weeks' gestation. The lack of similar associations with IUFD and infant deaths after 1 hour of age indicated that these social factors may affect peridelivery mortality by influencing the decision to provide active resuscitation. Unlike these social factors, gestational age and SGAs (biological factors) were associated with mortality in all three periods.

Based on our estimates, a periviable infant born to a teenage mother who lives in a municipality with the lowest income tertile and who already has a child has only half the chance of surviving the peridelivery period after the decision to provide resuscitation is made, compared with a child with the same risk born to a wealthier mother of advanced age who does not have a child. Our results suggest that social characteristics in combination with gestational age may strongly influence the decision making as to whether the infant is resuscitated. As clinical data directly measuring the decision-making process were not available in our database, we used peridelivery mortality as a proxy for the decision not to provide resuscitation. It is possible that the observed association between social factors and peridelivery deaths may not be due to the social factors influencing the decision making, but may rather reflect the baseline regional disparity in access to high-quality perinatal care, or maternal characteristics (eg, smoking, obesity) related to the risk of obstetrical complications and morbidity of their offspring. The lack of similar associations between social factors and IUFD or deaths after 1 hour of age in this study opposed such a possibility; however, future research should consider such possibilities as well as possible influences of other regional disparities (such as incidences of emergency situations).

Our results highlight the difficulties parents face when told that their child may survive with a severe impairment, even if provided with the most intensive treatment, and that social factors play a large role in such recipiency. Although our study

Table 2 Association between social and infant characteristics with fetal/infant mortality in three periods among infants delivered at 22–24 weeks of gestation

	Primary outcome	Secondary outcomes	
	Peridelivery deaths† Adjusted RR (95% CI)	Intrauterine fetal deaths‡ Adjusted RR (95% CI)	Death after 1 hour of age§ Adjusted RR (95% CI)
Social factors			
Municipal annual income			
Lowest tertile	1.32 (1.20 to 1.44)***	0.95 (0.91 to 0.99)*	1.01 (0.93 to 1.10)
Middle tertile	1.08 (0.98 to 1.19)	0.95 (0.91 to 0.99)*	1.00 (0.92 to 1.08)
Highest tertile	1 (reference)	1 (reference)	1 (reference)
Maternal age			
<20	1.43 (1.17 to 1.75)***	1.10 (0.98 to 1.23)	1.09 (0.85 to 1.39)
20–34	1.14 (1.03 to 1.27)*	1.08 (1.03 to 1.13)**	0.99 (0.91 to 1.08)
≥35	1 (reference)	1 (reference)	1 (reference)
Not married	1.49 (1.32 to 1.69)***	1.26 (1.19 to 1.34)***	1.14 (0.97 to 1.33)
≥1 Previous live born	1.11 (1.02 to 1.21)*	0.89 (0.86 to 0.92)***	1.06 (0.99 to 1.14)
Biological factors			
≥1 Previous stillbirth	**2.48 (2.26 to 2.73)*	1.43 (1.37 to 1.50)***	1.07 (0.86 to 1.33)
Gestational age			
22 weeks	6.43 (5.66 to 7.30)***	1.49 (1.43 to 1.56)***	3.05 (2.80 to 3.32)***
23 weeks	2.88 (2.52 to 3.30)***	1.18 (1.13 to 1.23)***	1.70 (1.56 to 1.85)***
24 weeks	1 (reference)	1 (reference)	1 (reference)
Male infant	1.03 (0.95 to 1.11)	0.97 (0.93 to 1.00)	1.11 (1.04 to 1.19)***
Small for gestational age	1.24 (1.11 to 1.39)***	2.40 (2.32 to 2.48)***	1.69 (1.54 to 1.84)***
Year of birth (/year)	0.92 (0.91 to 0.94)***	0.99 (0.98 to 0.99)***	0.93 (0.92 to 0.94)***

†Among all deliveries.
‡Among all fetuses alive at onset of delivery (excluding intrauterine fetal death).
§Among births alive at 1 hour of age.
*p<0.05, **p<0.01, ***p<0.001.
RR, risk ratio.

is the first to investigate the role of social factors in decision making for resuscitation at birth of infants of the extremely lower gestations, studies in the UK have shown that socioeconomic variations exist in decision making for the termination of pregnancy after antenatal detection of Down syndrome[15] and other congenital anomalies.[16] Our finding that such social disparities do not influence infant survival after the first hour of life also matches findings from the UK showing that survival of very preterm births (22–31 weeks' gestational age) was unrelated to neighbourhood income.[17]

Our study raises the concern that making decisions about a child's life may strongly depend on their parents' social background, as well as infants' biological characteristics. If 'individual' decision making of whether or not to resuscitate[1] is related to socioeconomic inequity, it may mean that 'selection of life' is based on socioeconomic factors rather than the biological viability of fetuses and infants. Although it is reasonable to consider the social situations of parents and families to provide appropriate individualised care to their children, making a decision of life or death based on socioeconomic situations of parents and families may not be justifiable. The findings of this study highlight the need for increased social support after delivery for parents and families with social difficulties, such as teenage mothers or low-income families. Furthermore, caregivers should make sure such families are well informed of the social welfare that would be available if their children become handicapped, before they make the decision on delivery.

Our results also suggest the potential existence of an argument in the decision-making process of resuscitation. Does the extent to which parents are involved in the process change by social background? Would the practitioners present information to the families differently, and would they be more willing to try to convince the parents not to ask for intensive care, according to their personal negative perception of the family's current status? As institutional and societal support should aim for such children and their families to make best use of their potential, future studies to understand and how the current decision-making process is and should be conducted are required.

These problems may have been negligible previously when the chances of such infants surviving were slim. However, in our study, moderate proportions of infants at 22, 23 and 24 weeks' gestational age lived if they survived the initial 1 hour after birth, which was likely due to active resuscitation (survival rates of 45%, 67% and 80%, respectively) (table 1). Reports from Japan,[18] Sweden[19] and Germany[20] showed that survival rates without major complications or disabilities can be as high as 9%–12%, even for infants born at 22 weeks if provided with active resuscitation, and has given rise to intensive debate on how care should be provided to periviable deliveries at these extremely low gestational ages.[11 21]

The main strengths of our study include its complete population coverage including those on stillbirths, as well as separate reporting of intrauterine and intrapartum stillbirths. As mothers facing delivery would choose different institutions based on whether they would want their child resuscitated or not, institution-based studies including larger hospitals with a well-equipped neonatal intensive care unit would underestimate the rate of non-resuscitated infants; thus, a population-based study is required for such an analysis. Neonatal deaths in the early hours of life have been

misclassified as stillbirths in many settings, especially in the lower gestational ages,[4] which has been a barrier to studying survival rates at these lower gestations. However, as such misclassification is more likely to occur for IPFDs rather than antepartum fetal deaths, we used the term 'peri-delivery deaths', which combines IPFDs and neonatal deaths within 1 hour of life, and is less prone to such misclassification.

Our study has several limitations. First, the income data were not available at the individual level and the municipal average was used as a surrogate. However, although area-level estimates do not necessarily agree with individual-level incomes, they can be used as a proxy when individual income data are not available,[22 23] as carried out in previous studies on socioeconomic inequalities and perinatal outcomes.[16 17] Second, as we lacked detailed clinical data and were not able to investigate other direct measures of active resuscitation such as provision of antenatal steroid, caesarean delivery for fetal indication or intubation and other invasive procedures,[7 11 24] we were not able to observe the relationship between social factors and provision of active care directly. To interpret our findings, we had to compare how the same factors were related to IUFD and infant survival later in life, which are more likely to be biological. The same limitation is applied to interpreting the risk factors observed for IUFD, for which the interpretation should be limited to 'risk factors for IUFD *among* those delivered at 22 to 24 weeks of gestation', and not 'risk factors for IUFD *at* 22 to 24 weeks of gestation', as the latter should be based on births at all gestational ages above 22 weeks rather than limited to those at 22–24 weeks. (Such an analysis has been conducted in the online supplementary appendix as a sensitivity analysis. It also showed that annual income was most strongly associated with deliveries at 22–24 weeks that ended in peridelivery death, compared with IUFD or delivery of live births surviving the first hour at 22–24 weeks.) However, we believe our study may stimulate further research to assess the role such factors play in this decision-making process. Third, our study was conducted in Japan, where care provided to infants at the extremely low gestational ages is generally more intensive and survival rates are higher compared with other populations[18 25]; thus, the effect of social disparity in resuscitation may be more prominent than elsewhere. However, we believe this will become a significant problem with advances in neonatal care in other populations, even where palliative care is currently the standard for births at these extremely low gestational ages.

CONCLUSION

Social risk factors significantly increase the mortality of an infant born at 22–24 weeks' gestation during delivery and the first hour after delivery, although they do not increase mortality in utero or after the first hour of birth. This implies a potential social discrepancy in decision making on whether to resuscitate an infant with borderline viability.

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Contributors NM designed the study, acquired data, conducted analyses, wrote the initial manuscript and approved the final manuscript as submitted. TI contributed to the design of the study, interpretation of data, revised it critically for important intellectual content and approved the final manuscript as submitted. OS, KW and SK contributed to the interpretation of data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted. NM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Socioeconomic inequity in survival for deliveries at 22–24 weeks of gestation

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Comprehensive Assessment of Risk Factors of Cause-Specific Infant Deaths in Japan

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ABSTRACT

Background: Public attention is given to infants with socially high risks of child abuse and neglect, while clinical attention is provided to infants with a biologically high risk of diseases. However, few studies have systematically evaluated how biological or social factors cross over and affect cause-specific infant mortality.

Methods: We linked birth data with death data from the Japanese national vital statistics database for all infants born from 2003–2010. Using multivariate logistic regression, we examined the association between biological and social factors and infant mortality due to medical causes (internal causes), abuse (intentional external causes), and accidents (unintentional external causes).

Results: Of 8,941,501 births, 23,400 (0.26%) infants died by 1 year of age, with 21,884 (93.5%) due to internal causes, 175 (0.75%) due to intentional external causes, and 1,194 (5.1%) due to unintentional external causes. Infants with high social risk (teenage mothers, non-Japanese mothers, single mothers, unemployed household, four or more children in the household, or birth outside of health care facility) had higher risk of death by intentional, unintentional, and internal causes. Infant born with small for gestational age and preterm had higher risks of deaths by internal and unintentional causes, but not by intentional causes.

Conclusions: Both biological as well as social factors were associated with infant deaths due to internal and external causes. Interdisciplinary support from both public health and clinical-care professionals is needed for infants with high social or biological risk to prevent disease and injury.

Key words: infant death; vital statistics; risk factor; unintentional injury; intentional injury

INTRODUCTION

Infant death, in many cases, is not due to one single cause but to an unfortunate complex assembly of risk factors.[1] Many studies on infant mortality have focused on either social factors and their relation to child abuse and neglect,[2–4] or on biological risk factors, such as low birth weight, preterm birth, congenital abnormalities, or other perinatal medical complications, and their association with death due to medical causes.[5,6]

However, the effects of biological and social risk factors on infant death may intercorrelate with each other. Prematurity of infants increases the likelihood of child protection service registration.[7] Parents of infants with biological risks tend to face difficulties in parenting because of psychological distress[8,9] or postpartum depression.[10] Families with social risk may have difficulty in parenting, so their infants may have a higher risk of becoming severely sick.[11–15]

Comprehensive assessment of biological and social risk factors of cause-specific infant death will be useful to detect and provide adequate support to infants who have multiple risk factors, thereby reducing risk of subsequent deaths. However, no study has comprehensively and simultaneously assessed how biological and social risk factors relate to deaths due to medical causes, accidents, and abuse. Thus, we aimed to assess how biological and social risk factors were related to cause-specific infant death using a population-based database in Japan.

METHODS

Data source and linkage process

The Japanese vital statistics database was established in 1899 in accordance with the Family Registry Law and Provisions Regarding Notification of Stillbirths and is maintained by the Ministry of Health, Labour and Welfare. We used birth and infant death data recorded in the database for the period 2003–2011. This starting year was selected because the 10th revision of the International Classification of Diseases (ICD-10) was introduced in 2003 and updated the ICD-9.

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Birth and death records are not linked in the database and do not have unique identifiers. Due to limited data quality on birth characteristics included in the death records, deterministic linkage using common variables between the two datasets was only able to link 88% of the death certificates to a birth certificate. Thus, we used the probabilistic linkage method developed by Fellegi and Sunter[16] to link the two sets of data. This linkage method uses multiple common variables (in our case, date of birth, mother's date of birth, gestational week of delivery, birth weight, multiplicity, birth order, sex, and nationality) to calculate the likelihood that two records are a true match, and assigns matches based on this probability. Such data linkage algorithms have been shown to be powerful and have been implemented in studies in the United States[17] and Australia.[18] Detailed methodology is described in Appendix 1.

We matched 25,413 out of 25,451 (99.96%) infant death certificates to their corresponding birth certificates, of which there were 100,175,174. As we did not have data on infant deaths in 2012, which would include infant deaths among those born in 2011, we excluded all births in 2011 and limited our analysis to 8,941,501 births in the period of 2003–2010.

Classification of infant death

Our main outcome of interest was cause-specific infant death. We utilized ICD-10 codes (V01–Y98), which indicated external causes of mortality. External causes were sub-classified into unintentional injury (V01–X59, Y85–86), intentional injury (X85–Y09, Y87.1), and undetermined injury (injury for which we could not judge the presence of intention) (Y10–Y34, Y87.2, Y89.9) in line with previous studies.[19,20]

Definition of variables

We categorized maternal and paternal age into ≤19, 20–24, 25–29, 30–34, 35–39, and ≥40 years; place of residence as a government-designated city (population over 500,000), other city (population 30,000–500,000), or a town or village (population under 30,000), based on the official classification by name of municipal governments; and family employment status at birth as follows: employed, self-employed, agricultural work or irregular employed, and unemployed. The number of children in the household was categorized into 1, 2–3, and ≥4 children. Single mothers included unmarried, divorced, and widowed mothers. We defined preterm birth as birth before 37 completed weeks of gestation. Small for gestational age (SGA) was defined as a birth weight lower than the 10th percentile of the Japanese gestational age-specific birth weight standards.[21]

We defined the following as biological risk factors of infant death: male infant, multiple births, SGA, preterm delivery, previous experience of stillbirth, and older maternal age (40 and older). Similarly, we defined the following as social risk factors of infant death: younger maternal age (19 and younger), non-Japanese mother, birth outside of a health care facility, single mother, unemployed household, and four or more children in the household.

Statistical analysis

First we compared infant, parent, and household characteristics between infants who were alive at age 1 year and those who had died from internal or external causes using chi-square test. Second, we compared cause-specific mortality by infant age in days or weeks. We used Cuzick's non-parametric trend test to examine the association between increasing age (every 4 weeks) and mortality, as well as with mortality due to internal and external causes. For neonatal deaths, we also observed whether differences existed between timing of death (day 0, day 1, days 2–6, and days 7–27) and cause of death using the chi-square's test, or Fisher's exact test if the numbers were small and included an expected cell of less than five.

Third, we conducted multivariable nominal logistic regression analysis to examine independent associations of risk factors related to death by both internal and external causes, the latter of which was also subdivided into unintentional injury, intentional injury, and undetermined injury. This analysis was conducted separately for single and multiple births, as multiple births are more likely to be due to fertility treatments, which are related to parental social backgrounds, and multiplicity is a well-known risk factor for biological problems of the infant, including prematurity and SGA.[22,23] All multivariable models included infant, mother, and household characteristics as examined in the univariate analysis except parity, which was highly correlated with the number of children in the household. Place of residence and year of birth were also included in the models to account for regional differences and secular changes in healthcare.

Lastly, we focused on maternal age, a well-known social factor associated with unintentional or intentional injury in many studies,[24,25] and analyzed its associations with infant mortality at different life stages (day 0–1, day 2 to <4 weeks, 4 weeks to <12 weeks, 12 weeks to <24 weeks, and 24–52 weeks) using multivariable logistic regression.

For data linkage we used LinkPlus (Center for Disease Control and Prevention, Atlanta, GA, USA), and for all other analyses, we used STATA/MP, version 14.0 (Stata Corp LP, College Station, TX, USA).

Ethical considerations

This study was approved by the official ethics review board of the University of Tsukuba (Document No. 1009, 10/01/2015). Authors obtained permission for secondary use of information from the vital statistics according to Article 33 of the Statistics Act, which states that researchers may utilize questionnaire information pertaining to statistical surveys provided that the study protocol is based on a governmental grant and the findings would contribute to the development of academic research.

RESULTS

Overall, of the 8,941,501 infants born in the period from 2003 through 2010, 23,400 (0.26%) died before their first birthday, with an average infant mortality rate (IMR) of 2.62 per 1,000 live births. Internal causes accounted for 93.5% of total infant deaths ($n = 21,884$, 2.45/1,000 live births); unintentional injury covered 78.8% of external causes ($n = 1,194$, 0.13/1,000 live births); intentional injury ($n = 175$) accounted for 11.5% of external causes and 0.75% of all infant deaths, and a small number of external deaths related to medical treatments or medications ($n = 29$) accounted for the remaining deaths due to external causes (Table 1).

In Table 2 we show infant, parental, and household characteristics by cause of death. Among parental and household characteristics, non-Japanese mothers, single mothers, unemployed household, four or more children in the household, and previous history of stillbirth were significantly associated with

death due to both internal and external causes. Having a father of non-Japanese nationality was significantly associated with death due to external causes only. Maternal and paternal ages were related to infant death due to both internal and external causes, with the nadir at ages 25–29 years. Among infant characteristics, male, SGA, preterm birth, being a subsequent child, and birth outside of a health care facility were related to deaths due to internal causes as well as external causes. Infant mortality due to both internal and external causes monotonically declined by year of birth, with the exception of a high infant mortality rate due to

Table 1. Cause of death among 8,941,501 infants born from 2003–2010

	n	/1,000 live births
All deaths	23,400	2.62
Death by internal causes	21,884	2.45
Death by external causes	1,516	0.17
Unintentional injury	1,194	0.13
Intentional injury	175	0.020
Undetermined injury	118	0.013
Medical-related death	29	0.0032

Table 2. Child, parent and household characteristics of infants who survived until their first birthday, infants who died due to internal causes, and infants who died due to external causes among 8,941,501 infants born in Japan in 2003–2010

			Alive *n* = 8,918,101		Internal causes *n* = 21,884			External causes *n* = 1,516		
			n	%	*n*	%	a)	*n*	%	b)
Child	Sex	Male	4,576,267	51.3%	11,904	54.4%	***	874	57.7%	***
		Female	4,341,834	48.7%	9,980	45.6%		642	42.3%	
	Multiplicity	Singleton	8,729,002	97.9%	19,827	90.6%	***	1,473	97.2%	
		Twin, triplet or higher	189,099	2.1%	2,057	9.4%		43	2.8%	
	SGA	No	8,108,686	90.9%	14,759	67.4%	***	1,325	87.4%	***
		Yes	658,929	7.4%	6,603	30.2%		142	9.4%	
	Gestational age	37 weeks or above	8,424,180	94.5%	11,410	52.1%	***	1,389	91.6%	***
		Under 37 weeks	493,921	5.5%	10,474	47.9%		127	8.4%	
	First child	No	4,585,023	51.4%	12,469	57.0%	***	868	57.3%	***
		Yes	4,333,078	48.6%	9,415	43.0%		648	42.7%	
	Birthplace	Health care facility	8,864,420	99.4%	21,565	98.5%	***	1,469	96.9%	***
		Home or other	53,681	0.6%	319	1.5%		47	3.1%	
	Year of birth	2003	1,145,834	12.8%	3,259	14.9%	***	204	13.5%	*
		2004	1,134,372	12.7%	2,982	13.6%		206	13.6%	
		2005	1,086,594	12.2%	2,794	12.8%		205	13.5%	
		2006	1,118,806	12.5%	2,710	12.4%		191	12.6%	
		2007	1,117,353	12.5%	2,769	12.7%		185	12.2%	
		2008	1,119,920	12.6%	2,619	12.0%		166	10.9%	
		2009	1,096,777	12.3%	2,436	11.1%		153	10.1%	
		2010	1,098,445	12.3%	2,315	10.6%		206	13.6%	
Father	Age, years	40 and over	837,797	9.6%	2,883	13.8%	***	159	11.2%	***
		35–39	1,902,261	21.8%	4,784	23.0%		334	23.5%	
		30–34	3,115,825	35.8%	6,772	32.5%		437	30.8%	
		25–29	2,144,581	24.6%	4,581	22.0%		316	22.3%	
		20–24	667,404	7.7%	1,678	8.1%		162	11.4%	
		19 and under	42,569	0.49%	122	0.59%		11	0.78%	
	Nationality	Japanese	8,498,899	97.6%	20,303	97.5%		1,360	95.8%	***
		Non-Japanese	211,544	2.4%	517	2.5%		59	4.2%	
Mother	Age, years	40 and over	210,169	2.4%	1,094	5.0%		45	3.0%	***
		35–39	1,477,938	16.6%	4,417	20.2%		239	15.8%	
		30–34	3,312,312	37.1%	7,458	34.1%		479	31.6%	
		25–29	2,748,257	30.8%	5,703	26.1%		420	27.7%	
		20–24	1,036,535	11.6%	2,676	12.2%		266	17.5%	
		19 and under	132,883	1.5%	536	2.4%		67	4.4%	
	Nationality	Japanese	8,683,154	97.4%	21,173	96.8%	***	1,420	93.7%	***
		Non-Japanese	234,947	2.6%	711	3.2%		96	6.3%	
	Marital status	Married	8,710,437	97.7%	20,820	95.1%	***	1,419	93.6%	***
		Single, divorced, widowed	207,658	2.3%	1,064	4.9%		97	6.4%	
Household	Employment status	Employed	6,703,467	78.0%	15,478	74.3%	***	1,018	70.4%	***
		Self-employed, agricultural work or irregular employed	1,683,442	19.6%	4,530	21.7%		346	23.9%	
		Unemployed	209,275	2.4%	836	4.0%		83	5.7%	
	Number of children	1	4,333,078	48.6%	9,415	43.0%	***	648	42.7%	***
		2–3	4,329,694	48.5%	11,323	51.7%		790	52.1%	
		4 or more	255,329	2.9%	1,146	5.2%		78	5.1%	
	Experienced stillbirth	No	8,870,395	99.5%	21,543	98.4%	***	1,502	99.1%	*
		Once or more	47,706	0.53%	341	1.6%		14	0.92%	
	Place of residence	Government-designated city	2,236,049	25.1%	5,366	24.5%		352	23.2%	
		Other city	5,524,382	61.9%	13,686	62.5%		949	62.6%	
		Town, village	1,157,670	13.0%	2,832	12.9%		215	14.2%	

[a]Between infants alive at age one and those who died due to internal causes.
[b]Between infants alive at age one and those who died due to external causes.
*$P < 0.05$ **$P < 0.01$ ***$P < 0.001$. SGA: Small for gestational age. Missing value: SGA ($n = 151,057$: 1.7% of total), paternal age ($n = 64$), maternal age ($n = 88$), single mother ($n = 6$), employment status ($n = 323,026$: 3.6% of total), and number of children (10,419: 0.12% of total).

Table 3. Infant deaths by age and causes: analysis of 23,400 infants among those born from 2003–2010

	Total death (n = 23,400)[‡]		Death by internal causes (n = 21,884)[a]		Death by external causes (n = 1,516)[b]		External causes					
							Unintentional injury (n = 1,194)		Intentional injury (n = 175)		Undetermined injury (n = 118)	
Timing of death	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Week 0	8,607	36.8%	8,491	38.8%	116	7.7%	30	2.5%	81	46.3%	4	3.4%
Day 0	5,474	23.4%	5,382	24.6%	92	6.1%	19	1.6%	69	39.4%	3	2.5%
Day 1	1,133	4.8%	1,122	5.1%	11	0.73%	5	0.42%	5	2.9%	1	0.85%
Day 2–6	2,000	8.5%	1,987	9.1%	13	0.86%	6	0.50%	7	4.0%	0	0.00%
Week 1–3	3,286	14.0%	3,217	14.7%	69	4.6%	48	4.0%	10	5.7%	5	4.2%
Week 4–7	2,171	9.3%	2,044	9.3%	127	8.4%	103	8.6%	15	8.6%	9	7.6%
Week 8–11	1,525	6.5%	1,370	6.3%	155	10.2%	135	11.3%	9	5.1%	9	7.6%
Week 12–15	1,254	5.4%	1,114	5.1%	140	9.2%	120	10.1%	8	4.6%	11	9.3%
Week 16–19	1,153	4.9%	1,021	4.7%	132	8.7%	110	9.2%	8	4.6%	14	11.9%
Week 20–23	1,047	4.5%	897	4.1%	150	9.9%	126	10.6%	6	3.4%	17	14.4%
Week 24–27	913	3.9%	774	3.5%	139	9.2%	108	9.0%	15	8.6%	13	11.0%
Week 28–31	799	3.4%	682	3.1%	117	7.7%	102	8.5%	4	2.3%	10	8.5%
Week 32–35	683	2.9%	596	2.7%	87	5.7%	73	6.1%	7	4.0%	6	5.1%
Week 36–39	561	2.4%	484	2.2%	77	5.1%	67	5.6%	4	2.3%	5	4.2%
Week 40–43	507	2.2%	436	2.0%	71	4.7%	60	5.0%	4	2.3%	4	3.4%
Week 44–47	445	1.9%	379	1.7%	66	4.4%	56	4.7%	3	1.7%	4	3.4%
Week 48–52	447	1.9%	377	1.7%	70	4.6%	56	4.7%	1	0.6%	7	5.9%

[‡]Nonparametric trend test performed for total deaths among every 4 weeks of infant age. P for trend <0.001.
[a]Two infants were not included due to missing of timing of death by internal causes.
[b]29 infants were not included died from non-injury related external causes (ie, medical treatment related deaths, such as medications or surgeries).

external causes for those born in 2010 (who would have been under age 1 on the day of the Great East Japan Earthquake).

Table 3 shows the number of deaths by infant age and cause. The total number of deaths significantly decreased with increasing age (P for trend <0.001). Half of the subjects (n = 11,893, 50.8%) died within the first 4 weeks of life. Among neonatal deaths, over half of deaths due to internal causes and all deaths due to external causes occurred on day 0 or 1; the majority of these (82.7% of deaths by internal causes, and 89.3% of deaths by external causes) occurred on day 0. Deaths due to intentional injuries occurred with the highest frequency on days 0–1 (n = 74, 42.3% of neonatal deaths). The number of deaths due to internal causes decreased with increasing weeks of age during the neonatal period, while the number of deaths by unintentional injury and undetermined injury increased.

When background characteristics for deaths during the neonatal period were compared by timing of death, we found that births outside of health care facilities had a higher proportion of early neonatal deaths due to both internal and external causes, especially for deaths at days 0–1, compared to births in the later neonatal period (days 2–6 and days 7–27). The proportion of preterm infants among deaths due to internal causes was higher in the early neonatal period (days 0–1 and days 2–6) than the late neonatal period (days 7–27), while the proportion of SGA infants was highest for deaths at days 2–6. The proportion of infants born to single mothers among deaths due to internal causes was higher at days 0–1 compared to later in the neonatal period, while the proportion of infants from employed households was higher among deaths later in the neonatal period. For deaths due to external causes, multiplicity, maternal nationality, maternal marital status, and number of children were significantly different between deaths at different periods (eTable 1). When deaths on days 0 and 1 were compared, deaths due to internal causes on day 0 were more likely to be related to preterm, SGA, and birth outside a health care facility than those on day 1. However, we failed to detect any significant difference in the background characteristics of patients who died on days 0 and 1 in terms of external causes and intentional injury (data not shown).

Figure 1 illustrates relationships between biological or social risk factors and cause-specific infant deaths from the multivariable logistic regression model, with eTable 2 showing the estimated adjusted odds ratios (ORs) as well as the 95% confidence intervals (CIs).

For singleton infants, the biological risk factors associated with at least a two times higher risk of death were SGA (OR 4.4; 95% CI, 4.3–4.6) and preterm birth (OR 14.5; 95% CI, 14.1–15.0) for internal causes, and preterm birth (OR 2.7; 95% CI, 1.5–4.8) for undetermined injury.

All social risk factors—young maternal age (≤19 years), birth outside of a health care facility, having a non-Japanese mother or single mother, living in a unemployed household, and having four or more children in the household—were significant risk factors for death by internal causes. Among these factors, birth outside of a health care facility (OR 3.2; 95% CI, 2.7–3.8) was the only factor associated with at least a two times higher risk.

Social risk factors showing an increased risk of unintentional injury by at least two-fold were maternal age of 20–24 years (OR 2.0; 95% CI, 1.7–2.4), maternal age of 19 years and under (OR 4.1; 95% CI, 3.0–5.7), and having a high number of children in the household (OR 2.5; 95% CI, 1.8–3.3). Similarly, for undetermined injury, the factors were birth outside of a health care facility (OR 6.5; 95% CI, 1.6–26.5), maternal age of 19 years and under (OR 3.7; 95% CI, 1.4–9.8), having a non-Japanese mother (OR 2.8; 95% CI, 1.3–5.8), living in an unemployed household (OR 3.3; 95% CI, 1.5–7.3), and having a high number of children in the household (OR 3.4; 95% CI, 1.6–7.3). For intentional injury, the factors were birth outside of a health care facility (OR 15.9; 95% CI, 7.0–36.3), having a non-Japanese mother (OR 6.9; 95% CI, 4.4–10.8) and single mother (OR 3.0; 95% CI, 1.5–5.9).

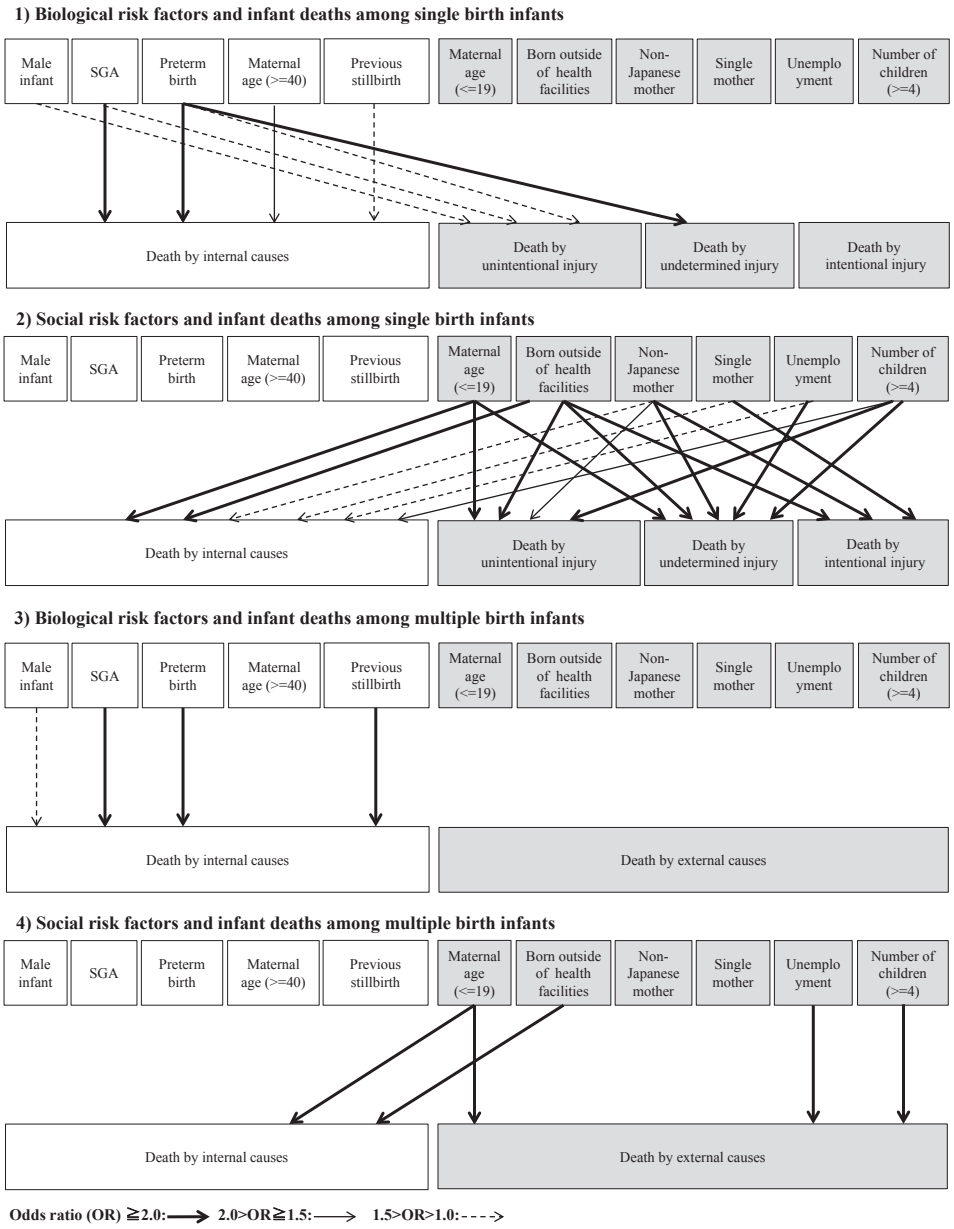

Figure 1. Association between biological or social risk factors and infant deaths by causes. Analysis of 8,941,501 infants born in Japan in 2003–2010.

For multiple births, the biological risk factors associated with at least a two times higher risk of death were SGA (OR 2.1; 95% CI, 2.0–2.4), preterm birth (OR 5.6; 95% CI, 4.9–6.4), and experience of stillbirth (OR 5.1; 95% CI, 4.0–6.5) for internal causes. Social risk factors showing an increased risk of death due to internal causes at least two-fold were birth outside of a health care facility (OR 14.3; 95% CI, 5.8–35.6) and maternal age of 19 years and under (OR 2.1; 95% CI, 1.4–3.0). For deaths due to external causes, social risk factors showing at least a two times higher risk were maternal age of 19 years and under (OR 11.7; 95% CI, 2.4–55.8), living in an unemployed household (OR 4.5; 95% CI, 1.2–17.4), and having a high number of children in the household (OR 3.0; 95% CI, 1.1–8.5). On the other hand, none of the biological risk factors of interest doubled risk of death by external causes.

In Figure 2, we show the association between young maternal age and infant mortality at various time intervals (fulll multinominal logistic regression models by each time intervals were not shown in eTable 2). Infants with mothers aged 20 to 25 years old, or 19 years and under, had a significantly higher risk of death due to internal causes as well as external causes at all time periods, except for death due to internal causes at days 0–1. However, while the effect of younger maternal age was steadily around three to four times higher for death due to external causes, the adverse effect of younger maternal age on death due to internal causes gradually rose as infant age increased up until 6 months of age.

DISCUSSION

This is the first study to comprehensively and simultaneously examine the effect of biological and social risk factors on cause-specific infant deaths. Infants with high social risk (births outside of a health care facility; or to teenage, non-Japanese, or single mothers; or from an unemployed household or household with

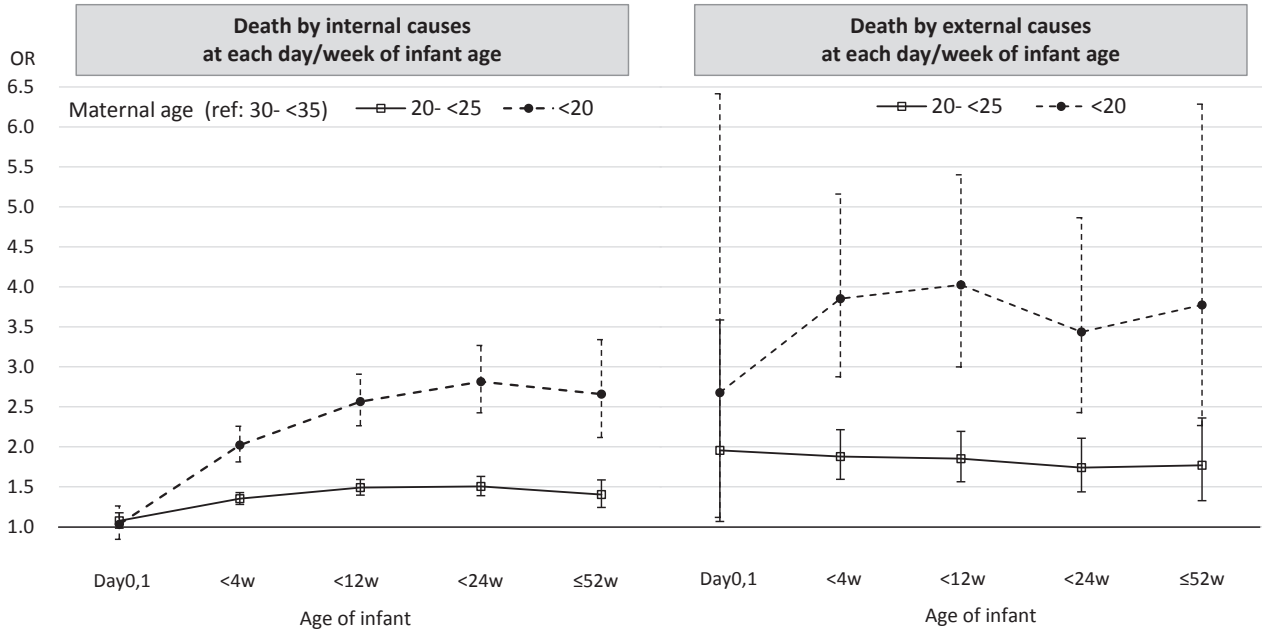

Figure 2. Young maternal age and infant death at each day/week of infant age compared to mothers aged 30–34 years old.

four or more children) had a higher risk of death not only due to external causes, but also due to internal causes. Infants with biological risk factors (SGA and preterm infants) had a higher risk of death due to disease as well as external causes. Young mothers have increased risk of death due to disease, especially during the later period of infanthood.

Biological risk factors surrounding infant death

In our study, we found that for both singletons and multiples, infants who were born SGA, preterm, or to women with prior experience of stillbirth showed an increased risk of death due to internal causes. Advanced age of the mother (40 years and older) was a significant risk factor only for singletons, while male infants were significantly related to deaths by internal causes among multiple births. These risk factors are consistent with previous studies examining infant all-cause mortality.[5,26–28]

Biological risk factors were related not only to deaths due to internal causes, but also to those due to external causes. We found that male, SGA, and preterm infants were at higher risk of death due to unintentional injury, and preterm infants were at higher risk of death due to undetermined injury among singleton infants. We failed to find significant associations between biological risk factors and unintentional or intentional injury of death among multiple birth infants; however, this may have been due to the small number of external causes of death in our study. Two previous studies on linked birth and death data in the United States[19,29] reported that being male and of low birth weight (LBW) were risk factors for fatal unintentional injury, which is consistent with our findings. Such characteristics of premature infants are known to increase the risk of postpartum depression,[10] adversely influencing parent-infant interaction, child safety practice,[30] and quality of maternal supervision.[31] Thus, our findings suggest that for such infants, health professionals should pay attention not only to the child's health condition, but also to provide the family supportive resources to prevent dangerous situations that could lead to unintentional or intentional injuries. In our study, we failed to find prematurity of infants to be a risk factor of intentional injury, which was shown in a United States study.[19,29] This disparity in findings may have been due to the fact that the previous study did not concurrently adjust for birth outside of a health care facility, a possible confounder strongly associated with both LBW/preterm delivery and intentional injury. In our study, nearly 40% of intentional injuries occurred on day 0, suggesting unexpected birth is a strong driving factor.

Social risk factors surrounding infant death

In our study, children born to teenage mothers, in unemployed households, and in households with a high number of children had significantly higher risk of death by external causes for both singletons and multiples. We also found that having a non-Japanese mother and giving birth outside of a health care facility were significantly related to external causes of death only among singleton infants. For deaths by internal causes, teenage pregnancy and birth outside of a health care facility were significant risk factors for internal causes of deaths among infants of both singleton and multiple births. Having a single or non-Japanese mother and being born in an unemployed household or a household with a high number of children were significantly associated with death due to internal causes only among singleton infants.

Although no previous study has specifically looked at the association between social factors and infant death due to internal causes as in our study, our findings are similar to those from studies reporting that infants of teenaged and unmarried mothers,[11–13,15] and of a higher order of birth,[13–15] had increased risk of death due to specific internal causes, including lower respiratory tract infection,[12] diarrhea,[13] intussusception,[14] and necrotising enterocolitis.[15] Socially high-risk mothers tend to be isolated and have less resources to obtain knowledge on child-caring or ask for support when necessary, which may inhibit them from seeking medical care when needed.

Among social risk factors, birth outside of a health care facility was most strongly associated with death by intentional injury. Previous research has also shown that delivery outside of a health care facility increases risk of neonaticide.[32,33] However, interestingly, we found that this group of children retains a higher

risk for unintended injury and death by internal causes, even beyond the neonatal period. Women who deliver outside of a health care facility share backgrounds with mothers who did not receive prenatal care[34] due to out-of-pocket expenses, had a lack of knowledge about prenatal care, or had an unwanted pregnancy, including those women who wanted to have an abortion but were not able to.[35] To prevent infant deaths, our study suggests that health professionals need to provide continuous support on childrearing to mothers who delivered outside of a health care facility, even beyond the neonatal period.

Young maternal age

Young maternal age has been reported to be a significant risk factors for falls,[36] traffic accidents,[36] neonaticide,[33,34] and child abuse and neglect.[37,38] In our study, young maternal age, especially teenage mothers and those in their early twenties, showed a significantly higher risk of both external and internal causes of infant death. In addition, we found that risk of infant mortality by internal causes due to younger maternal age increased with infant age. This phenomenon may reflect that parenting difficulties or a lack of care-seeking behavior among young mothers becomes more apparent in the later months of infancy. During this period, childcare becomes more eventful, as infants start to move around, begin eating solids, and become more prone to developing fevers, and younger mothers may not be able to keep up with the increased demand in parenting skills. Understanding the difficulties young mothers are facing and providing opportunities to receive adequate support and information may not only be important in the beginning of infancy, but also in the later infantile period.

Limitations and future directions

A key strength of this study is its focus on both social and biological factors simultaneously to provide a comprehensive assessment of how such risk factors relate to cause-specific deaths among infants, using a nationwide survey of all births in Japan. Our findings emphasise the importance of paying attention to risk factors of infant death by both internal and external causes for those infants living in socio-demographic and socio-economic risk factors, as well as for infants with biological risk factors that increase the risk of severe disease.

However, our study has several limitations. First, as we used ICD-10 codes from the death certificates (filled in by the physician who confirmed the death) to classify cause of death, miscoding may have occurred; for example, death from abuse or neglect may be overlooked and mistakenly diagnosed as death from internal causes. Second, although we used a linkage process that successfully linked over 99.9% of the death certificates to birth certificates, our linkage process relied on a combination of common variables. Although previous reports have shown this method to be possibly more valid than deterministic record linkage,[39] we were not able to link records using unique identifiers as has been done in other countries, such as the United States. Third, as we derived the timing of death by subtracting time of birth as reported on the birth certificate from time of death reported on the death certificate, the accuracy of the timing may have been affected by misreporting of timing of birth, especially of unattended births occurring outside a hospital. Such misclassification would likely influence the calculation of the timing of death on day 0–1, and may explain why we failed to find any difference in background characteristics between infants who died on day 0 or day 1 due to intentional injury or external causes of death. Fourth, as our analysis was limited to social variables derived from the birth certificate, we could not evaluate other important socio-economic factors, such as income, education, residence, or neighborhood situations, or other more personal factors related to child-rearing, such as maternal mental health, co-residence with other family members, relationships between family members, and perceptions toward childrearing. To evaluate such detailed information, a multi-disciplinary system collecting information from a wide range of resources, such as the Child Death Review system, is needed.[4,40] If preventive interventions are implemented in the future, follow-up studies are also needed to evaluate changes in risk factors for infant deaths.

Conclusion

Infants with biological risk factors had a higher risk of death from unintentional external causes as well as internal causes, and infants of socially high-risk mothers had a high risk of death from both external and internal causes. Interdisciplinary support from both public health and clinical-care professionals is needed to prevent diseases and injuries among infants with high social or biological risks.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.2188/jea.JE20160188.

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