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Leitung: Prof. Dr. med. Rüdiger von Kries

MÜTTERLICHES RAUCHEN IN DER SCHWANGERSCHAFT ALS RISIKOFAKTOR FÜR KINDLICHES ÜBERGEWICHT

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Christina Sobotzki (geb. Riedel)
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Berichterstatter:	Prof. Dr. med. Rüdiger von Kries, MSc.
Mitberichterstatter:	Prof. Dr. Eva Grill Prof. Dr. Berthold Koletzko
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
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Inhalt

Zusammenfassung

Übergewicht und Adipositas ist ein weltweites Problem, das bereits im Kindesalter eintritt. Neben einer unausgewogenen Energiebilanz gibt es weitere Faktoren, die die Entwicklung des Kindes bereits im Mutterleib beeinflussen und das Risiko für späteres Übergewicht erhöhen. Eine kürzlich erschienene Arbeit hat gezeigt, dass 7% der Wahrscheinlichkeit im Alter zwischen 7 und 10 Jahren adipös zu sein, durch mütterliches Rauchen während der Schwangerschaft erklärt wird. Dieser Zusammenhang zwischen mütterlichem Rauchen in der Schwangerschaft und Übergewicht und Adipositas des Kindes wurde jedoch aufgrund von potentiellem Residual Confounding immer wieder in Frage gestellt.

In der vorliegen Dissertation wurde untersucht, wann in der Kindheit der Zusammenhang des mütterlichen Rauchens in der Schwangerschaft und späterem Übergewicht erkennbar wird (longitudinale Quantilregression unter Zuhilfenahme der Boostingschätzmethode) und ob dieser Zusammenhang durch residuales Confounding erklärt werden könnte (negative control design).

In den Ergebnissen zeigte sich, das höhere, weiterhin ansteigende BMI z-score Differenzen bei Kindern, deren Mütter in der Schwangerschaft geraucht haben, im Vergleich zu Kindern, deren Mütter nicht in der Schwangerschaft geraucht haben, im Mittel und Median ab einem Alter zwischen 4 und 6 Jahren eintreten. Diese Unterschiede wurden für die unteren und oberen BMI z-score Quantile in Abhängigkeit von Geschlecht und Alter gefunden. Des Weiteren wurde in einer Meta-Analyse die gepoolten, gegenseitig adjustierten Effekte des mütterlichen Rauchens denen des väterlichen Rauchens oder des Rauchens im Haushalt auf das kindliche Übergewicht und Adipositas gegenübergestellt und dabei ein höherer Effekt für das mütterliche Rauchen im Vergleich zum väterlichen Rauchen festgestellt. Dieses Ergebnis lässt einen direkten intrauterinen Dosis-Effekt des Nikotins vermuten, da Kinder beim aktiven Rauchen der Mutter stärker betroffen sind als beim Passivrauchen.

Um dieses Ergebnis weiter zu bestärken oder einen eventuellen Schwellenwert zu erkennen, wäre der nächste Schritt, den Dosis-Effekt des Rauchens der Mutter mittels einer Individual Patient Data Meta-Analyse auf Linearität näher zu untersuchen.

Summary

Overweight and obesity are a worldwide problem already in infancy. Beside a not well-balanced energy balance (in the later life) there are also other factors that influence the fetus already in utero and increase its risk for later overweight. A recent state of the art paper suggested that 7% of the probability of obesity at 7 to 10 years of age could be explained by maternal smoking in pregnancy. This empirical evidence for a causal association between intrauterine exposure to nicotine and overweight in the offspring has been questioned, however, because of potential residual confounding.

This thesis examined when a higher BMI in children of mothers who smoked during pregnancy emerge during their life (longitudinal quantile regression with boosting estimation) and if these associations are explainable by residual confounding (negative control approach)?

Increasing mean and median BMI z-score differences emerged between the ages 4 and 6 years in offspring of mothers who smoked during pregnancy compared to offspring of mothers who did not smoke during pregnancy. The shape and size of age-specific effect estimates for maternal smoking during pregnancy varied by age and gender across the BMI z-score distribution. In addition in the meta-regression comparing mutually adjusted effect estimates of maternal smoking during pregnancy with those of paternal and household smoking on childhood overweight and obesity, higher effect estimates were detected for maternal smoking during pregnancy compared to paternal or household smoking. These findings point to a direct intrauterine dose effect of the nicotine, because the nicotine exposure in the fetus after maternal smoking is stronger compared to the exposure with passive smoke

The next step to prove the trajectory of the dose-effect of maternal smoking during pregnancy would be to perform an individual patient data meta-analysis. Constant rising values would prove the linear dose-effect.

Einleitung

Hintergrund

Übergewicht und Adipositas haben sich im 20. Jahrhundert zu einem weltweiten Problem entwickelt. Im Jahre 2008 waren mehr als 1,4 Milliarden bzw. 35% der Menschen über 20 Jahren übergewichtig. Von diesen waren 200 Millionen Männer und 300 Millionen Frauen adipös [1]. Übergewicht und Adipositas bei Erwachsenen werden – international anerkannt über die Höhe des Body Mass Index (BMI) definiert. Dieser wird aus dem Körpergewicht in Kilogramm dividiert durch die Körpergröße in Metern zum Quadrat (kg/m²) berechnet. Als übergewichtig werden Erwachsene mit einem BMI ≥ 25 kg/m² bezeichnet und als adipös mit einem BMI ≥ 30 kg/m². Da sich die Relation von Körpergröße und -gewicht während des Wachstums ständig ändert, ist diese Definition bei Kindern nicht anwendbar. Bei diesen werden Übergewicht und Adipositas durch alters- und geschlechtsspezifische BMI-Perzentile definiert. Als Perzentil wird die Rangposition innerhalb einer Population bezeichnet [2]. Liegt der BMI des Kindes auf der 90. Perzentile, bedeutet das, dass 10% der Probanden über und 90% unter dem BMI-Wert des Kindes liegen. Je nachdem welche Referenzpopulation man der Berechnung zugrunde legt, können diese Werte schwanken.

In Deutschland sind heute mehr als 50% der Erwachsenen sowie 16% der Kinder und Jugendlichen übergewichtig [3]. Hierbei kann vom Kindes- zum Jugendalter eine steigende Prävalenz beobachtet werden. In einer deutschlandweiten Studie von 2007 bei Kindern im Alter zwischen 3 und 17 Jahren lag die Anzahl der übergewichtigen bzw. adipösen Kinder im Alter zwischen 3 und 6 Jahren bei ca. 9% bzw. 3%. Bei den 7 bis 10-Jährigen waren 15.9 % der Jungen und 14.8 % der Mädchen übergewichtig und 7% bzw. 5.7% adipös. Bei Teenagern zwischen 14 und 17 Jahren erhöhte sich die Zahl der Übergewichtigen und Adipösen auf 17.2% bzw. 8.2% bei den Jungen und auf 17.0% bzw. 8.9% bei den Mädchen [4].

Übergewicht entsteht durch eine unausgeglichene Energiebilanz, also ein Missverhältnis zwischen Kalorienaufnahme und Kalorienverbrauch [5]. Dies wird durch energiereiche Ernährung und mangelnde körperliche Aktivität negativ beeinflusst. Zudem sind weitere potentielle, das Übergewicht fördernde Faktoren, Bestandteil aktueller Forschung. Neben genetischen Faktoren, von denen ausgegangen wird, dass sie beispielsweise im Zusammenhang mit bestimmten Umweltfaktoren das Risiko für späteres Übergewicht erhöhen [6-8] und sozioökonomische Faktoren [9], wird die metabolische Programmierung in den letzten Jahren stark diskutiert.

Zahlreiche experimentelle und epidemiologische Studien haben gezeigt, dass während der prä- und postnatalen Entwicklung einige Faktoren, wie mütterliches Übergewicht, exzessive Gewichtszunahme oder Gestationsdiabetes, das spätere Risiko für Krankheiten wie Adipositas oder Diabetes erhöhen können [10]. Einen Überblick dazu verschafft Abbildung 1.

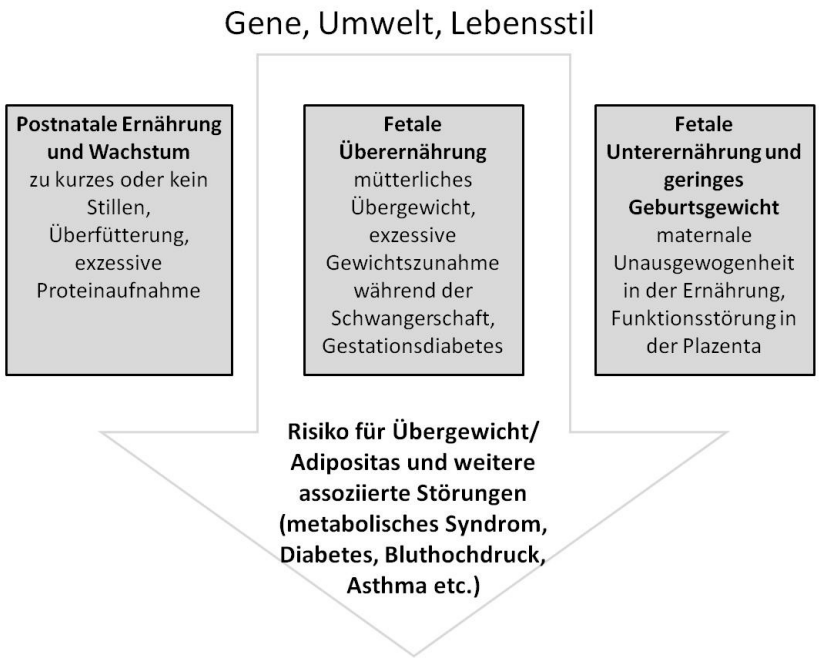

Abbildung 1: Frühe metabolische Programmierung (in Anlehnung an Brands und Koletzko [11] und Koletzko et al. [12])

In welchem erheblichem Maße pränatale Faktoren das Adipositasrisiko bei Kindern prägen, führten Gillman und Ludwig [13] in einer kürzlich erschienenen Übersichtsarbeit aus. Die Autoren postulierten, dass 7% der Wahrscheinlichkeit im Alter zwischen 7 und 10 Jahren adipös zu sein, durch mütterliches Rauchen während der Schwangerschaft erklärt würde. Die Annahme eines kausalen Zusammenhangs von Rauchen in der Schwangerschaft und Übergewicht im Kindesalter basiert beim Menschen ausschließlich auf diversen Beobachtungsstudien [14-19] und Meta-Analysen [20,21], die den Einfluss des während der Schwangerschaft aufgenommenen Nikotins auf das kindliche Übergewicht untersuchten und dabei positive Assoziationen gefunden haben. Die Ergebnisse waren hinsichtlich Eintritt und Stärke des Effekts sehr heterogen [17-19,22-27]. Zudem wird der angenommene kausale Zusammenhang zwischen mütterlichem Rauchen und dem Übergewicht des Kindes auf Grund eines möglichen Residual Confoundings immer wieder in Frage gestellt [28,29]. Unter Residual Confounding versteht man die verbleibende Verzerrung des Effekts, obwohl bereits nach zahlreichen möglichen Confoundern, also Störgrößen, adjustiert wurde [30]. Beim Übergewicht des Kindes könnten auch andere Ursachen diesen Effekt bewirken, da zum

Beispiel Frauen, die rauchen, durchschnittlich einen ungesünderen Lebensstil aufweisen, als Frauen, die nicht rauchen. Sie achten beispielsweise weniger auf eine gesunde Ernährung [31] und bewegen sich tendenziell weniger [32]. Die Bestätigung eines kausalen Zusammenhangs kann aus ethischen Gründen allerdings nicht mit randomisierten Studien geklärt werden.

Es gibt jedoch Möglichkeiten zu überprüfen, ob die Annahme eines kausalen Zusammenhangs gerechtfertigt ist. Eine ist der Vergleich mit randomisierten Tierexperimenten. Holloway et al. [33] verabreichte weiblichen Ratten während der Trächtigkeit und der Stillzeit 1 mg Nikotin pro Körpergewicht pro Tag, was in etwa einem gemäßigten Raucher entspricht. Im Vergleich zu den Kontrollen stieg das postnatale Körpergewicht der Nachkommen nach dem Abstillen in der 7. Woche (ab der 10. Woche signifikant) bis zu 26. Woche deutlich an, vgl. Abbildung 2. Ähnliche Auswirkungen des Nikotins auf das spätere Gewicht [34,35] oder auf das perivaskuläre Fettgewebe [34-36] wurden auch in weiteren Tierstudien gezeigt.

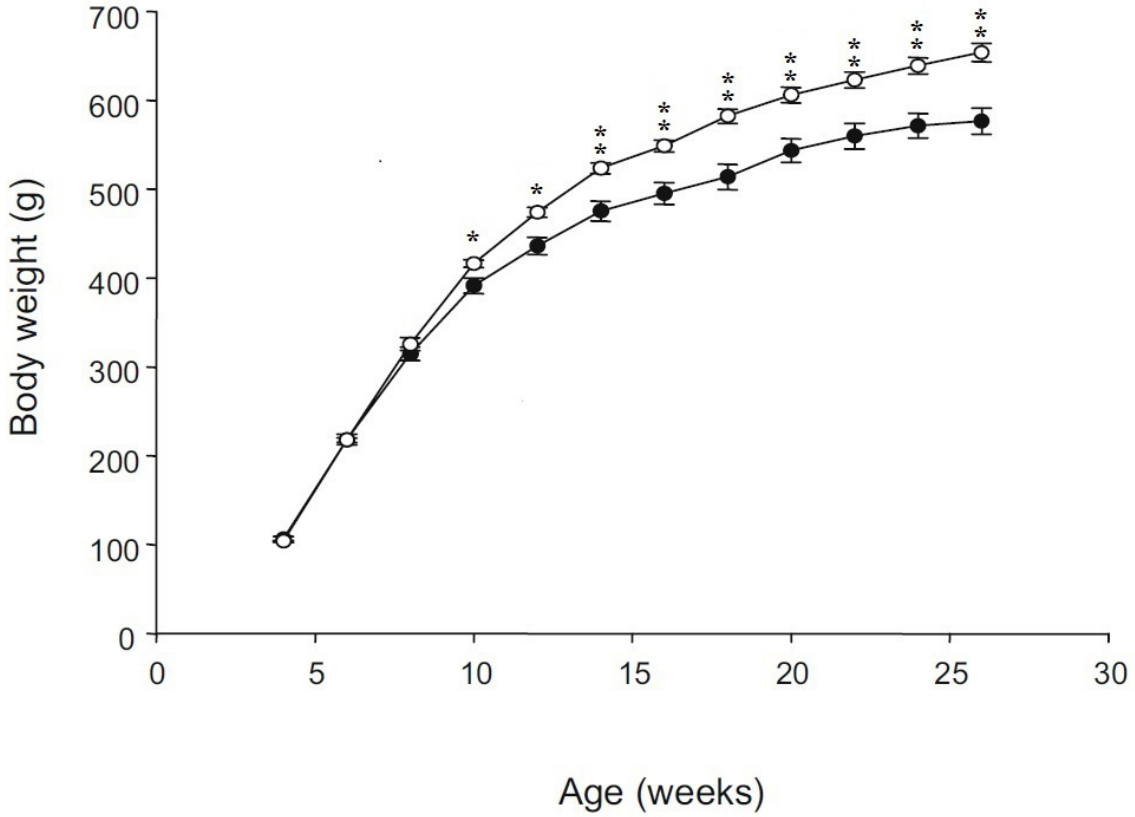

Abbildung 2: Postnatales Wachstum der Nachkommen von Ratten (schwarzer Kreis: Kontrollgruppe; weißer Kreis: Versuchsgruppe) während der Schwangerschaft und Stillzeit (nach (Holloway, Lim et al. 2005)) (*p<0.05,p>0.01).**

Es stellt sich die Frage, ob diese Dynamik mit altersabhängig steigenden Gewichtsdifferenzen auch beim Menschen vorzufinden ist. Laut Quinn [37] entsprechen 13.7 Rattentage einem Menschenjahr. Ein signifikanter Anstieg wurde bei Ratten nach ungefähr 70 Tagen festgestellt, was beim Menschen ca. einem Alter von 5 Jahren entspricht.

Eine weitere Möglichkeit zur Überprüfung des kausalen Zusammenhangs, ist der Ansatz den Effekt des mütterlichen Rauchens in der Schwangerschaft mit einer negativen Kontrolle zu vergleichen (negative control design [38])[39-41]. Bei einer negativen Kontrolle wird kein Effekt auf den Outcome erwartet [41]. Hat dieser im gegenseitig adjustierten Modell also keinen Effekt, geht man von einem intrauterinen Einfluss aus. Sind die Effektstärken jedoch sehr ähnlich, dann scheinen sie durch residuales Confounding verzerrt zu sein.

Bearbeitete Fragestellung

Bei dieser Arbeit standen demnach zwei zentrale Fragen im Fokus:

1. Können altersabhängig steigende Gewichtsverläufe, wie sie aus Tierexperimente bekannt sind, auch beim Menschen (Kindern von Müttern die in der Schwangerschaft geraucht haben) nachgewiesen werden und ab welchem Alter treten diese auf.
2. Gibt es einen Anhalt dafür, dass der Effekt des Rauchens der Mutter in der Schwangerschaft auf das kindliche Übergewicht und Adipositas durch residuales Confounding verzerrt ist?

Die erste Fragestellung wurde in der Publikation *"Differences in BMI z-scores between offspring of smoking and nonsmoking mothers: a longitudinal study of German children from birth through 14 years of age"* untersucht und basiert auf zusammengefassten Daten von zwei Deutschen Kohorten: der Kieler Adipositas Präventionsstudie (Kiel Obesity Prevention Study/KOPS) und der Multizentrische Allergiestudie (MAS), die in 6 Abteilungen für Geburtshilfe in 5 deutschen Städten (Berlin, Düsseldorf, Freiburg, Mainz, München) durchgeführt wurde. Insgesamt lagen bei 1.049 Kindern Gewicht- und Größenmessungen von der Geburt bis zum Alter von 14 Jahren vor. Bei der Analyse wurden zwei unterschiedliche statistische Methoden angewendet. Zum einen longitudinale Quantilregression unter Zuhilfenahme der Boostingschätzmethode, um den Einfluss des mütterlichen Rauchens während der Schwangerschaft auf verschiedene Bereiche des BMI z-scores zu unterschiedlichen Zeitpunkten zu untersuchen, in diesem Fall dem 10%, 25% (untere), 50%

(Median), 75%, 90% (obere) Perzentil. Der BMI z-score wird benutzt, um Kinder alters- und geschlechtsabhängig vergleichbar zu machen [42]. Er stellt den BMI des Kindes im Vergleich zu einer Standard- oder Referenzpopulation mit Mittelwert 0 und Standardabweichung 1 dar. Zum Vergleich mit anderen Studien wurden außerdem additive gemischte Modelle berechnet, die den Einfluss des mütterlichen Rauchens in der Schwangerschaft auf den BMI z-score Mittelwert schätzen.

Ebenso wie bei den Gewichtsverläufen der Tierexperimente, wurden bei Kindern, deren Mütter in der Schwangerschaft geraucht haben, im Mittel und Median (50% Quantil) höher steigende BMI z-score Werte im Vergleich zu denen beobachtet, deren Mütter nicht geraucht haben. Signifikante Unterschiede traten zwischen 4 und 6 Jahren auf und stiegen bis zum Alter von 14 Jahren weiterhin an. Mit 4 bis 6 Jahren lag das 50% Quantil des BMI z-score der Mädchen beispielsweise bei 0.12 [95%CI 0.01;0.21] und im Alter von 14 Jahren bei 0.30 [95%CI 0.08;0.39]. Bei den unteren Quantilen war der Effekt bei den Mädchen stärker ausgeprägt als bei den Jungen, wohingegen bei den oberen Quantilbereichen der Effekt bei Jungen stärker ausgeprägt war.

Es gibt bereits einige Studien, sowohl Querschnittstudien [22,25,43,44] als auch longitudinale Studien [15,23,24,45-47], die sich mit den Auswirkungen des mütterlichen Rauchens während der Schwangerschaft auf den Verlauf des BMIs, des BMI z-scores oder dem Risiko für Übergewicht und Adipositas beschäftigt haben und dabei auch altersabhängig steigende Unterschiede aufzeigen konnten. Allerdings basieren bisherige Studien entweder auf aufeinander folgenden, zu unterschiedlichen Alterszeitpunkten durchgeführten Querschnittsmessungen [22,25,43,48], oder es sind Längsschnittdaten, bei denen die untersuchen Kinder maximal 4 Jahre alt waren [17,18,27] oder sie benutzen eine schwer zu interpretierende Statistik [46]. Vergleichbare Studien, welche den längeren longitudinalen Verlauf mit statistischen Methoden modelliert haben, haben sich bisher immer auf den Mittelwert bezogen und nicht die gesamte BMI-Verteilung betrachtet [15,23,24,45].

Der zweite Teil der Arbeit widmet sich der Frage, ob die Effekte des mütterlichen Rauchens in der Schwangerschaft auf das kindliche Übergewicht durch residuales Confounding zustande kommen. Es gibt verschiedene Ansätze mit einer negativen Kontrolle einen intrauterinen Effekt des mütterlichen Rauchens zu untersuchen. Zum einen könnte man die Effektstärken an unterschiedlichen Zeitpunkten betrachten. Der Effekt des Rauchens vor oder nach der Schwangerschaft sollte bei einem intrauterinen Einfluss deutlich kleiner sein als der Effekt des Rauchens in der Schwangerschaft [40]. Hier ergibt es jedoch das Problem, dass die

Expositionen der 3 Zeitpunkte, vor, in und nach der Schwangerschaft eng miteinander korreliert sind und es damit schwierig ist die Effekte voneinander zu trennen. Eine weitere Möglichkeit sind Geschwisterstudien, bei denen die Geschwister nicht der gleichen Exposition ausgesetzt waren [40], jedoch den gleichen Genen und Umweltsituationen unterliegen. Iliadou et al. [29] beispielsweise untersuchte männliche Geschwisterpaare im Alter von 18 Jahren. Er fand ein signifikant erhöhtes Risiko übergewichtig zu sein bei beiden Söhnen nur, wenn die Mutter in beiden Schwangerschaften geraucht hat. Die Effektstärken waren geringer, wenn die Mutter nur in einen der beiden Schwangerschaften rauchte. Beim Zweiten Sohn war die Effektstärke zusätzlich deutlich höher, wenn die Mutter in der ersten Schwangerschaft geraucht hat (1.20 (0.88–1.65)) im Vergleich zur zweiten Schwangerschaft (0.96 (0.58–1.57)). Diese Ergebnisse deuten auf residuales Confounding hin, jedoch war die Fallzahl zu gering um einen intrauterinen Effekt ausschließen zu können. Letztendlich gibt es noch die Möglichkeit den Effekt des mütterlichen Rauchens mit dem Effekt des väterlichen Rauchens zu vergleichen. Bei einem direkten intrauterinen Einfluss sollte der Einfluss des mütterlichen Rauchens in der Schwangerschaft deutlich höher sein als der des Vater [39-41]. Eine ähnliche Effektstärke würde darauf hindeuten, dass die Assoziation durch Störfaktoren, welche mit dem Rauchen und dem erhöhten BMI assoziiert sind, für den Effekt verantwortlich sind [40].

Es gibt bereits einige Studien, welche den Ansatz der negativen Kontrolle anwenden und die Effektstärken des väterlichen Rauchens oder des Passivrauchen mit denen des mütterlichen Rauchen verglichen haben [14,15,45,49-53]. In einigen, jedoch nicht allen Studien, wurden höhere Effekte für mütterliches Rauchen in der Schwangerschaft gefunden [49,50,52,53]. Diese Studien wurden in der Meta-Analyse „*Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking - a meta-analysis*“[54] zusammengefasst, um die „wahren“ Effektstärken des mütterliches Rauchens während der Schwangerschaft sowie des väterlichen Rauchens, oder des Rauchens im Haushalt in dem das Kind lebt, gegenseitig adjustiert mit einer hohen Fallzahl zu ermitteln und sie damit auf residuales Confounding zu untersuchen.

In 12 Studien mit insgesamt 109.838 Mutter-Kind Paaren konnte gezeigt werden, dass der Einfluss des mütterlichen Rauchens in der Schwangerschaft auf das kindliche Übergewicht und der Adipositas stärker ist als der des Vaters. Dies weist damit auf einen direkten biologischen Effekt des intrauterinen Einfluss des Rauchens auf die Entwicklung des Kindes hin. Die Effekte des mütterlichen Rauchens adjustiert für das häusliche Passivrauchen waren

geringer und ähnlich. Dies lässt sich durch eine mögliche Überadjustierung des mütterlichen Rauchens (häusliches passives Rauchen kann auch das aktive mütterliche Rauchen miteinschließen) erklären, da hierdurch der Effekt des mütterlichen Rauchens in der Schwangerschaft abgeschwächt wird.

Zusammenfassende Bewertung

Der erste Teil der Arbeit bestätigt, dass die Ergebnisse der randomisierten Tierexperimente auch bei Menschen beobachtet werden können. Mütterliches Rauchen in der Schwangerschaft führte zu zunehmend größeren BMI z-score Werten ab einem Alter zwischen 4 und 6 Jahren. Auch der zweite Teil der Arbeit deutet auf einen direkten intrauterinen Effekt des mütterlichen Rauchens hin, indem die Effektstärken im gegenseitig adjustierten Modell bei der Mutter höher waren als die des Vaters.

Zunächst muss die Frage geklärt werden, ob sich die Ergebnisse von Tierexperimenten auf den Menschen übertragen lassen bzw. ein biologischer Effekt des mütterlichen Rauchens möglich ist. Raucht die Mutter in der Schwangerschaft, wird das Nikotin innerhalb von 30 bis 60 Sekunden in den arteriellen Kreislauf aufgenommen. Von dort gelangt es über die Plazenta in den fötalen Kreislauf, wo es, sobald es ins Fruchtwasser aufgenommen wird, vom Fötus über die Haut absorbiert wird [55]. Ein Einfluss danach auf den Metabolismus des Kindes scheint demnach plausibel. Auch der deutlich höhere Effekt des mütterlichen Rauchens ist plausibel, wenn man davon ausgeht, dass durch aktives Rauchen deutlich höhere Nikotindosen auf den Fötus einwirken, wie auch im Haar von Neugeborenen gemessene Cotininwerte, einem Abfallprodukt des Nikotins [56], zeigten [57].

Es muss jedoch auch hinterfragt werden, ob der Vater tatsächlich eine gute negative Kontrolle darstellt um residuales Confounding ausschließen zu können, da bei einer negativen Kontrolle angenommen wird, dass diese keinen oder nur einen sehr viel kleineren Einfluss haben sollte, als in diesem Fall das mütterliche Rauchen. In der vorliegenden Meta-Analyse war ein Effekt zudem trotz gegenseitiger Adjustierung weiterhin vorhanden. Des Weiteren konnte Cotinin in einigen Studien auch in nichtrauchenden schwangeren Frauen nachgewiesen werden, wenn diese Passivrauch ausgesetzt waren [41,58]. Dieser Frage ging einer kürzlich erschienen Publikation von Taylor et al. [41] nach, die Cotininkonzentrationen in rauchenden und nichtrauchenden schwangeren Frauen vergleichen. Die Cotininlevel nichtrauchender Frauen mit rauchendem Partner lagen um 2 Größenordnungen unter dem Level aktiv rauchender

Frauen. Der deutliche Unterschied unterstützt demnach die Annahme, dass die Einflüsse vom väterlichen Rauchen im Vergleich zum mütterlichen Rauchen minimal sind und damit der Vater als negative Kontrolle verwendet werden kann.

Ein möglicher eigener biologischer Effekt des väterlichen Rauchens kann allerdings nicht ausgeschlossen werden, wenn eine niedrige Dosis ausreicht, um einen Effekt auf das kindliche Übergewicht zu bewirken. Ebenso besteht die Möglichkeit, dass der Effekt des väterlichen und mütterlichen Rauchens später nach der Schwangerschaft zustande kommt oder das beide Effekte, das mütterliche und väterliche Rauchen, weiterhin durch residuales Confounding verzerrt sind [38,54].

Ersteres und letzteres könnten als nächsten Schritt in einer Individual Patient Data (IPD) Meta-Analyse weiter untersucht werden, indem ein Dosis-Effekt aus allen Studien, die Daten zu den anthropometrischen Daten der Kinder und der Anzahl der gerauchten Zigaretten der Mütter in der Schwangerschaft erhoben haben, errechnet werden würde. Da die Nikotinkonzentration, denen das Ungeborene ausgesetzt ist, beim Passivrauch wahrscheinlich ähnlich dem einer Mutter ist, die nur wenig raucht, würde ein linearer Anstieg des Risikos für Übergewicht und Adipositas bei Kindern, abhängig davon wie viel Zigaretten die Mutter in der Schwangerschaft geraucht hat, einen tatsächlichen Effekt des passiven Rauchens in der Schwangerschaft suggerieren. Demnach würde der intrauterine Effekt noch höher sein als bisher angenommen, da die Effekte für das mütterliche und väterliche Rauchen addiert werden müssten, um den „wahren“ intrauterine Einfluss auf die Nachkommen zu ermitteln. Sollte der Dosis-Effekt jedoch nur bis zu einem bestimmten Punkt stark ansteigen und ab einer bestimmten Nikotindosis gleich bleiben, würde diese Beobachtung für die Schwellenwert-Theorie sprechen [28,29], die besagt, dass ein Schwellenwert des Nikotinlevels existiert, der schon bei geringen Dosen des Nikotins, egal ob intrauterin von der Mutter oder passiv vom Vater, Veränderungen herbeiführt, die bewirken, dass die Nachkommen später übergewichtig oder adipös werden. Dies liegt aber im Widerspruch zu den hier gefundenen höheren Effektstärken für aktives mütterliches Rauchen und würde demnach darauf hinweisen, dass beide elterlichen Effekte durch residuales Confounding zustande kommen.

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Abbildungsverzeichnis

Abkürzungsverzeichnis

BMI Body Mass Index

IPD Individual Patient Data

Differences in BMI z-scores between offspring of smoking and nonsmoking mothers: a longitudinal study of German children from birth through 14 years of age

Authors: Christina Riedel

Nora Fenske

Manfred J. Müller

Sandra Plachta-Danielzik

Thomas Keil

Linus Grabenhenrich

Rüdiger von Kries

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Differences in BMI *z*-Scores between Offspring of Smoking and Nonsmoking Mothers: A Longitudinal Study of German Children from Birth through 14 Years of Age

Christina Riedel,[1] Nora Fenske,[2] Manfred J. Müller,[3] Sandra Plachta-Danielzik,[3] Thomas Keil,[4] Linus Grabenhenrich,[4] and Rüdiger von Kries[1]

[1]Institute of Social Paediatrics and Adolescent Medicine, and [2]Department of Statistics, Ludwig-Maximilians University of Munich, Munich, Germany; [3]Institute of Human Nutrition and Food Science, Christian-Albrechts-University of Kiel, Kiel, Germany; [4]Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany

Background: Children of mothers who smoked during pregnancy have a lower birth weight but have a higher chance to become overweight during childhood.

Objectives: We followed children longitudinally to assess the age when higher body mass index (BMI) *z*-scores became evident in the children of mothers who smoked during pregnancy, and to evaluate the trajectory of changes until adolescence.

Methods: We pooled data from two German cohort studies that included repeated anthropometric measurements until 14 years of age and information on smoking during pregnancy and other risk factors for overweight. We used longitudinal quantile regression to estimate age- and sex-specific associations between maternal smoking and the 10th, 25th, 50th, 75th, and 90th quantiles of the BMI *z*-score distribution in study participants from birth through 14 years of age, adjusted for potential confounders. We used additive mixed models to estimate associations with mean BMI *z*-scores.

Results: Mean and median (50th quantile) BMI *z*-scores at birth were smaller in the children of mothers who smoked during pregnancy compared with children of nonsmoking mothers, but BMI *z*-scores were significantly associated with maternal smoking beginning at the age of 4–5 years, and differences increased over time. For example, the difference in the median BMI *z*-score between the daughters of smokers versus nonsmokers was 0.12 (95% CI: 0.01, 0.21) at 5 years, and 0.30 (95% CI: 0.08, 0.39) at 14 years of age. For lower BMI *z*-score quantiles, the association with smoking was more pronounced in girls, whereas in boys the association was more pronounced for higher BMI *z*-score quantiles.

Conclusions: A clear difference in BMI *z*-score (mean and median) between children of smoking and nonsmoking mothers emerged at 4–5 years of age. The shape and size of age-specific effect estimates for maternal smoking during pregnancy varied by age and sex across the BMI *z*-score distribution.

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Introduction

The association of maternal smoking in pregnancy and low birth weight was established several decades ago (Simpson 1957) and is believed to be attributable to intrauterine growth retardation and shortened gestation (Wang et al. 2002). Surprisingly, a number of observational studies in the late 1990s suggested that children of mothers who smoked have a higher body mass index (BMI) later in life and implicitly a higher prevalence of overweight (Fried et al. 1999; Vik et al. 1996; von Kries et al. 1999). This has been confirmed in two meta-analyses of observational studies in populations 3–33 years of age; these studies reported odds ratios of approximately 1.5 for overweight in the children of smoking mothers, though neither meta-analysis addressed age-specific effects (Ino 2010; Oken et al. 2008).

Various aspects of the life-course effect of maternal smoking in pregnancy are not well understood. Some found positive associations (Apfelbacher et al. 2008; Braun et al. 2010; Durmus et al. 2011; Matijasevich et al. 2011; Suzuki et al. 2013), whereas others found no association (Fried et al. 1999; Howe et al. 2012) even if the power was high enough (Harris et al. 2013). Studies in older children have reported a higher prevalence of overweight/higher BMI values in children of smoking mothers for both sexes (Fried et al. 1999; Howe et al. 2012; Power and Jefferis 2002; Salsberry and Reagan 2005; von Kries et al. 2002) or some in boys only (Suzuki et al. 2011, 2012). Crucial questions still remain unanswered: When does a higher BMI in children of smoking mothers emerge? Does the association increase with age? Is the increase in BMI constant over the entire distribution, or does the association differ at the upper tail of the distribution?

We addressed these questions by pooling data from two German cohorts with repeated BMI measurements between birth and 14 years of age and information on maternal smoking during pregnancy and various potential confounders. Potential age-specific effects of maternal smoking during pregnancy across different parts of the BMI distribution were estimated using longitudinal quantile regression, an innovative statistical approach (Fenske et al. 2013).

Methods

Study population and data sources. In Northern Germany, the Kiel Obesity Prevention Study (KOPS), a cluster randomized intervention study, has been performed between 1996 and 2001 by the Institute of Human Nutrition and Food Science of the Christian-Albrechts-University of Kiel in the context of the school entry health examination (SEH; 12,254 children participated in the SEHs during these years) (Plachta-Danielzik et al. 2012b). From these districts in Kiel, 54.6% of the children were randomly chosen and contacted during the recruitment period; among those, 4,997 children (74.7%) agreed to participate in the study (see Supplemental Material, Figure S1) (Plachta-Danielzik et al. 2011). This cohort was representative of all children in Kiel attending the SEH in the recruitment period, as shown by a

Address correspondence to C. Riedel, Ludwig-Maximilians University of Munich, Institute of Social Paediatrics and Adolescent Medicine, Division of Epidemiology, Haydnstr. 5, 80336 Munich, Germany. Telephone: 49-89-552734-142. E-mail: christina.riedel@med.uni-muenchen.de

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nonresponse analysis (Plachta-Danielzik et al. 2008). Follow-up information was collected during examinations performed in the school setting, including one examination when the children were in the 4th grade (conducted in 2000–2005, n = 4,487), and a second when the children were in the 8th grade (during 2004–2010, n = 6,263) (Plachta-Danielzik et al. 2012b). Because of privacy policy, KOPS was not allowed to directly follow-up the children from the SEH; therefore, a pseudonymized study code was used to allow tracking of 1,671 at the 4th and 748 at the 8th grade of the original population. Of these 748 children, 161 children took part in a school intervention program and were excluded. The anthropometric measurements of height and weight were taken by trained nutritionists or collected from the baby check-up booklets (a document given to all parents at birth in which the medical examination results of the child are documented for the first 10 years of life). A self-administered questionnaire with questions on family characteristics and their body compositions was handed out to parents, to be returned by mail. Data on n = 330 children with information on weight and height measurements at 0 (birth), 6 (school entry), 10 (4th grade), and 14 (8th grade) years, maternal smoking during pregnancy, and various potential confounders were available.

Table 1. Comparison of population characteristics between the two German cohorts [n (%) or mean ± SD].

Variable	KOPS	MAS	p-Value
No. of children	330	781	
No. of observations	1,320	7,228	
Parental characteristics			
Maternal smoking during pregnancy			
Yes	69 (20.9)	150 (20.9)	
No	261 (79.1)	569 (79.1)	1.00
Maternal weight status			
Normal weight	244 (73.9)	549 (76.4)	
Overweight	64 (19.4)	127 (17.7)	
Obese	22 (6.7)	43 (6.0)	0.684
Highest maternal education (years)			
≤ 9	44 (13.3)	197 (27.4)	
10–12	106 (32.1)	237 (33.0)	
≥ 13	180 (54.5)	285 (39.6)	< 0.001
Paternal smoking			
Yes	126 (38.2)	176 (24.5)	
No	204 (61.8)	543 (75.5)	< 0.001
Child characteristics			
Sex			
Female	177 (53.6)	332 (46.2)	
Male	153 (46.4)	387 (53.8)	0.028
Classification of birth weight for gestational age			
Small	30 (9.09)	93 (12.9)	
Average	261 (79.1)	579 (80.5)	
Large	39 (11.8)	47 (6.5)	0.006
Preterm delivery (< 37 weeks)			
Yes	16 (4.8)	18 (2.5)	
No	314 (95.2)	701 (97.5)	0.059
Breastfeeding at any time after birth			
Yes	277 (83.9)	676 (94)	
No	53 (16.1)	43 (6)	< 0.001
Birth weight (g)	3,440 ± 559	3,422 ± 470	0.604
Birth length (cm)	51.6 ± 2.9	51.4 ± 2.3	0.219
BMI z-score at 6 years	–0.01 ± 1.0	0.11 ± 1.0	0.106
BMI z-score at 10 years	0.24 ± 1.1	0.36 ± 1.2	0.185
BMI > +1 SD[a] at 6 years (%)	10.6	17.8	0.044
BMI > +1 SD[a] at 10 years (%)	22.2	27.4	0.148
BMI > +2 SD[a] at 6 years (%)	2.1	4.9	0.176
BMI > +2 SD[a] at 10 years (%)	3.0	9.9	< 0.001
Variables for the sensitivity analyses[b]			
Television consumption			
> 1 hr	104 (42.6)	—	
≤ 1 hr	140 (57.4)	—	
Physical activity in a sports club			
> 2 hr	108 (45.0)	—	
≤ 2 hr	132 (55.0)	—	
Weight gain during the first year of life (kg)	—	12.7 (2.0)	
Early adiposity rebound (≤ 5.5 years)			
Yes	—	174 (31.8)	
No	—	374 (68.2)	

—, not available in the respective cohort.
[a]Overweight (BMI > +1 SD) is equivalent to BMI 25 kg/m^2 at 19 years, and obesity (BMI > +2 SD) is equivalent to BMI 30 kg/m^2 at 19 years (de Onis et al. 2007). [b]Difference in number of cases compared with those in the upper part of the table can be explained by an increasing number of missing values.

The second data source was the German Multicenter Allergy Study (MAS) that was launched in 1990. This longitudinal birth cohort study was initiated to investigate the natural course of atopy-related traits in early childhood (Bergmann et al. 1994; Karaolis-Danckert et al. 2008). In six obstetric departments in five German cities (Berlin, Düsseldorf, Freiburg, Mainz, Munich), a questionnaire on atopic diseases was distributed to parents of 7,609 infants who were born in 1990, with a response rate of 79%. The 1,314 healthy mature infants included in the study do not represent a random sample: 499 with a high risk for atopy were included by default, and 815 were selected at random from those children with no risk for atopy (Bergmann et al. 1994; Illi et al. 2006). They were followed up at 1, 3, 6, 12, 18, and 24 months of age, and then annually until the age of 20 years. Four hundred fifty-four (34.6%) of the enrolled children attended all 17 follow-ups, and 721 (54.9%) were examined at 13 years of age. Data on n = 719 children with information for the time periods of 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 10, and 13 years were available for the weight and height measurements, maternal smoking during pregnancy, and potential confounders.

Both cohort studies had obtained ethical approval by the respective local ethics committees. This approval included anonymous data analyses beyond the primary scope of the studies.

Outcome and explanatory variables. We estimated associations with the BMI z-score, defined according to World Health Organization (WHO) guidelines [WHO Child Growth Standards (0–5 years) (WHO Multicentre Growth Reference Study Group 2006) and WHO Reference 2007 (5–19 years) (de Onis et al. 2007)], including differences from the mean and from the 90th, 75th, 50th, 25th, and 10th quantiles of the BMI z-score distribution in the study population.

The main explanatory variable was maternal smoking during pregnancy, defined as a binary indicator reflecting any maternal smoking during pregnancy. To adjust for potential confounding in our model, we included maternal weight status at 6 (KOPS) and 10 years of age (MAS) [normal weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2)]; highest maternal education when the child was 6 years of age (KOPS) or a half-year (MAS) (≤ 9, 10–12, and ≥ 13 years of school education); classification of birth

weight for gestational age [small for gestational age (weight < 10th percentile according to German reference percentiles) (Voigt et al. 1996), appropriate for gestational age (weight between 10th and 90th percentile), or large for gestational age (weight > 90th percentile)]; preterm delivery (< 37 versus ≥ 37 weeks of gestation); breastfeeding defined as any breastfeeding after birth (yes vs. no); paternal smoking when the child was 6 years (KOPS) and 5 years of age (MAS) (yes vs. no). Unfortunately, maternal prepregnancy weight was not ascertained. The earliest available maternal weight was at 6 or 10 years in these cohorts, and was thus used in this analysis. Similarly, the earliest available maternal education data were collected at the age of 6 years or a half-year, respectively, and the earliest paternal smoking data was collected at the age of 6 or 5 years.

Statistical analysis. To test for structural differences between KOPS and MAS, we used Student's *t*-tests for continuous variables and Fisher's exact test for categorical variables. Local quantile regression (Yu and Jones 1998) was used to generate unadjusted BMI *z*-score quantile curves (for the 10th, 50th, and 90th quantiles) by age, sex, and maternal smoking.

We used longitudinal quantile regression based on boosting estimation (Fenske et al. 2013) because this method allowed us to simultaneously investigate our three research questions. We also estimated additive mixed models (AMMs) for the mean BMI *z*-score (Fahrmeir et al. 2013), to allow for a comparison with an established approach that has previously been applied to obesity data (Suzuki et al. 2011, 2012).

Quantile regression is a distribution-free approach to estimate effects of explanatory variables on quantiles of the BMI *z*-score distribution. The use of quantile regression allowed us to examine whether the association between smoking and BMI *z*-score is constant over the entire distribution (resulting in an upward shift of the entire distribution from the median value, without any change in the shape of the distribution) or variable, such that the estimated effect of smoking on the upper tail of the BMI distribution (i.e., at the 75th and 90th quantiles) differs from the estimated effect at the lower tail (the 10th and 25th quantiles) or median (50th percentile) of the distribution.

Compared with conventional linear quantile regression (Koenker 2005), the novel approach of additive quantile mixed models (AQMMs) offers additional flexibility in the model predictor. To estimate age-varying effects of maternal smoking during pregnancy on BMI *z*-scores, we included a product interaction term for age and maternal smoking in all models. To account for differences between the MAS and KOPS study populations, we included an additional interaction term for age and study. The potentially nonlinear shapes of these age-varying effects were estimated by P-splines with 20 knots (Eilers and Marx 1996). We adjusted all models for maternal weight status, maternal education, classification of birth weight for gestational age, preterm delivery, breastfeeding, and paternal smoking. To account for intraindividual correlation between repeated measurements typically occurring in longitudinal data, we included individual-specific intercepts and slopes (by age) in the additive predictor. Because some studies reported sex-specific differences (Fried et al. 1999; Howe et al. 2012; Suzuki et al. 2011, 2012), we stratified all analyses by sex. When using AMMs to estimate differences for the population mean, we modeled the same predictors as for AQMMs.

Model estimation for AQMMs was based on boosting and was conducted separately for the previously defined quantiles; this procedure was repeated on 100 subsamples on respectively two-thirds of the full data set to construct 95% CIs for the estimated effects (age-specific 2.5th and 97.5th quantiles of the empirical distribution obtained from 100 subsamples). The presented "best estimate" is the estimate on the complete dataset.

Additional sensitivity analyses were performed to consider further potential

Table 2. Overview of variables contained in the final dataset with n = 1,049 children by maternal smoking during pregnancy (yes vs. no) [n (%) or mean ± SD].

Variable	Maternal smoking during pregnancy	No maternal smoking during pregnancy	*p*-Value
No. of children	219	830	
No. of observations	1,755	6,793	
Parental characteristics			
Maternal weight status			
Normal weight	162 (74.0)	631 (76.0)	
Overweight	40 (18.3)	151 (18.2)	
Obese	17 (7.8)	48 (5.8)	0.525
Highest maternal education (years)			
≤ 9	89 (40.6)	152 (18.3)	
10–12	70 (32.0)	273 (32.9)	
≥ 13	60 (27.4)	405 (48.8)	< 0.001
Paternal smoking			
Yes	95 (43.4)	207 (24.9)	
No	124 (56.6)	623 (75.1)	< 0.001
Child characteristics			
Sex			
Female	113 (51.6)	396 (47.7)	
Male	106 (48.4)	434 (52.3)	0.324
Classification of birth weight for gestational age			
Small	37 (16.9)	86 (10.4)	
Average	172 (78.5)	668 (80.5)	
Large	10 (4.6)	76 (9.2)	0.004
Preterm delivery			
Yes	6 (2.7)	28 (3.4)	
No	213 (97.3)	802 (96.6)	0.830
Breastfeeding at any time after birth			
Yes	185 (84.5)	768 (92.5)	
No	34 (15.5)	62 (7.5)	0.001
Birth weight (g)	3,279 ± 492	3,467 ± 494	< 0.001
Birth length (cm)	50.7 ± 2.4	51.6 ± 2.5	< 0.001
BMI *z*-score at 6 years	0.34 ± 1.0	0.01 ± 1.0	< 0.001
BMI *z*-score at 10 years	0.54 ± 1.2	0.25 ± 1.1	0.020
BMI > +1 SD[a] at 6 years (%)	23.6	14.6	0.011
BMI > +1 SD[a] at 10 years (%)	34.7	23.6	0.007
BMI > +2 SD[a] at 6 years (%)	7.0	3.7	0.083
BMI > +2 SD[a] at 10 years (%)	11.3	6.9	0.088
Variables for the sensitivity analyses[b]			
Television consumption			
> 1 hr	27 (60.0)	77 (38.7)	
≤ 1 hr	18 (40.0)	122 (61.3)	0.014
Physical activity in a sports club			
> 2 hr	16 (37.2)	92 (46.7)	
≤ 2 hr	27 (63.0)	105 (53.3)	0.311
Weight gain during the first year of life (kg)	12.9 (1.7)	12.7 (2.0)	0.283
Early adiposity rebound (≤ 5.5 years)			
Yes	38 (35.8)	136 (30.8)	
No	68 (64.2)	306 (69.2)	0.492

[a]Overweight (BMI > +1 SD) is equivalent to BMI 25 kg/m^2 at 19 years, and obesity (BMI > +2 SD) is equivalent to BMI 30 kg/m^2 at 19 years (de Onis et al. 2007). [b]Difference in number of cases compared with those in the upper part of the table can be explained by an increasing number of missing values.

confounding variables that were available either in MAS or KOPS data: *a*) early adiposity rebound (AR) (< 5.5 years vs. ≥ 5.5 years). [The AR is the age at which the BMI rises again after its decrease around the age of 1 year; in these data the MAS study provided annual weight measurements. We defined early adiposity according to Rolland-Cachera et al. (1984): age < 5.5 years]; *b*) weight gain during the first year of life (kilograms); *c*) televison consumption at 6 years of age (> 1 hr/day vs. ≤ 1 hr/day); *d*) physical activity in a sports club at 6 years of age (> 2 hr/day vs. ≤ 2 hr/day).

All analyses were carried out with the statistical software R and the add-on packages mboost and gamm4 (http://www.r-project.org/foundation/).

Results

The proportion of children whose mothers smoked during pregnancy was identical in both data sets, with 20.9% of smoking mothers in both KOPS and MAS (Table 1). There were significant differences between both cohorts regarding sex, maternal education, classification of birth weight for gestational age, breastfeeding, and paternal smoking. However, birth weight and length as well as BMI *z*-scores at 6 and 10 years of age did not significantly differ between studies.

To assess whether the two data sets can be combined, we additionally evaluated potential differences in the BMI *z*-score increase by age in the respective cohorts (similar increments). Scatterplots showed a similar distribution of the BMI *z*-score values around the regression line of BMI *z*-score by age (see Supplemental Material, Figure S2), and the 95% CIs of the increment in BMI *z*-score per year overlapped (MAS: 0.032; 95% CI: 0.025, 0.038; and KOPS: 0.046; 95% CI: 0.036, 0.057). To assess the consistency of the association of potential confounders with the age-dependent BMI *z*-score values, we tested for potential effect modification of the association of the potential confounders considered in the final data set and BMI *z*-score by study by modeling interaction terms between study (MAS or KOPS) and the following confounders: sex, maternal weight status, maternal education, classification of birth weight, breastfeeding, preterm delivery, and paternal smoking. Interaction terms were not statistically significant except for the variables small for gestational age and preterm delivery (see Supplemental Material, Table S1). For both variables, positive associations with BMI *z*-scores were greater for the MAS study, possibly because only term or near-term children were recruited for MAS, in contrast with KOPS, where all children were recruited regardless of their gestational age.

Potential differences in risk factors for childhood obesity between smoking and nonsmoking mothers during pregnancy are shown in Table 2. Smoking mothers were more likely to be less educated than nonsmoking mothers. The children of smoking mothers were less likely to be breastfed and more likely to have a smoking father, and had a significantly lower mean birth weight and length (accounting for more children born small for gestational age) than the children of nonsmoking mothers. Mean BMI *z*-scores at 6 and 10 years of age were higher in the children of mothers who smoked during pregnancy.

Figure 1 shows all BMI *z*-scores according to age for all observations, and depicts the (unadjusted) time course of BMI *z*-score quantiles by age, sex, and maternal smoking during pregnancy. In boys (Figure 1A), the 10th BMI *z*-score quantile curve for children of smoking mothers is constantly higher than the curve for children of nonsmoking mothers. Regarding higher quantiles in boys, the curves of BMI *z*-score quantiles for children of smoking mothers were below or equal to the curves in children of nonsmoking mothers up to the age of 4 years, and became progressively higher thereafter. In girls (Figure 1B) of smoking mothers, the 10th BMI *z*-score quantile curve was below that of nonsmoking mothers during the first year of life. Afterward, both curves overlapped up to 5 years of age, when a progressively higher BMI emerged for children of smoking mothers until adolescence. For higher quantiles this difference emerged earlier, at the age of about 2–3 years.

The age-dependent adjusted differences between the BMI *z*-scores in boys and girls are depicted in Figure 2 (for underlying values, see Supplemental Material, Table S2). Emergence of higher BMI *z*-scores in children of smoking mothers was defined as the age when the lower limit of the 95% CI for BMI *z*-score difference first exceeds zero. This was considered statistically significant. In boys, the BMI *z*-score for the 10th quantile (Figure 2A) was 0.12 higher in association with maternal smoking versus nonsmoking at all ages. For lower BMI *z*-score quantiles (10th and 25th) in girls, the difference between the children of smokers versus nonsmokers emerges between 4 and 6 years of age, and increases until adolescence for the 10th quantile or remains constant over all ages for the 25th quantile. Similarly, for mean and median BMI *z*-scores in both boys and girls, significantly higher BMI *z*-scores in children of smoking mothers were estimated at 4–5 years of age (Figure 2B). For the 50th BMI *z*-score quantile, the estimated effect of maternal smoking was –0.06 at birth for both sexes, reflecting the child's lower birth weight compared with children of mothers who did not smoke during pregnancy. However, at 4–5 years of age in boys and girls, BMI *z*-scores were significantly higher in the children of smoking mothers compared with the children of nonsmoking mothers. In girls, the difference increased with age, such that the difference in the median BMI *z*-score increased from 0.12 (95% CI: 0.02, 0.24) at 5 years to

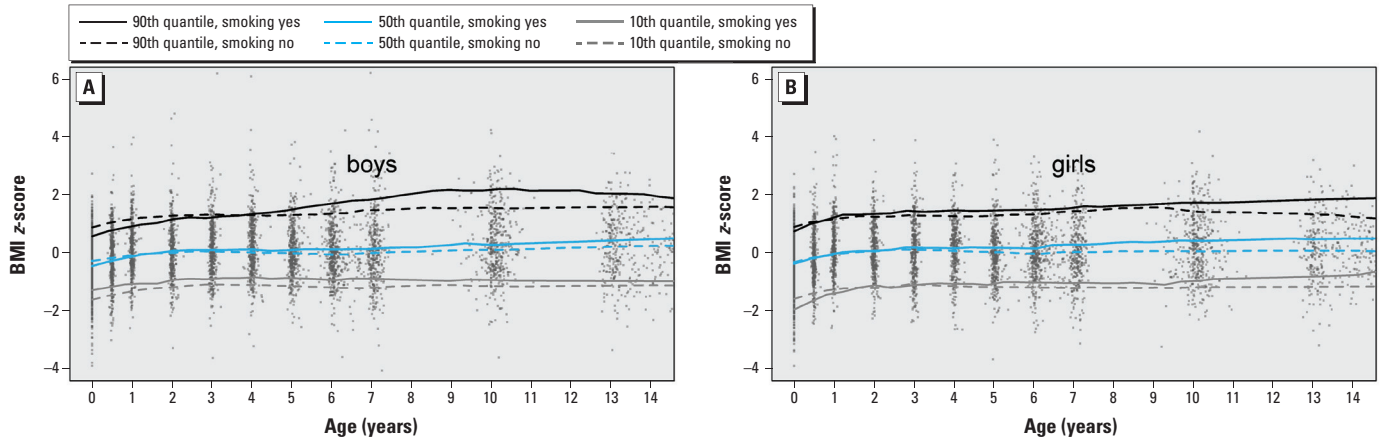

Figure 1. All observations (gray points) of boys (*A*) and girls (*B*) with empirical 10th, 50th, and 90th BMI *z*-score quantile curves by age and maternal smoking during pregnancy.

0.30 (95% CI: 0.08, 0.39) at 12.5 years of age, whereas the estimated difference in the mean BMI *z*-score increased linearly through 14 years of age. In boys, the difference in estimated mean and median BMI *z*-scores increased to about 7 years of age only. In the upper tail (90th quantile) of the BMI *z*-score distribution (Figure 2C) differences between the children of smokers versus nonsmokers were more pronounced in boys than in girls.

Among the potential confounders, large for gestational age was associated with significantly higher mean BMI *z*-scores, whereas small for gestational age and preterm delivery were associated with significantly lower mean BMI *z*-scores based on AMM models adjusted for smoking and all other covariates in the final model (see Supplemental Material, Table S3).

Estimated associations between maternal smoking and mean BMI *z*-scores were less precise and somewhat closer to the null when adjusted for covariates available for one study population only (television consumption and physical activity for KOPS; early adiposity rebound and weight gain during the first year of life in MAS) (see Supplemental Material, Table S4 and Figure S3).

Discussion

Based on differences in mean and median BMI *z*-scores, a positive association between smoking during pregnancy and overweight in children emerged at approximately 4–6 years of age and increased until adolescence. At lower quantiles the association was more pronounced in girls than in boys, whereas for higher quantiles the association was more pronounced and increased to a greater extent over time in boys compared with girls. Some previous studies have compared BMI or BMI *z*-scores in cohorts of children of smoking and nonsmoking mothers in repetitive cross-sectional analyses (Florath et al. 2013; Fried et al. 1999; Power and Jefferis 2002; Vik et al. 1996). The time period varied from birth to 33 years of age, although not all studies considered the life course since birth (Power and Jefferis 2002). In general, results of these studies suggest that the effect of maternal smoking on overweight in children increases with age. A few studies have attempted to model the longitudinal course in children after preschool years (Chen et al. 2006; Haga et al. 2012; Howe et al. 2012; Pryor et al. 2011; Suzuki et al. 2011, 2012). Pryor et al. (2011) and Haga et al. (2012) examined the impact of maternal smoking on predefined BMI accretion patterns in children, whereas our modeling was not based on such predefined patterns. Consistent with our findings, these authors reported that the association between maternal smoking during pregnancy became evident at 4–5 years of age and increased thereafter. Others have used

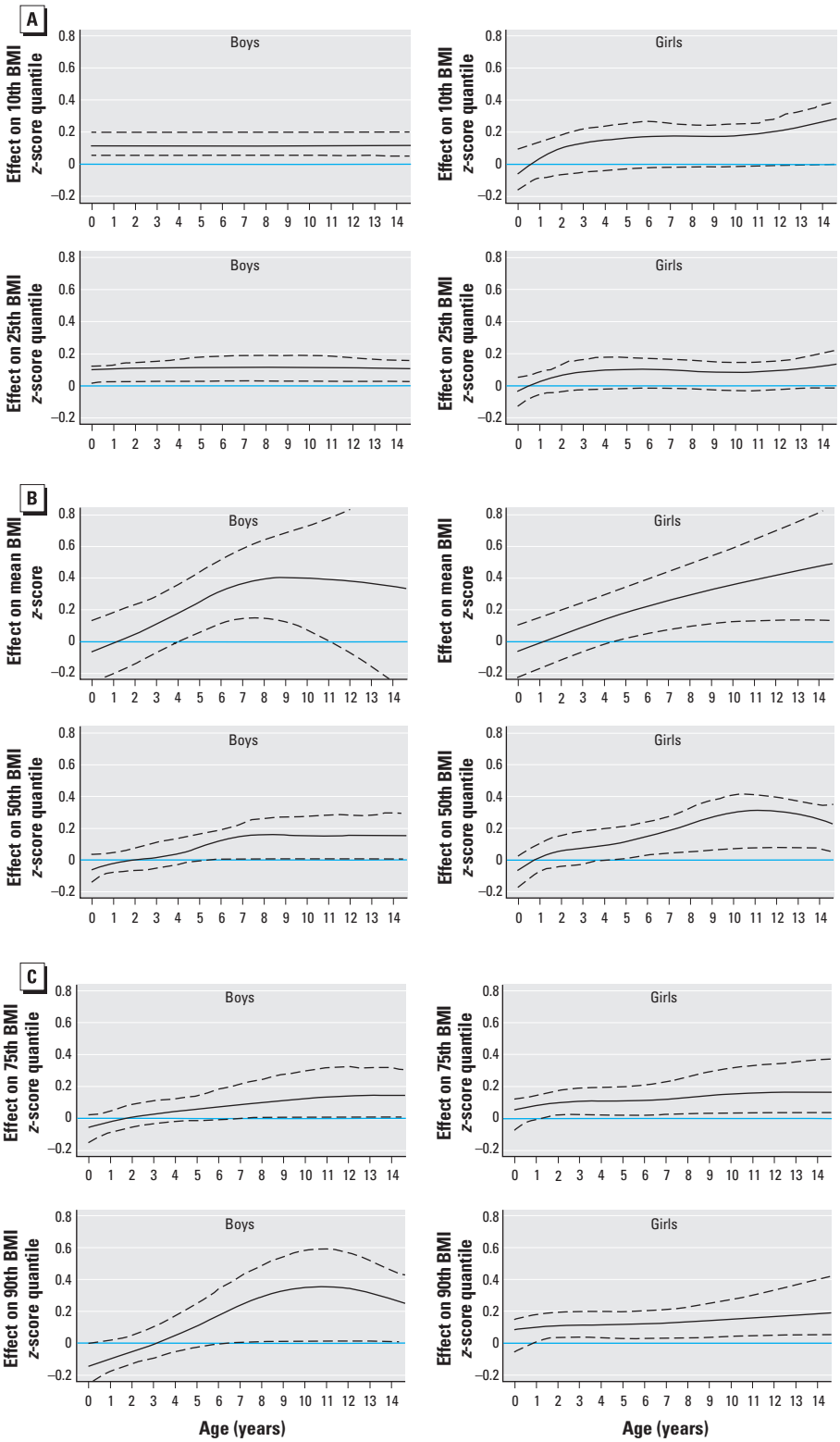

Figure 2. Age-varying effect estimates for maternal smoking during pregnancy (black lines) compared with nonsmoking during pregnancy (blue horizontal line at zero) for boys (left) and girls (right), adjusted by maternal weight status, highest maternal education, classification of birth weight for gestational age, preterm delivery, breastfeeding, paternal smoking, and by the interaction term of age and study. (*A*) 10th (upper row) and 25th (lower row) BMI *z*-score quantile resulting from AQMMs; (*B*) mean BMI *z*-score (upper row) resulting from AMMs, and 50th BMI *z*-score quantile (lower row) resulting from AQMMs; (*C*) 75th (upper row) and 90th (lower row) BMI *z*-score quantiles resulting from AQMMs. Results from the AQMMs: black lines = best estimates, dashed lines = 95% CI, based on the 100 subsamples; results from the AMMs: black lines = estimated effect, dashed lines = 95% CI.

more flexible models to evaluate the association between maternal smoking and weight in children, but effect estimates were limited to differences in mean BMI (Chen and Kelly 2005; Howe et al. 2012; Suzuki et al. 2011) and mean BMI *z*-scores (Suzuki et al. 2011, 2012) up to 10 years of age. In most cases, these studies also reported stronger associations between maternal smoking and child's weight with increasing age.

Differences by sex also have been reported by several studies, but with equivocal directions: higher effect estimates for boys than for girls (Fried et al. 1999; Power and Jefferis 2002; Suzuki et al. 2011, 2012) or vice versa (Chen et al. 2006; Howe et al. 2012). These equivocal findings might be related to differential effects on different parts of the BMI/BMI *z*-score distribution, pointing to the potential importance of quantile specific analyses.

The main strength of our analysis is a long follow-up from birth until early adolescence, which allowed modeling the BMI *z*-score life course across the BMI *z*-score distribution with adjustment for potential confounders. Therefore, the innovative contribution of our analysis is that it takes the longitudinal data structure into account in a flexible manner, and that it considers percentile-specific effects.

Assessment of maternal smoking during pregnancy was based on maternal self-reporting, which could lead to misclassification. However, Nafstad et al. (1996) demonstrated good consistency between maternal self-reported daily cigarette consumption and cotinine concentration in cord blood, suggesting fair validity of maternal reporting on smoking. Although that study was conducted in a sample with a somewhat higher prevalence of smoking mothers [Oslo cohort (Nafstad et al. 1996): 32.7%; 95% CI: 26.3, 39.6; and our cohort: 20.9%; 95% CI: 18.5, 23.5], this is unlikely to account for a different validity of the maternal reporting on smoking.

A limitation of our data is the lack of information regarding the extent of maternal smoking during pregnancy. Several studies reported evidence of a dose–response effect of the number of cigarettes smoked during pregnancy on the risk of overweight or obesity (Koshy et al. 2011; Montgomery and Ekbom 2002; Wideroe et al. 2003). We had data only on the number of cigarettes per day in the MAS cohort. Of 142 smoking mothers, 109 smoked 1–10 cigarettes/day during pregnancy, and only 33 smoked > 10 cigarettes. Mean BMI *z*-scores did not differ between those of children of heavy- and light-smoking mothers during pregnancy at respective ages (0, 1, 2, 3, 4, 5, 6, 7, 10, and 13 years) (data not shown), but this may have been attributable at least partly to the small number of heavy-smoking mothers. Another limitation is that only a subset of children from the original MAS and KOPS study had sufficient follow-up, outcome, and confounder data to be included in the present analysis, but there were no significant differences between the study samples and the full cohorts with regard to sex, birth weight, birth length, and BMI *z*-scores at different ages (data not shown).

We used additive mixed models and the innovative statistical approach of longitudinal quantile regression to estimate differences according to within-population BMI *z*-score quantiles and simultaneously investigate our three research objectives. A major strength of our approach was the inclusion of an age-varying effect of maternal smoking during pregnancy, which enabled us to identify the age at which the positive association emerges and to estimate nonlinear changes over time.

Although our findings do not provide direct evidence for a causal relation between maternal smoking during pregnancy and increasing BMI differences, they point to some similarities with randomized animal studies on intrauterine nicotine exposure (Gao et al. 2005; Oliveira et al. 2009; Somm et al. 2008). As in these animal studies, the impact of maternal smoking on BMI in the children appeared to increase with age. Changes in the hypothalamic regulation of energy homeostatic resulting in changes in appetite control and energy expenditure might be instrumental (Bruin et al. 2010; Grove et al. 2001; Holloway et al. 2005).

Previous studies have reported that associations with paternal smoking or secondhand smoke during and after pregnancy are similar to (Harris et al. 2013; Howe et al. 2012; Kleiser et al. 2009; Plachta-Danielzik et al. 2012a; von Kries et al. 2008) or stronger than (Apfelbacher et al. 2008; Florath et al. 2013; Raum et al. 2011) associations with maternal smoking during pregnancy, based on mutually adjusted models. Paternal and maternal smoking both may be markers of unmeasured family characteristics, and although adjusting for paternal smoking did not eliminate age-varying associations between maternal smoking during pregnancy and BMI *z*-scores, residual confounding cannot be ruled out as an alternative explanation for our findings.

Conclusion

Given combined data from two longitudinal cohort study populations, we estimated higher mean and median BMI *z*-scores in the children of mothers who smoked during pregnancy compared with other children, with significant differences emerging at 4–6 years of age and increasing over time. Whether this is a reflection of an epigenetic priming mechanism accounting for progressively increasing effects or residual confounding by an incremental unknown exposure remains unclear.

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Supplemental Material

Differences in BMI *z*-Scores between Offspring of Smoking and Nonsmoking Mothers: A Longitudinal Study of German Children from Birth through 14 Years of Age

Christina Riedel, Nora Fenske, Manfred J. Müller, Sandra Plachta-Danielzik, Thomas Keil, Linus Grabenhenrich, and Rüdiger von Kries

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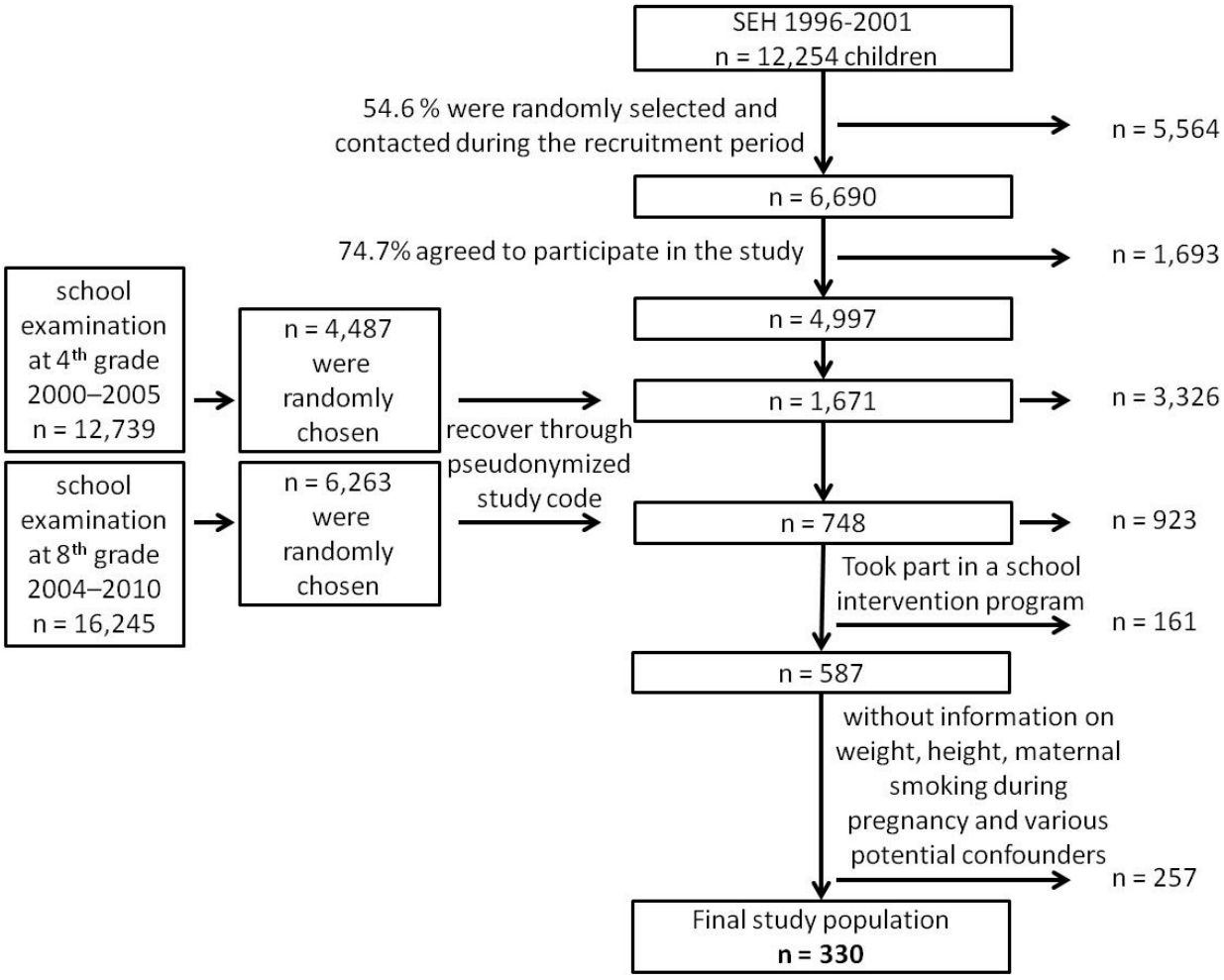

Figure S1: Flow chart of sample size of KOPS.

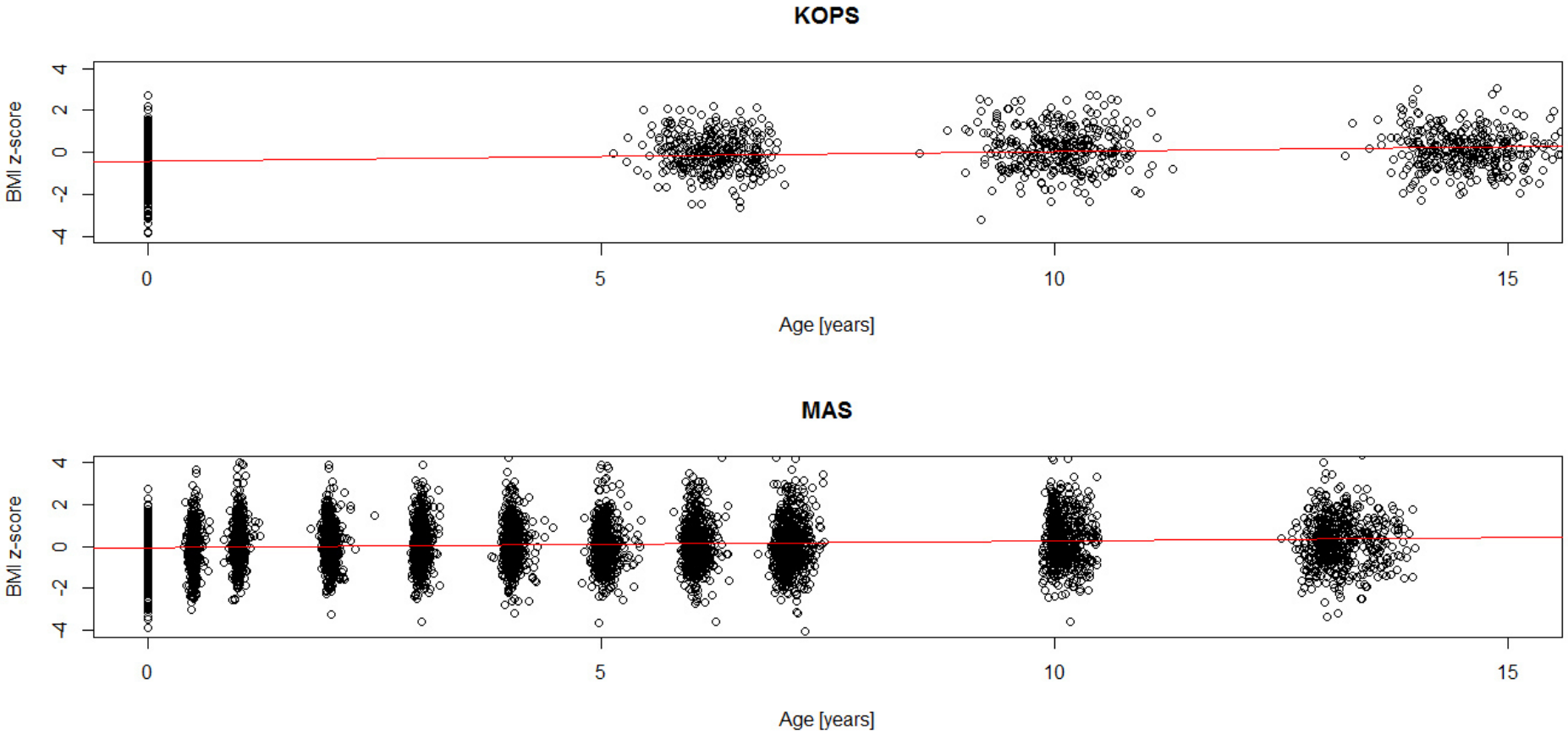

Figure S2: Distribution of BMI *z*-score values of both cohorts. The red line presents the linear regression estimation for BMI *z*-score and age.

Table S1: P-values and t-values of interaction of all variables of the full model and the study variable.

Interaction variables	**t-value**	**p-value**
Gender = male & study = MAS	0.128	0.898
Maternal weight status = overweight & study = MAS	0.002	0.998
Maternal weight status = obese & study = MAS	-0.323	0.746
Maximal maternal education = ≤ 9 years of school education & study = MAS	-0.415	0.678
Maximal maternal education = 10-12 years of school education & study = MAS	-1.539	0.124
Large for gestational age & study = MAS	-0.313	0.754
Small for gestational age & study = MAS	2.765	0.006
Breastfeeding & study = MAS	1.296	0.195
Preterm delivery & study = MAS	3.121	0.002
Paternal smoking & study = MAS	-0.649	0.516

Table S2: Estimated effects (Best estimate (95% CI)) and mean (95% CI)) for the age-varying effects of maternal smoking during pregnancy at the ages of 0, 2.5, 5, 7.5, 10, 12.5 and 14 years with quantile regression for the 10th, 25th 50th, 75th and 90th BMI *z*-score quantiles and mean regression for mean BMI *z*-score.

Model	**0 years**	**2.5 years**	**5 years**	**7.5 years**	**10 years**	**12.5 years**	**14 years**
10th quantile							
boys	0.12 (0.06,0.20)	0.12 (0.06,0.20)	0.12 (0.06,0.20)	0.12 (0.06,0.20)	0.12 (0.06,0.20)	0.12 (0.06,0.20)	0.12 (0.05,0.20)
girls	-0.06 (-0.16,0.10)	0.12 (-0.06,0.20)	0.17 (-0.03,0.25)	0.18 (-0.02,0.25)	0.18 (-0.01,0.25)	0.22 (0.00,0.31)	0.27 (0.00,0.36)
25th quantile							
boys	0.10 (0.02,0.12)	0.11 (0.03,0.15)	0.11 (0.03,0.18)	0.12 (0.03,0.19)	0.12 (0.03,0.19)	0.11 (0.03,0.17)	0.11 (0.03,0.16)
girls	-0.03 (-0.12,0.05)	0.08 (-0.03,0.15)	0.10 (-0.01,0.18)	0.10 (-0.02,0.16)	0.08 (-0.03,0.14)	0.10 (-0.02,0.16)	0.12 (-0.01,0.20)
50th quantile							
boys	-0.06 (-0.14,0.03)	0.01 (-0.06,0.09)	0.08 (-0.01,0.16)	0.16 (0.01,0.25)	0.15 (0.01,0.27)	0.16 (0.01,0.28)	0.15 (0.01,0.30)
girls	-0.06 (-0.17,0.03)	0.07 (-0.03,0.17)	0.12 (0.01,0.21)	0.21 (0.05,0.29)	0.30(0.07,0.41)	0.30 (0.08,0.39)	0.26 (0.08,0.35)
75th quantile							
boys	-0.05 (-0.15,0.02)	0.02 (-0.04,0.10)	0.06 (-0.01,0.14)	0.09 (0.00,0.23)	0.13 (0.01,0.30)	0.14 (0.01,0.32)	0.15 (0.01,0.32)
girls	0.06 (-0.07,0.12)	0.10 (0.02,0.18)	0.11 (0.02,0.20)	0.13 (0.03,0.24)	0.15 (0.04,0.32)	0.16 (0.04,0.35)	0.16 (0.04,0.37)
90th quantile							
boys	-0.14 (-0.25,0.00)	-0.03 (-0.11,0.07)	0.11 (-0.03,0.25)	0.27 (0.01,0.44)	0.35 (0.01,0.58)	0.33 (0.01,0.56)	0.27 (0.01,0.48)
girls	0.09 (-0.05,0.15)	0.11 (0.04,0.20)	0.12 (0.03,0.20)	0.13 (0.03,0.22)	0.15 (0.04,0.28)	0.17 (0.05,0.35)	0.19 (0.05,0.4)
mean							
boys	-0.06 (-0.26,0.14)	0.08 (-0.10,0.26)	0.25 (0.06,0.44)	0.38 (0.15,0.61)	0.40 (0.08,0.73)	0.38 (-0.06,0.83)	0.35 (-0.24,0.94)
girls	-0.06 (-0.23,0.11)	0.07 (-0.08,0.22)	0.18 (0.02,0.35)	0.28 (0.09,0.47)	0.36 (0.12,0.59)	0.42 (0.14,0.70)	0.47 (0.13,0.81)

Table S3: Mutually adjusted effects of the categorical potential confounders on the mean BMI *z*-score and BMI *z*-score quantiles obtained from the final models estimating the effect of maternal smoking during pregnancy (AMMs and AQMMs).

Variable	**Gender**	**Mean**	**10th quantile**	**25th quantile**	**50th quantile**	**75th quantile**	**90th quantile**
Maternal weight							
overweight	boys	-0.01 (-0.16,0.15)	0.03 (-0.15,0.19)	0.03 (-0.07,0.13)	0.01 (-0.03,0.06)	0.02 (-0.02,0.07)	0.02(-0.04,0.09)
obese	boys	0.01 (-0.23,0.26)	-0.10 (-0.40,0.14)	-0.04 (-0.27,0.14)	0.01(-0.16,0.18)	0.05 (-0.08,0.20)	0.06 (-0.05,0.22)
overweight	girls	0.13 (-0.03,0.28)	0.03 (-0.10,0.17)	0.01 (-0.11,0.10)	0.04 (-0.05,0.12)	0.08 (-0.01,0.16)	0.08 (-0.01,0.16)
obese	girls	0.06 (-0.19,0.31)	-0.18 (-0.69,0.26)	-0.09 (-0.49,0.30)	-0.02 (-0.35,0.29)	0.01 (-0.31,0.32)	0.03 (-0.22,0.25)
Maternal education							
≤ 9 years of school education	boys	0.08 (-0.08,0.23)	-0.10 (-0.22,0.01)	-0.05 (-0.12,0.02)	-0.02 (-0.08,0.04)	-0.01 (-0.06,0.05)	0.00(-0.05,0.05)
10-12 years of school education	boys	0.02 (-0.12,0.15)	-0.01 (-0.09,0.08)	0.00 (-0.07,0.08)	0.03 (0.00,0.08)	0.07 (0.02,0.13)	0.08 (0.02,0.17)
≤ 9 years of school education	girls	0.12 (-0.04,0.27)	0.01 (-0.16,0.19)	0.03 (-0.11,0.19)	0.04 (-0.05,0.15)	0.05 (-0.02,0.18)	0.05 (-0.01,0.14)
10-12 years of school education	girls	0.07 (-0.07,0.21)	-0.09 (-0.18,0.03)	-0.02 (-0.09,0.07)	0.03 (-0.03,0.11)	0.10 (0.04,0.16)	0.13 (0.04,0.22)
Gestational age							
small	boys	-0.49 (-0.68,-0.30)	0.00 (-0.07,0.07)	0.01 (-0.03,0.08)	0.02 (-0.02,0.08)	0.04 (-0.02,0.09)	0.06 (-0.02,0.17)
large	boys	0.73 (0.51,0.95)	-0.13 (-0.39,0.08)	-0.08 (-0.26,0.07)	-0.03 (-0.16,0.08)	0.01 (-0.10,0.09)	0.02 (-0.05,0.11)
small	girls	-0.69 (-0.87,-0.51)	0.03 (-0.11,0.15)	0.06 (-0.05,0.16)	0.10 (0.01,0.18)	0.14 (0.04,0.23)	0.14 (0.05,0.22)
large	girls	0.64 (0.43,0.86)	-0.25 (-0.67,0.09)	-0.14 (-0.45,0.14)	-0.08 (-0.32,0.13)	-0.07 (-0.30,0.13)	-0.03 (-0.19,0.12)
Breastfeeding							
no	boys	-0.05 (-0.27,0.17)	-0.05 (-0.13,0.02)	-0.03 (-0.08,0.02)	0.02 (-0.03,0.05)	0.05 (-0.01,0.13)	0.06 (-0.02,0.19)
no	girls	0.16 (-0.06,0.38)	0.00 (-0.17,0.17)	0.05 (-0.07,0.19)	0.05 (-0.03,0.15)	0.10 (0.05,0.17)	0.14 (0.04,0.23)
Preterm delivery							
yes	boys	-0.66 (-1.02,-0.30)	-0.01 (-0.08,0.06)	0.02 (-0.03,0.08)	0.02 (-0.03,0.09)	0.03 (-0.02,0.11)	0.05 (-0.01,0.14)
yes	girls	-0.58 (-0.92,-0.25)	0.01 (-0.15,0.14)	0.05 (-0.07,0.16)	0.08 (0.00,0.18)	0.13 (0.04,0.21)	0.12 (0.05,0.21)
Paternal smoking							
yes	boys	-0.02 (-0.16,0.12)	-0.11 (-0.22,-0.03)	-0.05 (-0.13,0.01)	-0.02 (-0.09,0.02)	-0.01 (-0.07,0.04)	-0.01 (-0.07,0.05)
yes	girls	0.01 (-0.12,0.14)	-0.07 (-0.18,0.05)	-0.05 (-0.15,0.05)	0.00 (-0.07,0.07)	0.04 (-0.02,0.13)	0.05 (0.00,0.13)

Table S4: Univariate and multivariate effect estimates β (95%CI) of the potential confounders only available in either MAS (early adiposity rebound, weight gain during the first two years of life) or KOPS (TV consumption, physical activity) on the mean BMI *z*-score.

Variable	**Univariate**	**Multivariate**
TV consumption, >1 hour		
boys	0.35 (0.08,0.63)	0.35[a] (0.07,0.64)
girls	0.45 (0.23,0.68)	0.43[a] (0.20,0.66)
Physical activity in a sports club, ≤2 hour		
boys	0.13 (-0.16,0.41)	0.10[b] (-0.18,0.38)
girls	-0.21 (-0.46,0.04)	-0.20[b] (-0.43,0.04)
Early adiposity rebound		
boys	0.20 (0.03,0.36)	0.09[c] (-0.05,0.24)
girls	0.11 (-0.08,0.30)	0.02[c] (-0.13,0.18)
Weight gain during the first year of life		
boys	0.22 (0.19,0.25)	0.21[d] (0.17,0.24)
girls	0.21 (0.18,0.24)	0.21[d] (0.17,0.24)

[a]Adjusted by the interaction term of maternal smoking during pregnancy and age and by physical activity in a sports club. [b]Adjusted by the interaction term of maternal smoking during pregnancy and age and by TV consumption. [c]Adjusted by the interaction term of maternal smoking during pregnancy and age and by weight gain during the first year of life. [d]Adjusted by the interaction term of maternal smoking during pregnancy and age and by early adiposity rebound.

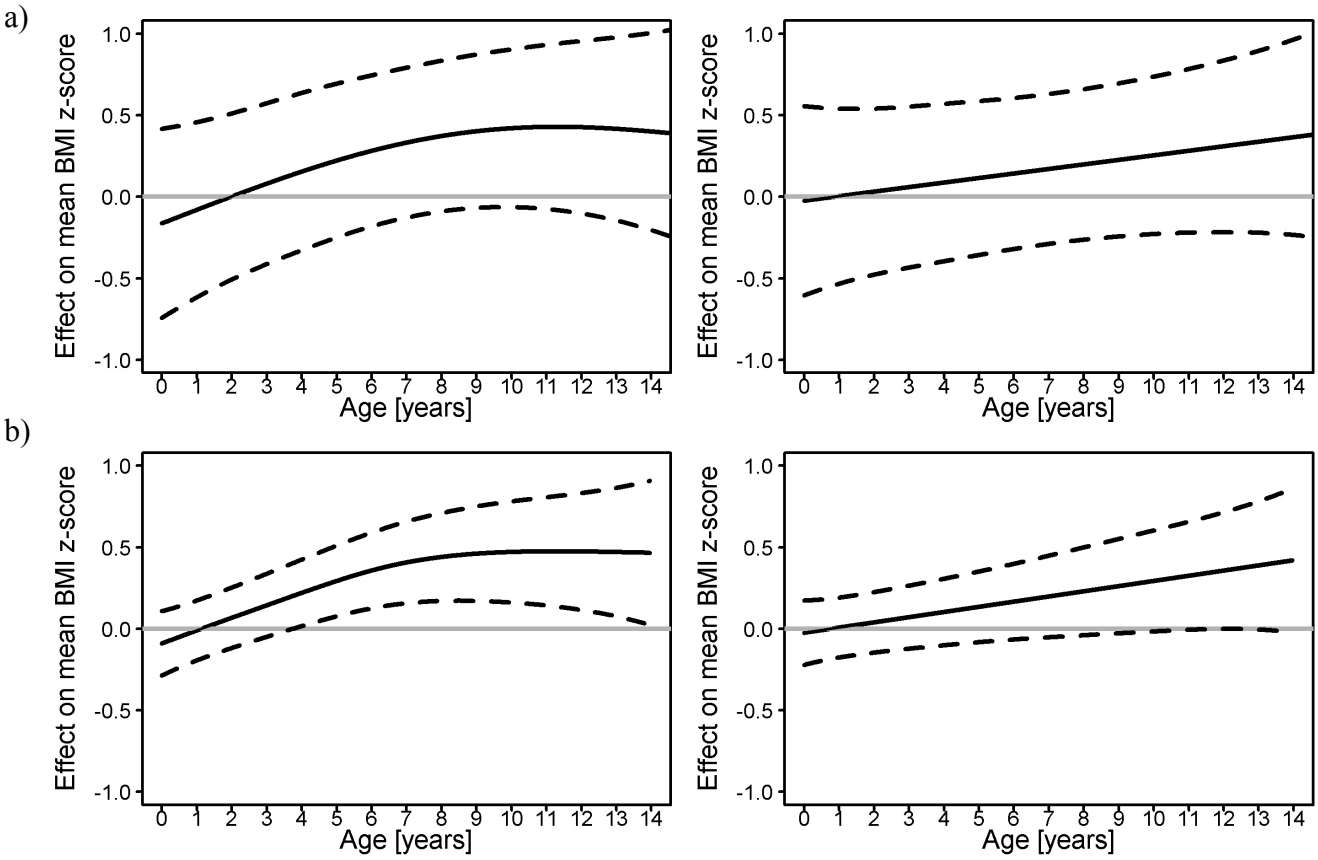

Figure S3: Age-varying effect of maternal smoking during pregnancy (black lines) compared to non-smoking mothers during pregnancy (grey horizontal line at zero) for boys (left panel) and girls (right panel) adjusted by a) TV consumption and physical activity in a sports club (KOPS n = 107 boys and 132 girls) and b) early adiposity rebound and weight gain during the first year of life (MAS n = 351 boys and 299 girls) resulting for mean BMI *z*-score values from the additive mixed model. The black lines show the estimated effect and the dashed lines the 95% CI.

Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking - a meta-analysis

Authors: Christina Riedel

Katharina Schönberger

Seungmi Yang

Gibby Koshy

Yang-Ching Chen

Stephanie Ziebarth

Rüdiger von Kries

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Life-course epidemiology

Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking—a meta-analysis

Christina Riedel,[1]* Katharina Schönberger,[1] Seungmi Yang,[2] Gibby Koshy,[3] Yang-Ching Chen,[4,5] Bamini Gopinath,[6] Stephanie Ziebarth[1] and Rüdiger von Kries[1]

[1]Ludwig Maximilian University of Munich, Institute of Social Paediatrics and Adolescent Medicine, Munich, Germany, [2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada, [3]Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, UK, [4]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan, [5]Department of Family Medicine, Taipei City Hospital, ZhongXing Branch, Taipei, Taiwan and [6]Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia

Corresponding author. Ludwig Maximilian University of Munich, Institute of Social Paediatrics and Adolescent Medicine, Division of Epidemiology, Haydnstr. 5, 80336 Munich, Germany. E-mail: christina.riedel@med.uni-muenchen.de

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Abstract

Background: Some studies reported similar effect estimates for the impact of maternal smoking in pregnancy and paternal smoking on childhood obesity, whereas others suggested higher effects for maternal smoking. We performed a meta-analysis to compare the effect of *in utero* exposure to maternal smoking and that of paternal or household smoking exposure *in utero* or after birth with mutual adjustment.

Methods: Meta-analysis of observational studies identified in MEDLINE, EMBASE and Web of Knowledge published in 1900–2013. Study inclusion criterion was assessment of the association of maternal smoking during pregnancy and paternal or household smoking (anyone living in the household who smokes) at any time with childhood overweight and obesity. The analyses were based on all studies with mutually adjusted effect estimates for maternal and paternal/household smoking applying a random-effects model.

Results: Data for 109 838 mother/child pairs were reported in 12 studies. The pooled odds ratios (ORs) for overweight 1.33 [95% confidence interval (CI) 1.23;1.44] ($n = 6$, $I^2 = 0.00\%$) and obesity 1.60 (95% CI 1.37;1.88) ($n = 4$, $I^2 = 32.47\%$) for maternal smoking during pregnancy were higher than for paternal smoking: 1.07 (95% CI 1.00;1.16) ($n = 6$, $I^2 = 41.34\%$) and 1.23 (95% CI 1.10;1.38) ($n = 4$, $I^2 = 14.61\%$), respectively. Similar estimates with widely overlapping confidence limits were found for maternal smoking during pregnancy and childhood overweight and obesity: 1.35 (95% CI 1.20;1.51) ($n = 3$,

$I^2 = 0.00\%$) and 1.28 (95% CI 1.07;1.54) ($n = 3$, $I^2 = 0.00\%$) compared with household smoking 1.22 (95% CI 1.06;1.39) ($n = 3$, $I^2 = 72.14\%$) and 1.31 (95% CI 1.15;1.50)] ($n = 3$, $I^2 = 0.00\%$).

Conclusions: Higher effect estimates for maternal smoking in pregnancy compared with paternal smoking in mutually adjusted models may suggest a direct intrauterine effect.

Key words: Maternal smoking, paternal smoking, household smoking, obesity, overweight, meta-analysis

Key Messages

- Maternal smoking during pregnancy is associated with overweight and obesity in the offspring.
- The effect estimates of maternal smoking during pregnancy on childhood overweight and obesity are higher than the effect estimates of paternal smoking any time.
- The observed differences in the effect estimates of maternal and paternal smoking may suggest an intrauterine effect of maternal smoking in pregnancy.

Introduction

A positive association between maternal smoking in pregnancy and having children who are overweight or have higher body mass index (BMI) values was confirmed in a number of meta-analyses[1–3] of observational studies. Nicotine traveres the placenta and the duration of the exposure in the fetus is longer than in the mother due to slower nicotine metabolism in the fetus.[4] A number of randomized animal studies reported higher weight gain in rats with intrauterine nicotine exposure.[5–7] The biological mechanism accounting for weight gain related to intrauterine nicotine exposure is, however, yet to be understood.[8]

Causal inference on the association between intrauterine exposure to nicotine and childhood overweight however, has been questioned because of potential residual confounding.[9,10] Major concerns regarding possible residual confounding were based on the observationthat children who were exposed to paternal or household smoking *in utero* or in infancy also had an increased risk of being overweight, and that this risk was similar in magnitude to that of children with intrauterine exposure to maternal smoking.[11–14] Larger effect estimates would be anticipated for maternal smoking in pregnancy than for paternal smoking with regard to the higher fetal nicotine exposure.[15]

Studies of the effect of paternal/household smoking on childhood overweight reported inconsistent results: some studies found no association between paternal or household smoking and childhood overweight[16,17] whereas other studies observed positive associations.[11,18,19] These equivocal findings point to the need for a meta-analysis to assess and compare the strength of mutually adjusted associations of maternal smoking in pregnancy and paternal/household smoking on childhood overweight.

In the present study, we conducted a meta-analysis to estimate and compare effects of maternal smoking in pregnancy with effects of paternal and household (anyone living in the household who smokes) smoking at any time on childhood overweight and obesity by a meta-analysis of studies that mutually adjusted for maternal and paternal/household smoking. The reason for selecting studies that used mutually adjusted maternal and paternal smoking was to allow for better (or easier) comparisons: since the maternal effect needs to be adjusted for paternal smoking, the effect of paternal smoking also needs to be adjusted for maternal smoking.

Methods

Search strategy

Studies were identified through searches of the three databases MEDLINE (1950–December 2013), EMBASE (1974–December 2013) and Web of Knowledge (1900–December 2013) by the following search terms: (offspring or children or toddlers or child or infant or adolescent* or adult*) AND (overweight or obesity or obese or adipose or adiposity or BMI) AND (smoke* or nicotine or 'second-hand smoke' or 'second-hand smoking' or 'household smoke' or 'household smoking' or cigarette* or fume or tobacco) AND (parents or parental or prenatal or (paternal and maternal) or (father and mother) or

'second-hand' or household). We also performed manual searches of cited references of electronically identified articles to further identify all relevant studies.

Data extraction

All search hits were exported to EndnoteX7, which was used to organize the references and eliminate duplicates. Two (C.R. and K.S.) of us independently assessed titles and abstracts by manual scrutiny according to the inclusion criteria: any study published in English if reporting odds ratios (ORs) / BMI differences / BMI z-score differences for maternal smoking during pregnancy and paternal / household smoking at any time on excess weight or obesity or BMI in their offspring. Disagreement regarding the relevance of specific articles prompted a second review of the titles and abstracts and was resolved by consensus. Additional inclusion criteria applied in the full text analyses as follows.

- No evident over-adjustment of parental smoking: Studies were considered as over-adjusted if the OR or BMI increment for maternal smoking during pregnancy and/or paternal/household smoking were not only mutually adjusted but further adjusted for maternal smoking before or after pregnancy or paternal/household smoking at different additional time points.
- Duplicate publication of the same cohort (the most recent publication meeting the inclusion criteria was used).

All studies with mutual adjustment for maternal and paternal/household smoking were included. For studies reporting associations between both maternal smoking during pregnancy and paternal/household smoking and childhood overweight/obesity without mutual adjustment for maternal smoking during pregnancy and paternal/household smoking, the corresponding author was contacted to provide mutually adjusted estimates.

Quality assessment

Quality assessment was based on AHRQ (Agency for Healthcare Research and Quality) quality assessment criteria for observational studies and was supplemented by specific criteria related to our research question. The included studies were evaluated as high quality if the study population was clearly described or if information about the study population was available elsewhere (in another article), the losses to follow-up were $\leq$20%, all anthropometric data were measured by investigators, maternal, paternal or household smoking was assessed close to the time of smoking or later, parental smoking status was measured based on cotinine and the effect estimates were at least adjusted for maternal obesity/BMI at any time and parental education, two important confounders of the effect of maternal smoking during pregnancy.[20–22] To be considered of high quality, studies could only be deficient in up to two of these criteria and to be considered of moderate quality in four of these criteria.

Statistical analyses

For meta-analyses we used ORs for overweight (including obesity) and/or obesity associated with exposure to maternal smoking during pregnancy and paternal smoking at any time or ORs for overweight (including obesity) and/or obesity associated with maternal smoking during pregnancy and any household smoking (father, mother or other) exposure at any time. For BMI differences, only two studies provided data. Regarding BMI z-score difference, there was only one study providing information on two birth cohorts. Pooled ORs were estimated using random-effects as defined by DerSimonian and Laird.[23] This method is based on the inverse-variance approach, making an adjustment to the study weights according to the extent of variation, or heterogeneity.[24] Heterogeneity between the studies was estimated by Higgins' I^2 that describes the percentage of total variation across studies due to heterogeneity rather than chance (categorization: 25% low, 50% moderate, 75% high heterogeneity).[25] We have assessed to what extent potentially important study-level covariates such as age, classifications of overweight or obesity, prevalence of maternal or paternal/household smoking and time of assessment of maternal or paternal/household smoking, account for the heterogeneity in mixed effect models by comparing the amount of heterogeneity in the random-effects and mixed-effect models.[26] We used funnel plots to detect potential publication bias[27] and tested the hypothesis that the number of missing studies is zero by a method introduced by Duval and Tweedie.[24,26] We performed several sensitivity analyses: (i) excluding studies with a higher risk of bias because of insufficient adjustment for established confounders; (ii) excluding studies that did not adjust for birthweight; (iii3) excluding studies without high quality; (iv) excluding studies with ages <5 years; (v) including studies with potential over-adjustment. All analyses were carried out with the statistical software R[28] and the add-on package *metafor*.[26]

Results

Electronic search yielded 2578 results. After title and abstract scan we excluded 2558 studies that did not assess both maternal smoking during pregnancy and paternal or household smoking and offspring's overweight or obesity

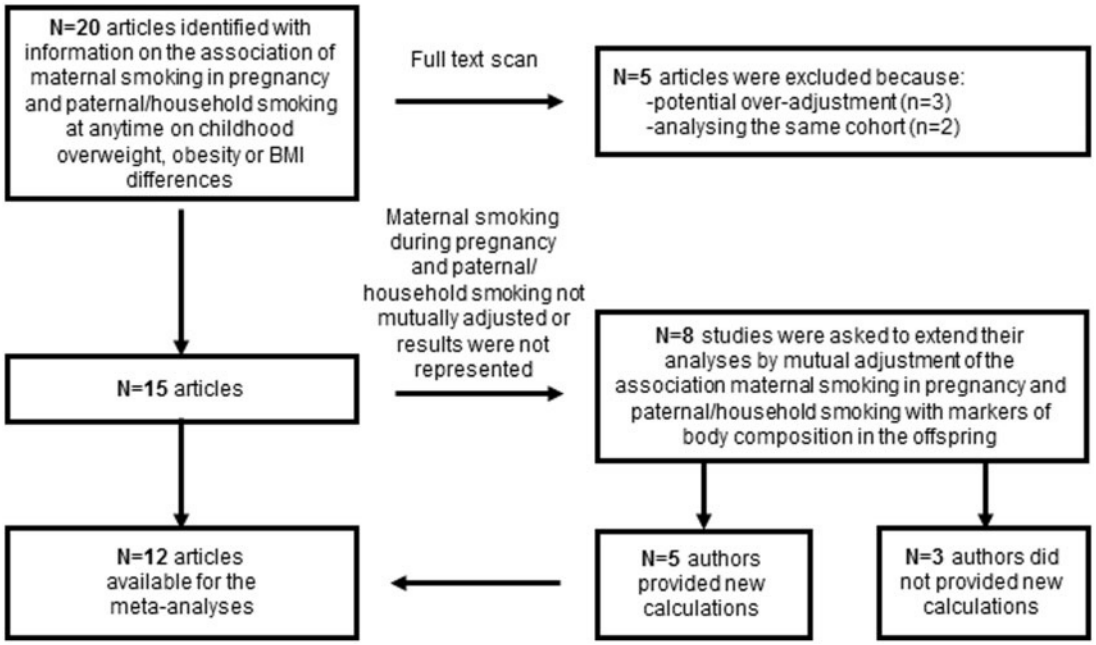

Figure 1. Flow chart of data sourcing and selection.

later in life. The full texts of the remaining 20 articles were reviewed and 5 studies were excluded for various reasons (see Figure 1). Eight articles reported the effect of maternal smoking during pregnancy and paternal/household smoking but did not adjust these factors mutually. The authors of these studies were contacted to supplement their analyses with mutually adjusted estimates (see Supplementary Table 1, available as Supplementary data at *IJE* online). From these studies, five authors (G.K.,[17] S.Y.,[29] Y.C.C.,[18] B.G.,[30] and R.v.K.[19]) provided unpublished additional data. In total, we included 12 studies in our meta-analysis.[11,12,14,17,18,19,29–34]

Study characteristics

Table 1 shows the characteristics of the included studies.

The studies were published between 2008 and 2013 in children from Taiwan, Australia, the USA, The Netherlands, the UK, Germany, Brazil, Finland and Belarus. Five of these were cross-sectional,[12,17,18,19,30], six were cohort studies[11,29,31–34] and one study pooled four population-based studies.[14] The age varied between 3 and 18 years. Ten studies[11,12,14,17,18,19,29–31,34] reported adjusted OR for childhood overweight (including obesity) and/or obesity. Definition of overweight/obesity varied across studies. Five studies[12,19,30,31,34] used the international cut-off values from the International Obesity Task Force (IOTF).[35] Another three studies [17,18,29] defined overweight (including obesity) and obesity as exceeding the 85th and 95th age-specific BMI percentiles, respectively based on the World Health Organization (WHO) cut-off values[36] or the United States Centers for Disease Control and Prevention (CDC) cut-off values.[37] One study[14] reported only overweight (including obesity) as outcome as defined by exceeding the 90th BMI percentile of the German cut-off values.[38] Two studies[29,32] reported BMI differences between offspring of smoking and non-smoking mothers and one reported BMI z-score differences analysing two different cohorts.[33] In eight studies[11,17,19,29,31–34] we could measure the effect of maternal smoking during pregnancy and compare with that of paternal smoking at any time, and in four studies[12,14,18,30] we could compare with that of household smoking at any time. The earliest years of birth were 1945–64[11] the latest 2002–06.[31] The prevalence of maternal smoking during pregnancy varied from 2.1%[29] to 33.5%,[33] the prevalence of paternal smoking from 20.5%[19] to 61%[29] and for household smoking from 23.3%[30] to 51.7%.[12]

Table 2 presents study quality assessment for each of the 12 studies included in our meta-analysis.

All studies described their study population in detail. Three[29,31,34] of the six[11,29,31–34] longitudinal studies had losses to follow-up ≤20%, and in three[11,32,33] studies this information was not reported. In all but one study,[11] the anthropometric data were objectively measured by investigators. The main study variables—maternal smoking during pregnancy and paternal/household smoking—were proxy-reported by mother or father in four studies,[12,29,30,32] reported by mother in three studies[11,31,33] and assessment was not clearly described in five

Table 1. Characteristics of the included studies

Author(s)	Year	Type of study	Size of study population	Age in years used in the meta-analyses	Country of study	Definition of outcome and respective BMI percentile cut-off	Reference percentile	Exposure and prevalence of maternal smoking	Exposure and prevalence of paternal smoking	Exposure and prevalence of household smoking	Year of birth (cohort studies) or study enrolment (cross-sectional studies)
Chen *et al.*[18]	2012	Cross-sectional study	7930	9–14	Taiwan	Overweight (incl. obesity): 85th percentile, obesity: 95th percentile	WHO	Any smoking during pregnancy 25% (198)	–	Any current smoking (father, mother or other family members) in the child's house at 12-year interview 29.3% (2396)	2007 and 2010[a]
Gopinath *et al.*[30]	2012	Cross-sectional study	2353	12	Australia	Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m^2 at age 18	IOTF	Any smoking during pregnancy 15.0% (319)	–	Any current smoking (father, mother or other family members) in the child's house at 12-year interview 23.3% (512)	2004–05
Harris *et al.*[11]	2013	Cohort study	35 370	18	USA	Overweight (incl. obesity): BMI >25 kg/m^2, obesity: BMI >30 kg/m^2	–	Smoking 1–14 (light), 15–24 (moderate) and 25+ (heavy) cigarettes/day during pregnancy 26.0% (8944)[b]	Smoking 1–14 (light), 15–24 (moderate), and 25+ (heavy) cigarettes/day during pregnancy 58.8% (19 943)[c]	–	1945–64 (years of birth) 1989 study enrolment

(Continued)

Table 1. Continued

Author(s)	Year	Type of study	Size of study population	Age in years used in the meta-analyses	Country of study	Definition of outcome and respective BMI percentile cut-off	Reference percentile	Exposure and prevalence of maternal smoking	Exposure and prevalence of paternal smoking	Exposure and prevalence of household smoking	Year of birth (cohort studies) or study enrolment (cross-sectional studies)
Heppe *et al.*[31]	2012	Birth cohort study	3610	4	Netherlands	Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m^2 at age 18	IOTF	Any smoking during pregnancy 23.0% (829)	Any smoking during pregnancy 38.0% (1371)	–	2002–06
Howe *et al.*[32]	2012	Birth cohort study	8887	10	UK	BMI-difference	–	Any smoking during pregnancy 20.5% (1824)	Any smoking during pregnancy 36.1% (3209)	–	1991
Kleiser *et al.*[12]	2009	Cross-sectional study	10 021	3–17	Germany	Obesity: extrapolated from adult BMI of 30 kg/m^2 at age 18	IOTF	Any smoking during pregnancy 17.5% (2273)[d]	–	Any current smoking (mother, father) at interview 51.7% (6796)[d]	2003–06
Koshy *et al.*[17]	2011	Cross-sectional study	3038	5–11	UK	Overweight (incl. obesity): 85th percentile, obesity: 95th percentile	WHO	Any smoking during pregnancy 30.3% (991)[d]	Any smoking during pregnancy 42.5% (875)[d]	–	1998 and 2006
Matijasevich *et al.*[33]	2011	Birth cohort study	1450 (1993 cohort) 3799 (2004 cohort)	4	Brazil	BMI z-score[g] difference	WHO	Any smoking during pregnancy 33.5% (1993 cohort) 28.0% (2004 cohort)[e]	Any smoking during pregnancy 44.8% (1993 cohort) 31.0% (2004 cohort)[e]	–	1993 and 2004
Pirkola *et al.*[34]	2010	Birth cohort study	4168	16	Finland	Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m^2 at age 18, obesity: extrapolated from adult BMI of 30 kg/m^2 at age 18	IOTF	Any smoking during pregnancy 11.4–18.3%[f]	Any smoking during pregnancy 31.2–42.9%[f]	–	1986

(Continued)

Table 1. Continued

Author(s)	Year	Type of study	Size of study population	Age in years used in the meta-analyses	Country of study	Definition of outcome and respective BMI percentile cut-off	Reference percentile	Exposure and prevalence of maternal smoking	Exposure and prevalence of paternal smoking	Exposure and prevalence of household smoking	Year of birth (cohort studies) or study enrolment (cross-sectional studies)
Plachta-Danielzik *et al.*[14]	2012	4 population-based studies (cross-sectional and birth cohort studies)	11 121	3–18	Germany	Overweight (incl. obesity): 90th percentile	KH	Any smoking during pregnancy 15.1% (1679)	–	Any current smoking (at least 1 parent smokes) at interview 47.8% (5316)	1996–2008
von Kries *et al.*[19]	2008	Cross-sectional study	5899	5–7	Germany	Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m^2 at age 18, obesity: extrapolated from adult BMI of 30 kg/m^2 at age 18	IOTF	Any smoking during pregnancy 20.9% (1230)	Any current smoking at interview 20.5% (1211)	–	2005 school entrance health examinations
Yang *et al.*[29]	2013	Birth cohort study	12 192	6.5	Belarusian	Overweight (incl. obesity): 85th percentile, BMI-difference	CDC	Any smoking during and after pregnancy 2.1% (292)	Any current smoking at 6.5-year interview 61% (6724)	–	1996–97

CDC, United States Centers for Disease Control and prevention; IOTF, International Obesity Task Force; KH, Kromeyer-Hauschild; WHO, World Health Organization.

[a]1st cohort: seventh- to eighth-grade children, enrolled in 2007; 2nd cohort: forth-grade children enrolled in 2010.

[b]Of 34 413 including those who quit smoking during pregnancy ($n = 1385$).

[c]Of 33 894.

[d]% of total population including missing values for outcome, exposure variable and other confounders.

[e]Data only available depending on group [gestational diabetes mellitus (normal weight, overweight), oral glucose tolerance test normal (normal weight, overweight), control].

[f]% of origin population at birth (5304 and 4287 births in the 1993 and 2004 cohorts, respectively).

[g]BMI-for-age z-scores according to the growth curves published by WHO in 2006.

-Not applicable.

Table 2. Quality of the included studies

Study	Population		Data collection / Outcome					Method
	Clearly describes study population?	Losses of follow-up	Outcome assessment (weight and height)	Method of assessment of exposure data (interview, questionnaire)	Smoking status defined from measured cotinine level, self report or proxy report	Time of reporting of maternal smoking during pregnancy	Time of reporting of paternal/household smoking during pregnancy/at interview	Adjusted for main potential confounders (maternal obesity/BMI and parental education)?
Chen *et al.*[18]	Yes	NA	Measured (recorded during school visits)	Questionnaire	Not clear[a]	At a later time	Contemporary	No[b]
Gopinath *et al.*[30]	Yes	NA	Measured	Questionnaire	Self-reported by mother and/or father	At a later time	Contemporary	No[b,c]
Harris *et al.*[11]	Yes	Not reported[d]	Reported	Questionnaire	Reported by mother only	At a later time	At a later time	Yes
Heppe *et al.*[31]	Yes	15%	Measured at the research centre	Questionnaire	Reported by mother only	Contemporary	Contemporary	Yes
Howe *et al.*[32]	Yes	Not reported	Measured in clinics	Questionnaire	Self-reported by mother and father	Contemporary	Contemporary	Yes
Kleiser *et al.*[12]	Yes	NA	Measured by trained staff	Interview	Self-reported by mother and/or father	At a later time	Contemporary	Yes
Koshy *et al.*[17]	Yes	NA	Measured	Questionnaire	Not clear[a]	At a later time	At a later time	No[b]
Matijasevich *et al.* [33]	Yes	Not reported (1993 cohort) and 11.4% (2004 cohort)	Measured by trained interviewers	Interview	Reported by mother only	Contemporary	Contemporary	Yes
Pirkola *et al.*[34]	Yes	20%	Measured by trained nurses	Questionnaire	Not clear[a]	Contemporary	Contemporary	No[c]
Plachta-Danielzik *et al.*[14]	Yes	NA	Measured	Not described	Not described	At a later time	Contemporary	Yes
von Kries *et al.*[19]	Yes	NA	Measured by public health nurses	Questionnaire	Not clear[a]	At a later time	Contemporary	Yes
Yang *et al.*[29]	Yes	18.8%	Measured by polyclinic pediatricians	Interview	Usually reported by mother	Contemporary	Contemporary	Yes

NA, not applicable.

[a]The questionnaire was distributed to parents by class teachers[17] or was sent by post.[18,34]

[b]Did not adjust for maternal obesity/BMI.

[c]Did not adjust for parental education.

[d]The Nurses' Health Study II was established in 1989: 116 430 female nurses participated. In 2001, mothers of these nurses were asked to complete a questionnaire regarding their daughter. Information on pregnancy and early-life exposure were obtained for 35 794 participants with a response rate of 76.5%.[11]

studies.[14,17,18,19,34] Five studies[29,31–34] assessed maternal smoking during pregnancy or after delivery and seven[11,12,14,17,18,19,30] at a later time in childhood. Ten studies[12,14,18,19,29–34] assessed paternal/household smoking at interview and two studies by recall of earlier smoking[11,17] at a later time. Eight studies[11,12,14,19,29,31–33] adjusted for both maternal obesity/BMI and parental education, and four studies[17,18,30,34] did so only for one[17,18,34] or none[30] of these factors.

Maternal smoking during pregnancy vs paternal smoking at any time

For childhood overweight and/or obesity, pooled ORs were greater for maternal smoking during pregnancy (vs no maternal smoking during pregnancy) than those for paternal smoking (vs no paternal smoking) (Figure 2a). Children of mothers who smoked during pregnancy had an increased risk of overweight and obesity later in life with a pooled OR of 1.33 (95% CI 1.23;1.44) and 1.60 (95% CI 1.37;1.88), respectively. Compared with effect sizes associated with maternal smoking during pregnancy, the magnitude of associations with paternal smoking was lower [pooled OR 1.07 (95% CI 1.00;1.16) for overweight and pooled OR 1.23 (95% CI 1.10;1.38) for obesity]. Low to moderate heterogeneity was suggested by the Higgins I^2 in all models. Mean BMI differences yielded similar magnitudes of the strength of the associations for maternal [0.14 (95 %CI −0.17;0.46)] and paternal smoking [0.15 (95% CI 0.13;0.26)] with a high heterogeneity of 84.11% (Figure 2b). There was only one study reporting the impact of maternal and paternal smoking on BMI z-scores for two cohorts followed up to the age of 4 years and yielding higher pooled effect estimates for maternal smoking during pregnancy compared with paternal smoking during pregnancy.

The funnel plots did not suggest selective reporting of studies with high effect sizes (see Figures S1 and S2, available as Supplementary data at *IJE* online).

Maternal smoking during pregnancy vs household smoking anytime

Comparing the effect estimates for maternal smoking in pregnancy (vs no maternal smoking during pregnancy) and household smoking any time (vs no household smoking any time) yielded similar effect estimates with widely overlapping confidence limits (Figure 3): 1.35 (95% CI 1.20;1.51) and 1.22 (95% CI 1.06;1.39) for overweight and 1.28 (95% CI 1.07;1.54) and 1.31 (95% CI 1.15;1.50) and for obesity. High heterogeneity was estimated for 'anytime household smoking' and overweight. The funnel plots did not indicate evident publication bias (Figure S3, available as Supplementary data at *IJE* online).

Sensitivity analyses

For paternal smoking, four sensitivity analyses were performed. One excluded studies with failure to adjust for maternal obesity and maternal/paternal education.[17,34] Higher effect estimates for maternal smoking in pregnancy compared with paternal smoking were confirmed (Figure S4, available as Supplementary data at *IJE* online). Excluding studies that did not adjust for birthweight[29,32,33] in the second sensitivity analysis or studies with ages of children <5 years[31] in the third sensitivity analysis yielded identical results (Figures S5 and S6, available as Supplementary data at *IJE* online). The last sensitivity analysis excluded studies with moderate or poor quality.[11,17] Restriction to studies with high quality did not reverse higher effect estimates for maternal smoking in pregnancy compared with paternal smoking although the 95% CIs for maternal smoking in pregnancy and paternal smoking were no longer disjunctive (Figure S7, available as Supplementary data at *IJE* online).

For household smoking, two sensitivity analyses were performed. Restriction to high quality studies[12,14,30] yielded almost identical results as did inclusion of studies with potential over-adjustment[39–41] for smoking at different time points (Figures S8 and S9, available as Supplementary data at *IJE* online).

Discussion

In studies with mutual adjustment for maternal smoking in pregnancy and paternal smoking any time, higher effect estimates for childhood overweight or obesity were observed for maternal smoking in pregnancy, whereas the effect estimates appear similar for maternal smoking in pregnancy and household smoking. Regarding BMI and BMI z-scores, the differences between maternal and paternal smoking were inconsistent. To our knowledge, this is the first meta-analysis comparing the effects of maternal smoking during pregnancy and paternal/household smoking on childhood overweight and obesity with mutual adjustment.

The main objective of our meta-analyses is not to quantify the independent effects of maternal and paternal/household smoking on the risk of overweight or obesity in the offspring but to compare differences of their effect estimates as a negative control approach with paternal smoking acting as a negative control.[42,43] We therefore included different age levels, different classifications of obesity and different levels of smoking in the analyses if they applied both to maternal and paternal/household smoking.

The higher effect differences between maternal smoking during pregnancy and paternal smoking any time than for maternal smoking during pregnancy and household smoking anytime are likely to reflect that maternal and paternal

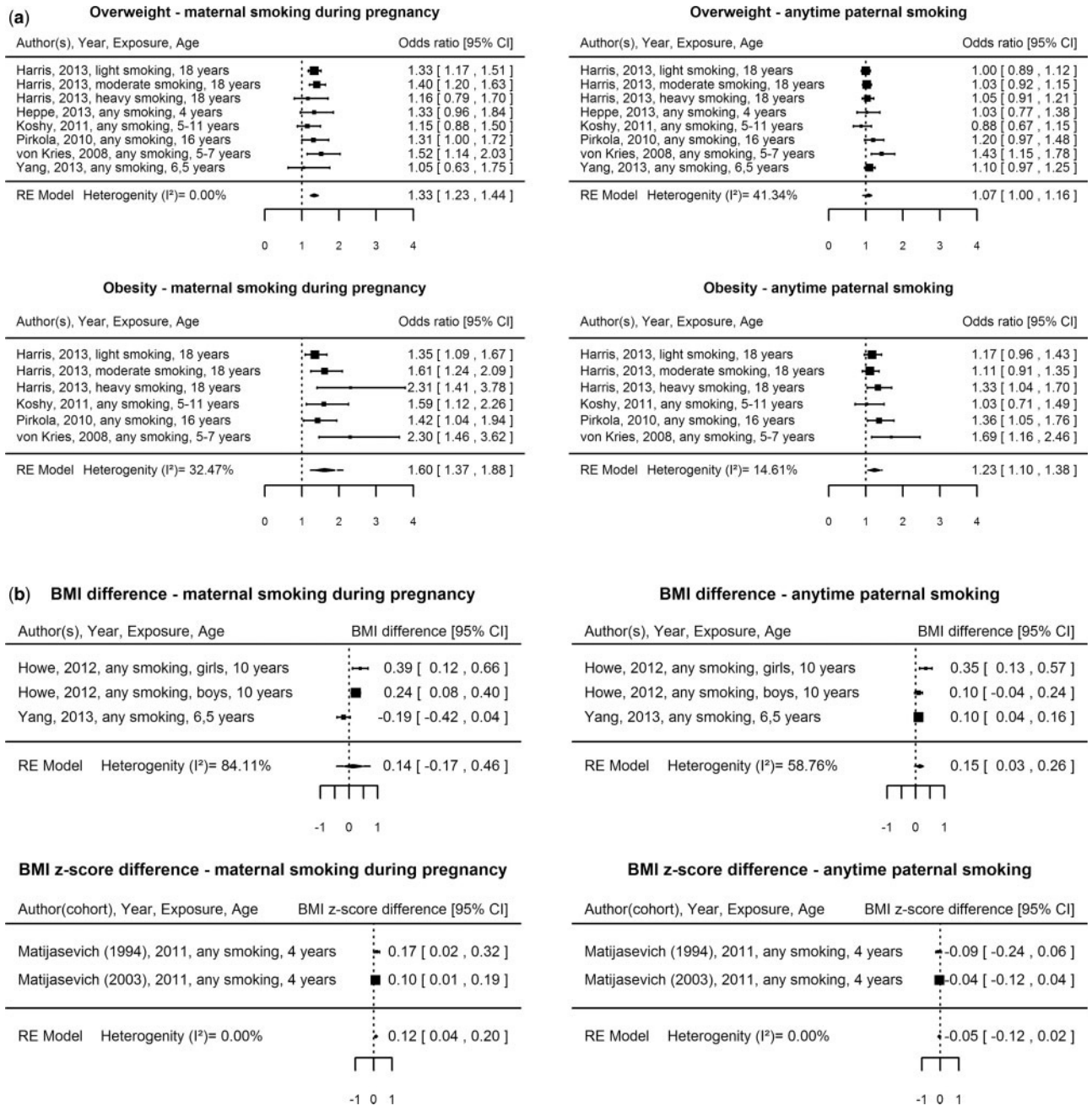

Figure 2. (a) Odds ratios in meta-analyses of association between maternal smoking during pregnancy (vs no maternal smoking during pregnancy) and paternal smoking any time (vs no paternal smoking any time) and overweight or obesity in childhood. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect. (b) Effects of maternal smoking during pregnancy (vs no maternal smoking during pregnancy) and paternal smoking any time (vs no paternal smoking any time) on childhood BMI differences (upper panel) and BMI z-score differences (lower panel) in children exposed and not exposed. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect in meta-analyses.

smoking can be clearly disentangled whereas postnatal maternal smoking is included in the case definitions for household smoking. Therefore similar effect estimates for maternal and household smoking appear plausible. The inconsistent differences between maternal and paternal smoking on BMI z-score and BMI may be a reflection of the small numbers of studies included.

Although the higher mutually adjusted effect estimates of maternal smoking in pregnancy than for paternal smoking provide a strong argument for a specific intrauterine

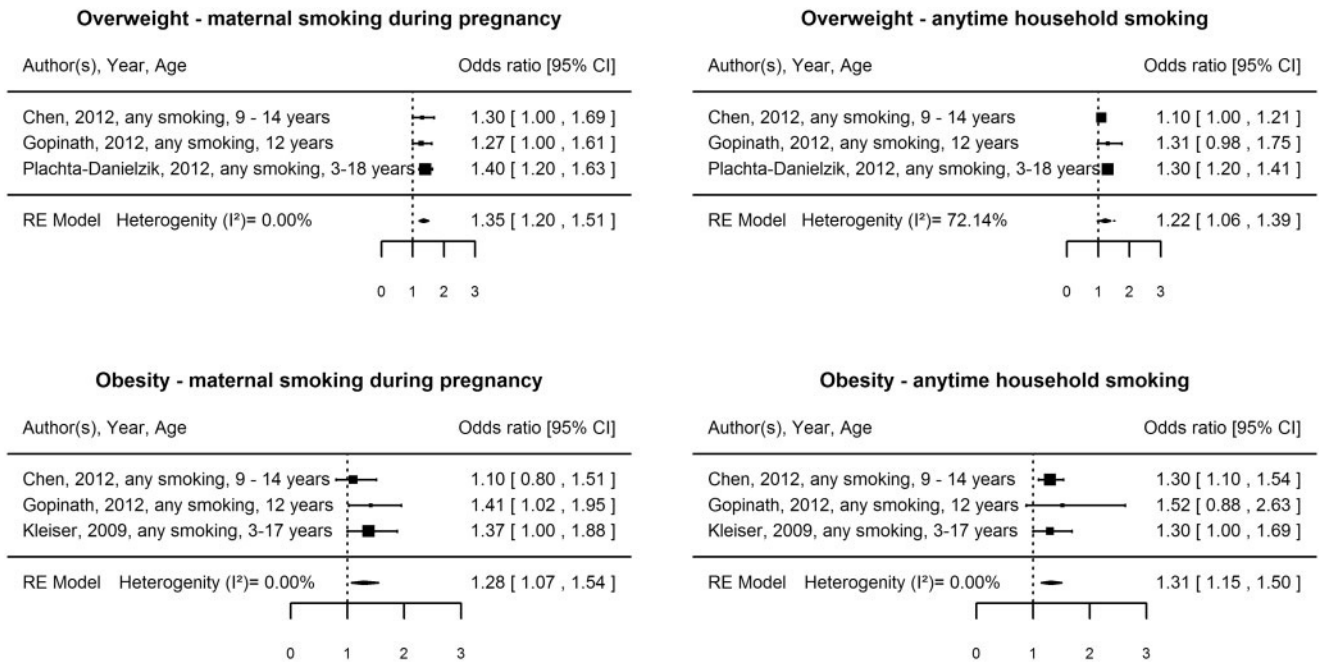

Figure 3. Odds ratios in meta-analyses of association between maternal smoking during pregnancy (vs no maternal smoking during pregnancy) and household smoking any time (vs no household smoking any time) and overweight or obesity in childhood. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

effect of maternal smoking, alternative explanations must be considered in face of the persistent effect of paternal smoking. The latter could be explained by: (i) uncontrolled, residual confounding of the association of both maternal smoking during pregnancy and paternal smoking and childhood overweight/obesity; (ii) a genuine effect of exposure to passive smoking in pregnancy; (iii) a genuine effect of postnatal smoking of father or mother.[43]

On item (i), some residual confounding is supported by a sibling study in 8445 women with two subsequent male births between 1983 and 1988 by Iliadou *et al.*[10] In the focus of this study were sibling pairs where one sibling was exposed to maternal smoking in pregnancy, whereas the other was not. In an analysis stratified by maternal smoking habits across the first and second pregnancies, an increased risk for overweight in young men could only be detected if the mother smoked during both pregnancies. Smoking in either pregnancy only was not associated with overweight in the exposed son. Similar findings were reported by Gilman *et al.*[9] who assessed the effects of maternal smoking during pregnancy on children's growth and development in 16 619 siblings by conditional likelihood methods. BMI in offspring of mothers who had been smoking during pregnancy was higher in the unconditional analyses. With adjustment for unmeasured family conditions by conditional-on-family specific intercepts which provided effect estimates that were free from bias due to potentially confounding factors to which both siblings were exposed, the effects of maternal smoking in pregnancy decreased and were no longer significant.

On item (ii), cotinine concentrations, irrespective of the substrate analysed, are by far higher in active than in passive smokers.[15,44] This also pertains to a measure for the cumulative nicotine exposure *in utero*: the amount of cotinine in the hair of newborns of actively smoking mothers was considerably higher (2.8 ± 0.8 ng/mg) than in the hair of newborns of mothers exposed to passive smoke only (0.6 ± 0.15 ng/mg) or in newborns who were unexposed to environmental tobacco smoke (ETS) and had non-smoking mothers (0.26 ± 0.04 ng/mg).[45,46]

Higher effect estimates for maternal smoking during pregnancy compared with paternal smoking would be compatible with a linear dose effect. There are some studies suggesting a linear dose effect of maternal smoking during pregnancy on overweight and/or obesity in childhood[19,47] whereas other studies[48,49] suggest a threshold effect, with a steep increase in effect size at low exposure levels flattening at higher exposure levels. Assuming a threshold effect, exposure to paternal smoking levels above the threshold might yield effects similar to those of maternal smoking exposure in pregnancy.

On item (iii), the effects for both paternal and maternal smoking on childhood overweight/obesity may reflect a causal relationship between postnatal smoking of either

parent and childhood overweight/obesity since most parents will continue smoking after pregnancy.[43]

The pathophysiology underlying the association between maternal smoking and overweight/obesity in the offspring, however, is far from being understood. There is some evidence that the risk is not mediated by low birthweight, both in animal[5,7,50] and human studies.[51,52] Catch-up growth, too, does not appear to be in the causal pathway.[51,53] Whereas smoking in the last trimester appears to account most for the offspring's risk for low birthweight,[54] first-trimester smoking appears to be more relevant for the offspring's risk for overweight/obesity.[55] Further research with regard to changes in the hypothalamic regulation of energy forth and appetite control might help to elucidate the aetiology of the association between maternal smoking in pregnancy and the risk for overweight/obesity in the offspring.[1,56]

A strength of our analyses is the search strategy based on using three databases and a broad search term. All but one[11] included studies were of high or moderate quality. Studies with potential over-adjustment were excluded.[39–41] Over-adjustment may be assumed if adjustment is made for a variable closely related to the exposure of interest;[57] because of multicollinearity, it can obscure a true effect or create an apparent effect even if none exists.[58] The study by Raum *et al.*,[41] for example, was excluded because of concomitant adjustment for maternal smoking during pregnancy, maternal smoking before pregnancy, maternal smoking during the first year after pregnancy and second-hand smoke at the age of 6 years: 97.2% of mothers who smoked during pregnancy had already smoked before pregnancy; 92.2% of children who were exposed to tobacco smoke during pregnancy were also exposed to maternal smoking during their first year of life.

A limitation is that our study included only five out of 12 studies reporting maternal and paternal/household smoking exposure status but no mutually adjusted effect estimates. The results could not be shown by sex since only one study[32] stratified analyses by gender. Howe *et al.*[32] found similar associations between boys and girls, suggesting there are no substantial differences in the associations of exposure to maternal and paternal/household smoking between sexes. Some, but not all of the studies eligible for this meta-analysis adjusted for birthweight which is associated with weight later in life. Excluding studies that did not adjust for birthweight[29,32,33] yielded identical results, suggesting no bias in estimates of our main results. Moderate and high heterogeneity was observed in some models. In the model of paternal smoking any time and childhood overweight, moderate heterogeneity was explained by differences in paternal smoking prevalence and in time of assessment of paternal smoking. In the model of household smoking and childhood overweight, high heterogeneity was explained by the prevalence of maternal smoking. Further variables (age, classifications of overweight or obesity) were taken into account but did not explain any heterogeneity. Different reference criteria to define overweight/obesity across studies might have contributed to a greater heterogeneity in our meta-analysis. However, a previous study suggests that identification of genuine risk factors for overweight or obesity does not depend on the choice of the reference system.[59] In fact, ORs associated with maternal smoking during pregnancy and childhood overweight or obesity ranged between 1.15 and 1.30 or 1.10 and 1.59 in studies using WHO, and between 1.27 and 1.52 or 1.37 and 2.30 in studies using IOTF for the reference, indicating similar effect sizes across different references. Mutual adjusted estimates, or interpreting those estimates, assume that there is no interaction between maternal and paternal/household smoking. An interaction may not be very likely, but we have no good evidence as to how the two interact with each other, and empirical studies to test effect modification/interaction of the two are very limited, particularly with pregnancy period involved. It is of note that studies included in our meta-analysis estimated ORs for overweight/obesity that was a common outcome, with a prevalence range of 9–32%. Thus, we should be cautious in interpreting the effect sizes in our study as ORs estimated for a common outcome overestimate risk ratios.[60] Finally, underreporting of the perhaps socially undesirable behaviour of smoking during pregnancy could result in underreporting of maternal smoking accounting for smoking mothers classified as non-smoking. In this case the strength of the effect of maternal smoking during pregnancy would be underestimated.[61]

Conclusion

Higher effect estimates in mutually adjusted models for maternal smoking in pregnancy compared with paternal smoking may suggest a direct intrauterine effect.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author contributions

C.R. and R.v.K. developed the study hypotheses and contributed to the first and final drafts of the manuscript. C.R. and K.S. conducted title and abstract scans, abstracted the information and evaluated the included studies. C.R. was responsible for data management and performed the statistical analysis. S.Z. contributed to the final draft of the manuscript. S.Y. supported this work by providing new calculations in addition to those in his previously published article, and contributed to subsequent drafts of the manuscript. G.K., B.G. and Y.C.C. supported this work by providing new calculations in addition to those in their previously published articles, and contributed to the final draft of the manuscript. C.R. will act as guarantor for the paper.

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Supplemental Material

Parental Smoking and Childhood Obesity: Higher Effect Estimates for Maternal Smoking in Pregnancy Compared to Paternal Smoking - A Meta-Analysis

Christina Riedel, Katharina Schönberger, Seungmi Yang, Gibby Koshy, Yang-Ching Chen, Bamini Gopinath, Stephanie Ziebarth, Rüdiger von Kries

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Table S1: Authors who were contacted to provide mutually adjusted estimates of studies without mutual adjustment for maternal smoking during pregnancy and paternal/household smoking on childhood overweight/obesity BMI/BMI z-score differences or if the results were not represented.

Corresponding Author	Article/Title	Journal, Volume, Issue, Pages	Year	Reason for contact	Did the corresponding author reply?
Bernard J. Brabin	Dose response association of pregnancy cigarette smoke exposure, childhood stature, overweight and obesity	European Journal of Public Health, 21, 3, 286-291	2010	Maternal smoking during pregnancy and paternal smoking was reported but not mutually adjusted	Yes, and the first author provided the effect estimates
Joe M. Braun	Socio-economic, familial and perinatal factors associated with obesity in Sydney schoolchildren	Journal of Paediatrics and Child Health, 48, 44-51	2012	Maternal smoking during pregnancy and household smoking was reported but not mutually adjusted	Yes. But he did not offer new estimates.
Ines Florath	Association of pre- and post-natal parental smoking with offspring body mass index: an 8-year follow-up of a birth cohort	Pediatric Obesity, Epub 2013 Feb 18	2013	Maternal smoking during pregnancy and paternal smoking was reported but not mutually adjusted	No
Rüdiger von Kries	Parental smoking and childhood obesity--is maternal smoking in pregnancy the critical exposure?	International Journal of Epidemiology, 37, 210-216	2007	Maternal smoking during pregnancy and paternal smoking was reported but not mutually adjusted	Yes, and he provided the effect estimates
Yungling Leo Lee	Environmental Factors Associated with Overweight and Obesity in Taiwanese Children	Paediatric and Perinatal Epidemiology, 26, 561–571	2012	Maternal smoking during pregnancy and household smoking was reported but not mutually adjusted	Yes, and the first author provided the effect estimates
Michelle A Mendez	Maternal smoking very early in pregnancy is related to child overweight at age 5–7 y	American Journal of Clinical Nutrition, 87, 1906-13	2008	Mutually adjusted effect estimates were only represented in figures	No
Paul Mitchell	Socio-economic, familial and perinatal factors associated with obesity in Sydney school children	Journal of Paediatrics and Child Health, 48, 44-51	2012	Maternal smoking during pregnancy and household smoking was reported but not mutually adjusted	Yes, and the first author provided the effect estimates
Seungmi Yang	Exposure to parental smoking and child growth and development: a cohort study	BMC Pediatrics, 13,104-114	2013	Mutually adjusted effect estimates were only represented in figures	Yes, and he provided the effect estimates

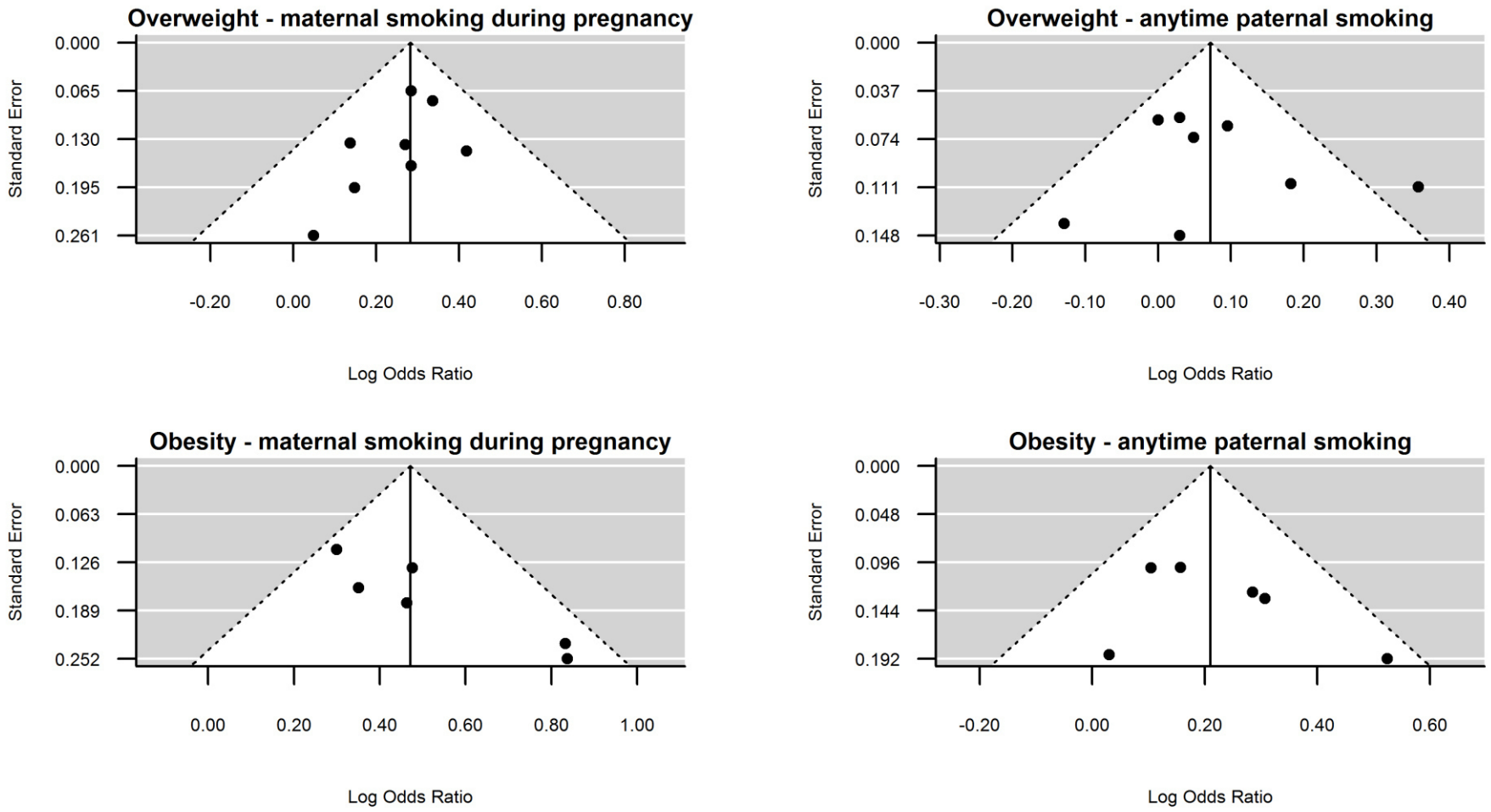


Figure S1: Funnel plot for assessment of publication bias in the model of comparison the ORs of the association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight or obesity in childhood. Each circle denotes a study included in the meta-analysis. The dashed vertical line represents the overall effect calculated with the random-effects model.

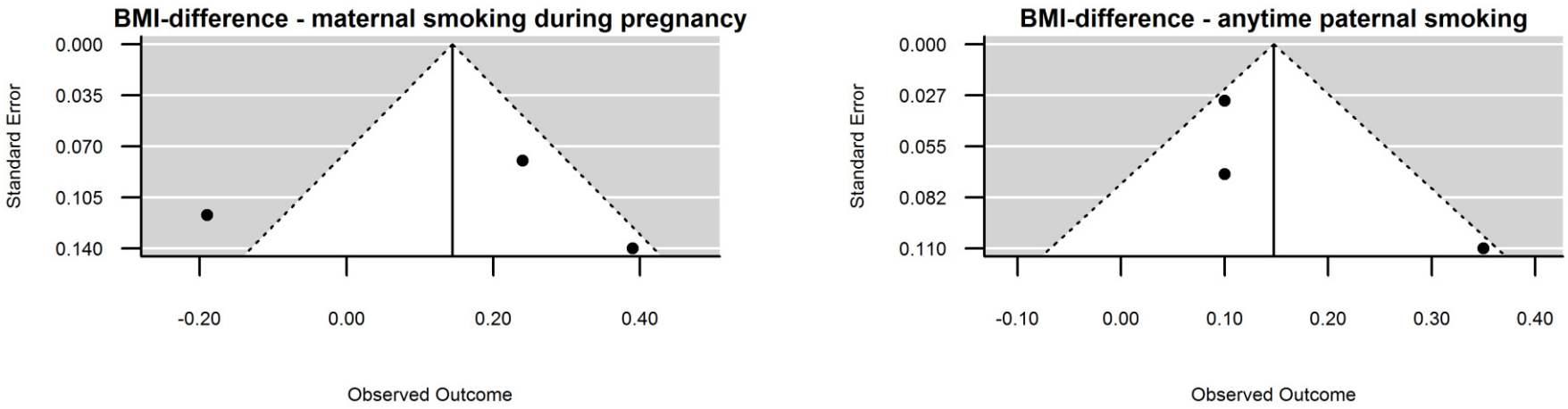


Figure S2: Funnel plot for assessment of publication bias in the model of comparison the BMI-differences between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight or obesity in childhood. Each circle denotes a study included in the meta-analysis. The dashed vertical line represents the overall effect calculated with the random-effects model.

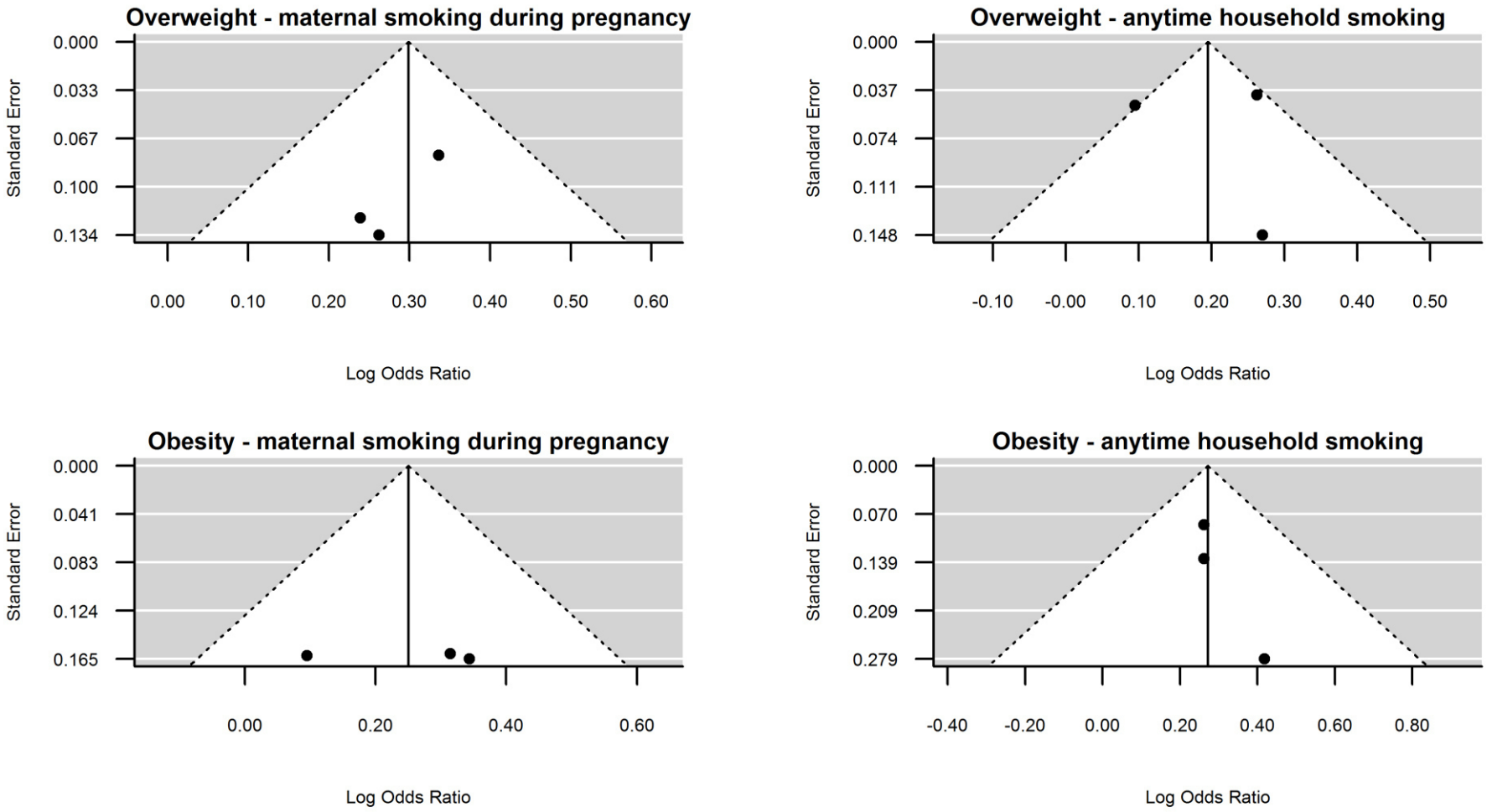


Figure S3: Funnel plot for assessment of publication bias in the model of comparison the ORs of the association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and household smoking anytime (vs. no household smoking anytime) and overweight or obesity in childhood. Each circle denotes a study included in the meta-analysis. The dashed vertical line represents the overall effect calculated with the random-effects model.

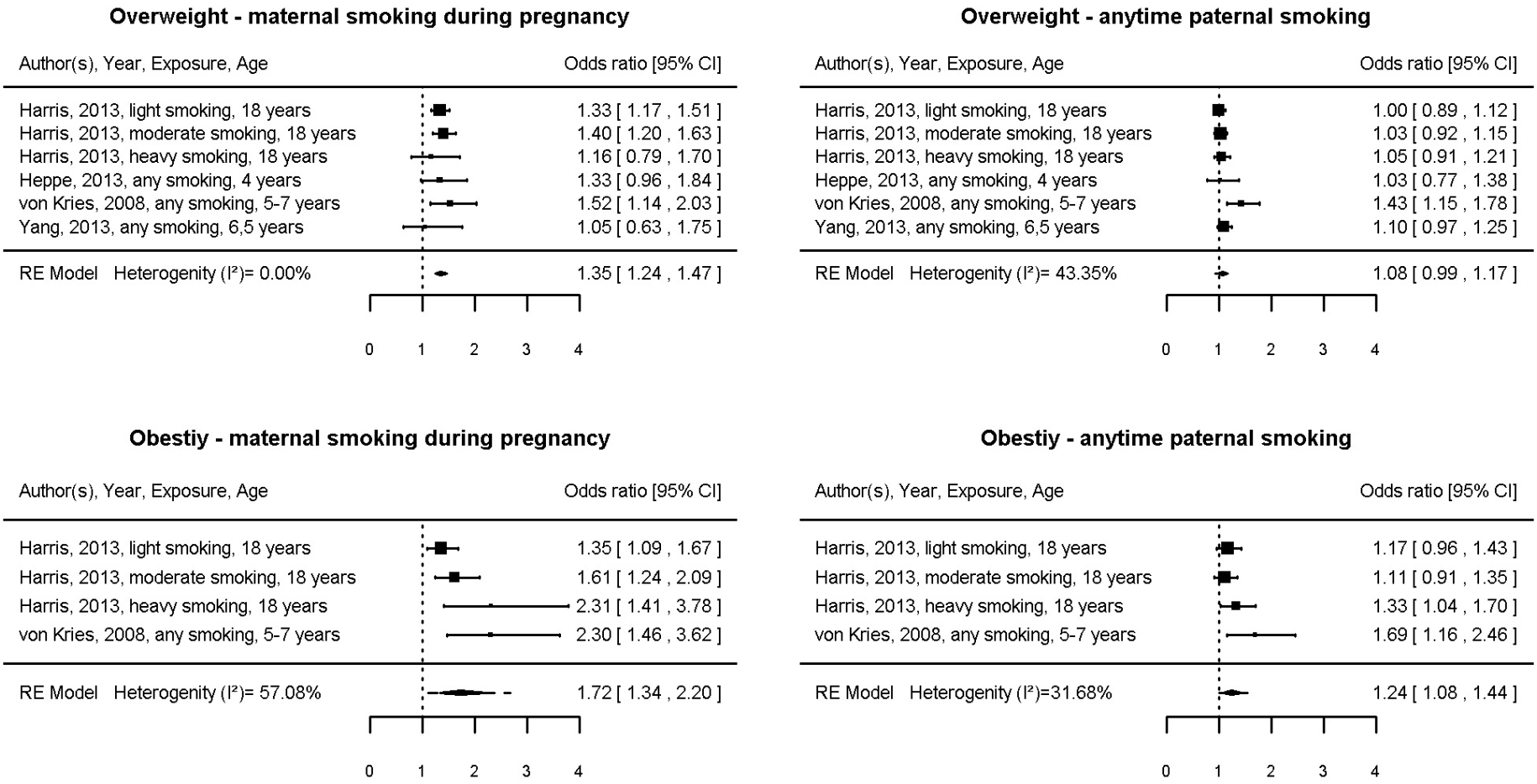
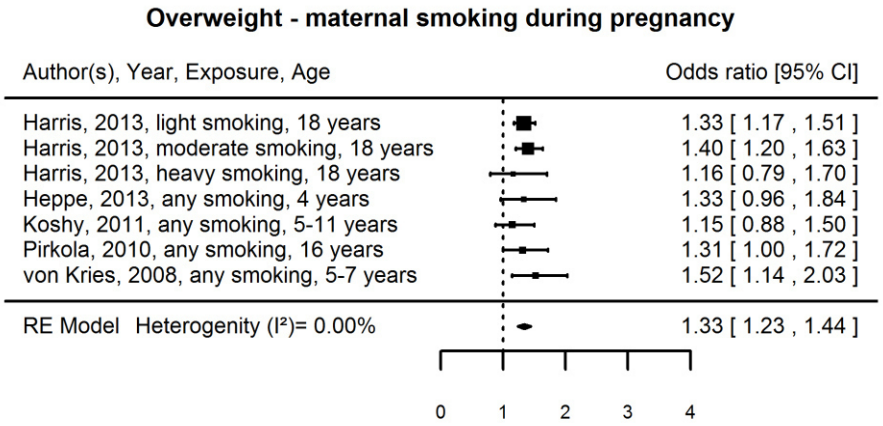


Figure S4: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight or obesity in childhood excluding studies that did not adjust for main potential confounders. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.



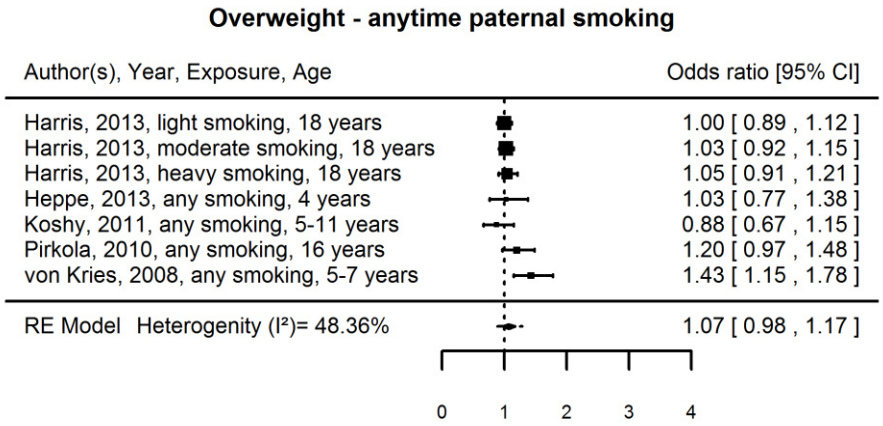


Figure S5: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight in childhood excluding studies that did not adjust for birth weight. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

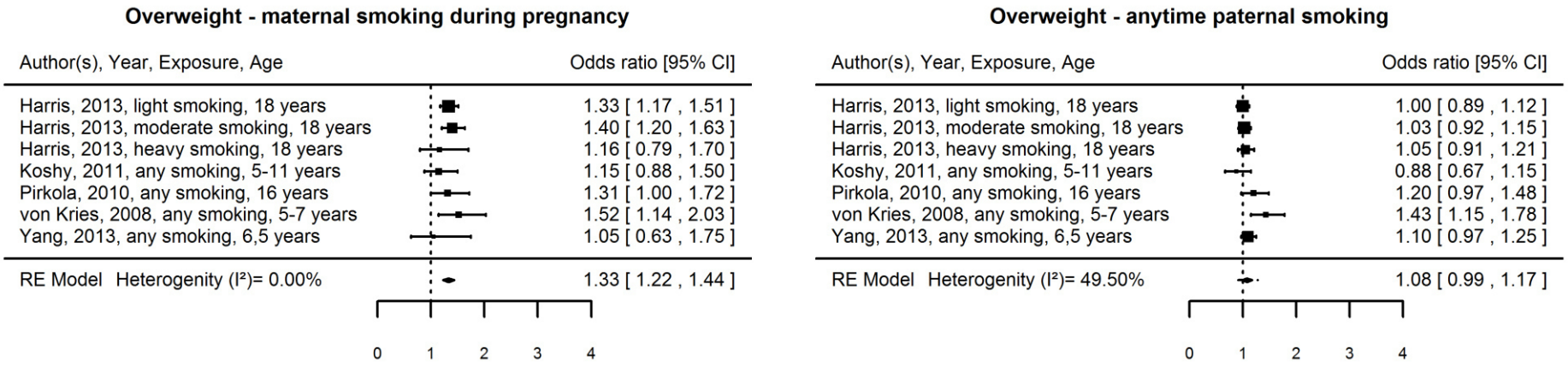


Figure S6: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight in childhood excluding studies with age of children < 5 years. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

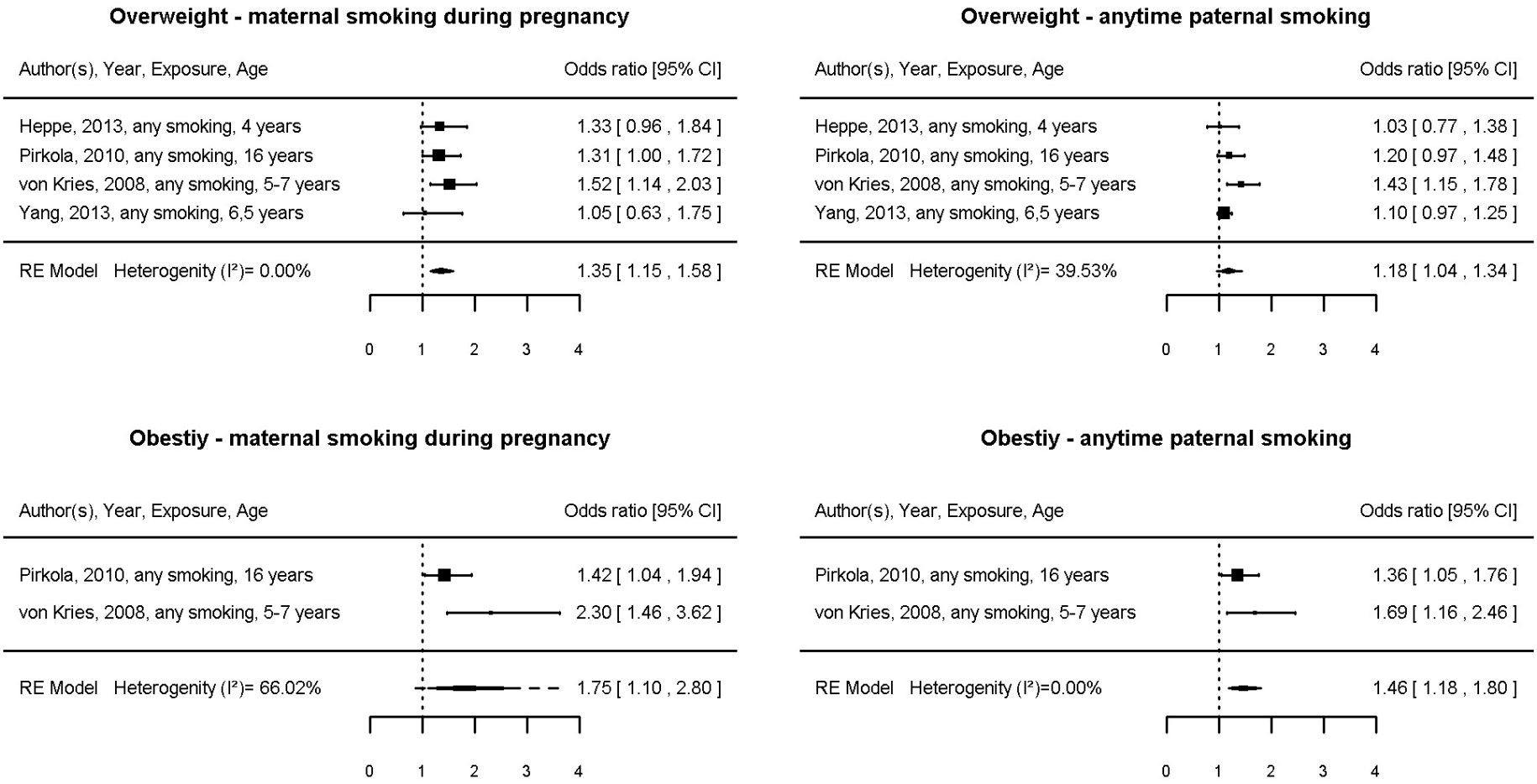


Figure S7: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and paternal smoking anytime (vs. no paternal smoking anytime) and overweight or obesity in childhood excluding studies without high quality. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

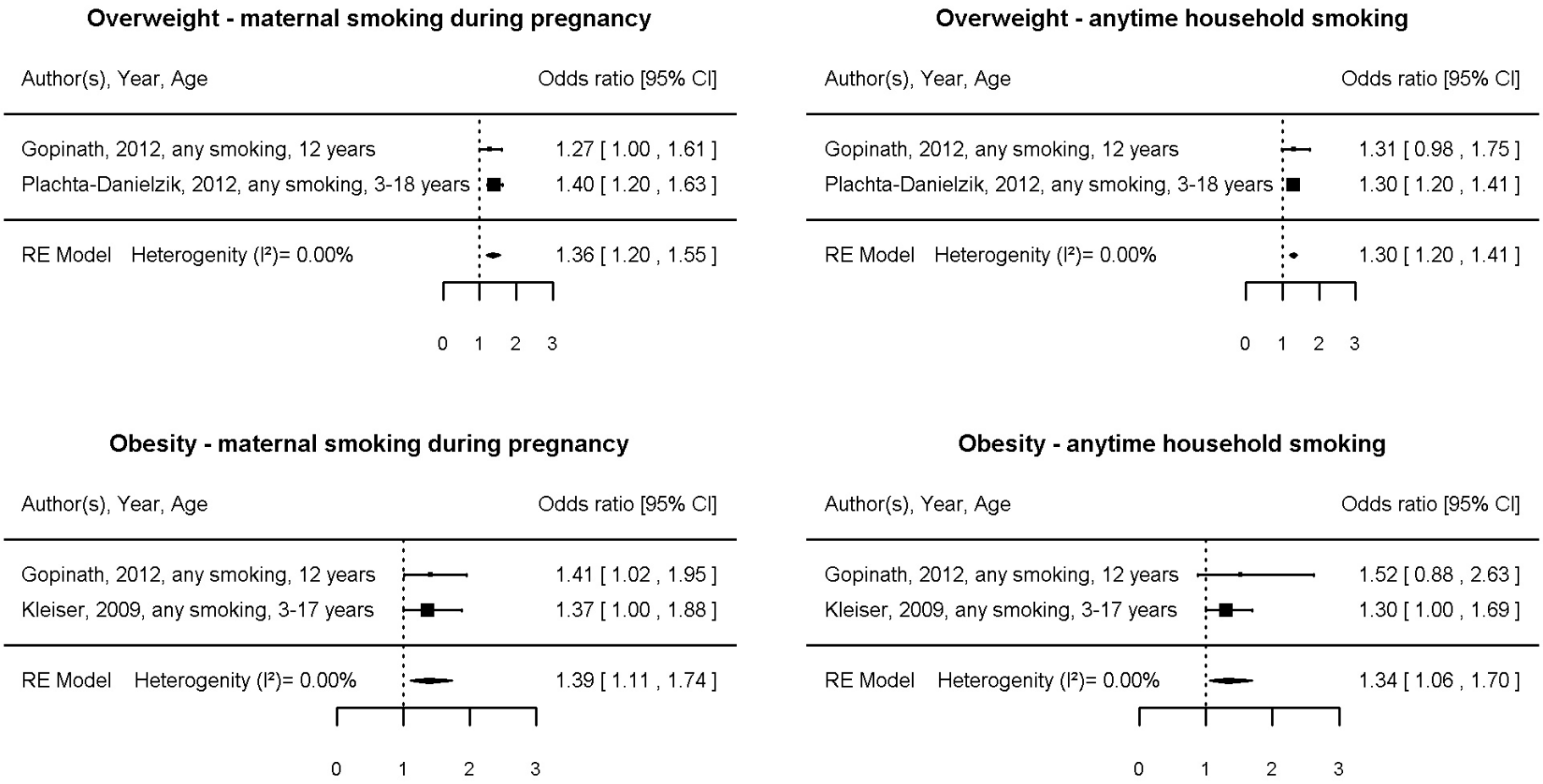


Figure S8: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and household smoking anytime (vs. no household smoking anytime) and overweight or obesity in childhood excluding studies without high quality. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

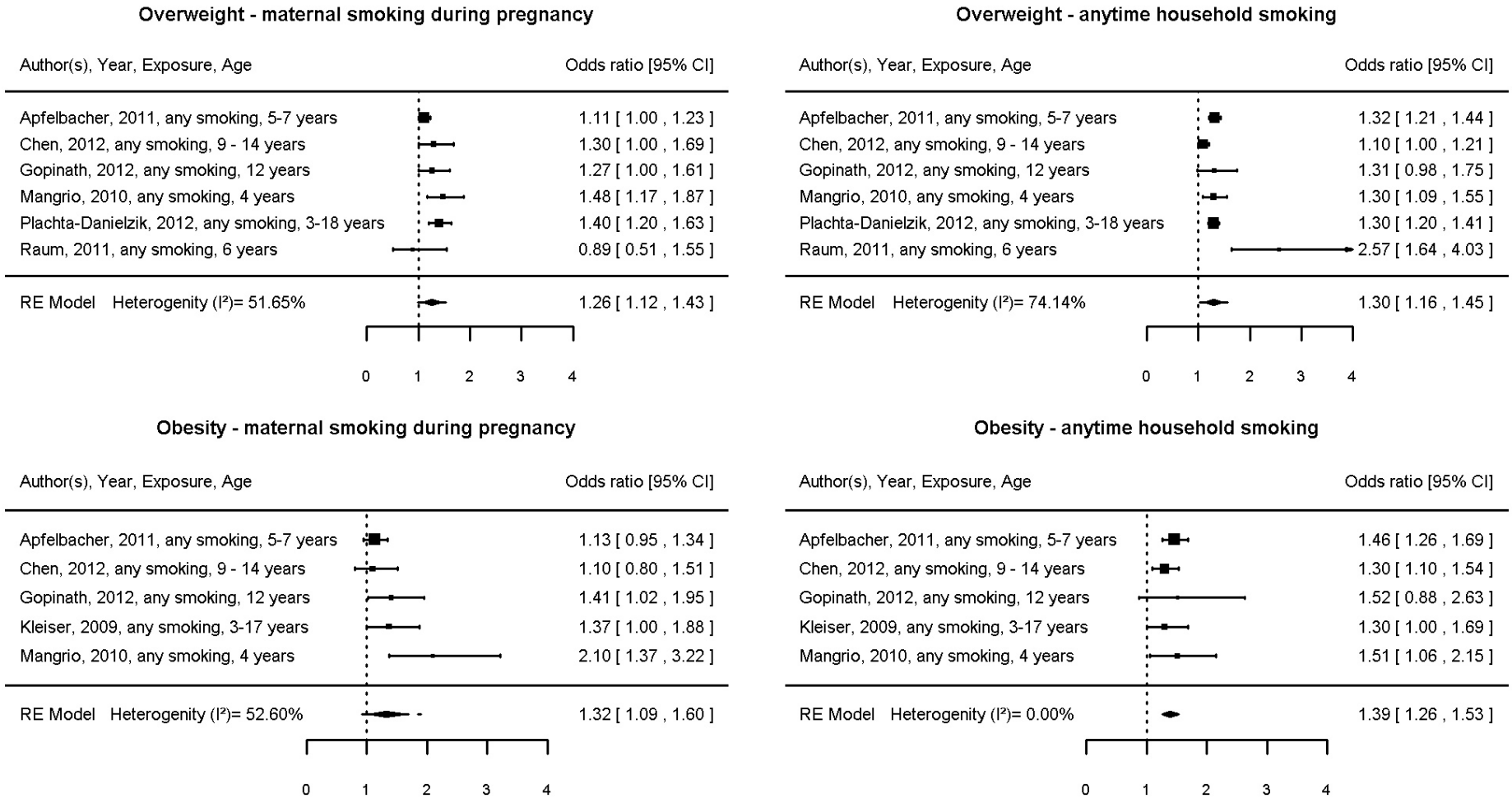


Figure S9: Odds ratio in meta-analyses of association between maternal smoking during pregnancy (vs. no maternal smoking during pregnancy) and household smoking anytime (vs. no household smoking anytime) and overweight or obesity in childhood considering studies with potential over-adjustment. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.

Lebenslauf Christina Sobotzki (geb. Riedel)

Persönliche Daten: Geburtsdatum/-Ort: 14.02.1984, München

Berufliche Erfahrung

seit 10/2011	*Statistikerin (Wissenschaftliche Mitarbeiterin / Doktorandin)* Institut für Soziale Pädiatrie und Jugendmedizin, Abteilung für Epidemiologie des Kindes- und Jugendalters mit dem Schwerpunkt Gesundheitsforschung, Ludwig-Maximilians-Universität, München

Praktika/Nebentätigkeiten

04/2011 – 09/2011	*Wissenschaftliche Hilfskraft* Institut für Soziale Pädiatrie und Jugendmedizin, Abteilung für Epidemiologie des Kindes- und Jugendalters mit dem Schwerpunkt Gesundheitsforschung, Ludwig-Maximilians-Universität, München
04/2010 – 03/2011	*Wissenschaftliche Hilfskraft* Statistisches Beratungslabor am Institut für Statistik, Ludwig-Maximilians-Universität, München
10/2008 – 04/2010	*Studentische Hilfskraft* Institut für Marktorientierte Unternehmensführung (Lehrstuhl Prof. Schwaiger), Ludwig-Maximilians-Universität, München
03/2001 – 03/2009	*Freie Mitarbeiterin* starmedia home entertainment GmbH & Co. KG, München
08/2008 – 12/2008	*Praktikantin und anschließende Werkstudentin* Client Vela GmbH (strategisches Beratungsunternehmen), München
04/2007 – 08/2007	*Praktikantin* Sony DADC Austria AG, Salzburg
10/2005 – 03/2007	*Service-Mitarbeiterin* Catering Service GVO, München

Studium/Schule

10/2009 – 09/2011	*Masterstudium der Biostatistik* Ludwig-Maximilians-Universität, München Thema der Masterarbeit: „Nichtlineare Quantilregressionseffekte in Daten zu Risikofaktoren für Übergewicht bei Kindern“ Abschluss: Master of Science Abschlussnote: 1,29
10/2005 – 08/2009	*Bachelorstudium der Betriebswirtschaftslehre* Ludwig-Maximilians-Universität, München

Schwerpunkte: Statistik, Marktorientierte Unternehmensführung, Strategie & Marketing
Abschluss: Bachelor of Science
Abschlussnote: 2,08

09/1994 – 07/2004 Josef-Hofmiller-Gymnasium, Freising, Abschluss: Abitur

Auszeichnungen

Aufnahme in die Dean‘s List und in das TOP-BWL Programm an der Ludwig-Maximilians-Universität am 07/2007 in München

Publikationen

Originalarbeiten:

1. Albers L, Milde-Busch A, Bayer O, et al. Prevention of headache in adolescents: population-attributable risk fraction for risk factors amenable to intervention. Neuropediatrics. 2013;44(1):40-45.

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4. Esser M, Lack N, Riedel C, Mansmann U, von Kries R. Relevance of hospital characteristics as performance indicators for treatment of very-low-birth-weight neonates. Eur J Public Health. 2014;24(5):739-744.

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6. Kirn V, Geiger P, Riedel C, et al. Cervical conisation and the risk of preterm delivery: a retrospective matched pair analysis of a German cohort. Archives of gynecology and obstetrics. 2014.

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8. Knabl J, Huttenbrenner R, Hutter S, et al. Gestational Diabetes Mellitus Upregulates Vitamin D Receptor in Extravillous Trophoblasts and Fetoplacental Endothelial Cells. Reproductive sciences. 2014.

9. Knabl J, Riedel C, Gmach J, et al. Prediction of excessive gestational weight gain from week-specific cutoff values: a cohort study. Journal of perinatology : official journal of the California Perinatal Association. 2014;34(5):351-356.

10. Nehring I, Riedel C, Baghi L, Moshammer-Karb T, Schmid R, Kries RV. [Psychosocial Situation of Families with Chronically Ill Children: A Survey of Parent Initiatives.]. Gesundheitswesen. 2014.

11. Riedel C. R-Package: GWG: Calculation of probabilities for inadequate and excessive gestational weight gain. 2013.

12. Riedel C, Fenske N, Muller MJ, et al. Differences in BMI z-scores between offspring of smoking and nonsmoking mothers: a longitudinal study of German children from birth through 14 years of age. Environmental health perspectives. 2014;122(7):761-767.

13. Riedel C, Schonberger K, Yang S, et al. Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking-a meta-analysis. International journal of epidemiology. 2014;43(5):1593-1606.

14. Riedel C, von Kries R, Buyken AE, et al. Overweight in adolescence can be predicted at age 6 years: a CART analysis in German cohorts. PLoS One. 2014;9(3):e93581.

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16. Schonberger K, Kirchgassner K, Riedel C, von Kries R. Effectiveness of 2+1 PCV7 vaccination schedules in children under 2 years: a meta-analysis of impact studies. Vaccine. 2013;31(50):5948-5952.
17. Schonberger K, Riedel C, Ruckinger S, Mansmann U, Jilg W, von Kries R. Impact of maternal carrier status on immunologic markers for protection after hepatitis B vaccination in infancy: a meta-analysis. Vaccine. 2012;30(44):6314-6326.
18. Schroeder AS, Von Kries R, Riedel C, et al. Patient-specific determinants of responsiveness to robot-enhanced treadmill therapy in children and adolescents with cerebral palsy. Developmental medicine and child neurology. 2014.
19. Sobotzki C, Riffelmann M, Kennerknecht N, et al. Latent class analysis of diagnostic tests for adenovirus, Bordetella pertussis and influenza virus infections in German adults with longer lasting coughs. Epidemiology and infection. 2015:1-7.
20. Tzschoppe A, Riedel C, von Kries R, et al. Differential effects of low birthweight and intrauterine growth restriction on umbilical cord blood insulin-like growth factor concentrations. Clinical endocrinology. 2015.
21. von Kries R, Reulen H, Bayer O, Riedel C, Diethelm K, Buyken AE. Increase in prevalence of adiposity between the ages of 7 and 11 years reflects lower remission rates during this period. Pediatr Obes. 2013;8(1):13-20.
22. von Tiedemann T, Albus A, Riedel C, Küchenhoff H. Qualität der ambulanten Behandlung schizophrener Patienten. Psychopharmakotherapie. 2011;18:257–262.

Kongressbeiträge:

1. Günther A, Kroke A, Riedel C, von Kries R, Joslowski G, Buyken A. Zusammenhang zwischen Stilldauer und Körperzusammensetzung sowie Körperfettverteilung im jungen Erwachsenenalter – vergleichende Analyse mit drei verschiedenen statistischen Verfahren. 50. Wissenschaftlicher Kongress der DGE. BonnMärz 2013.

2. Riedel C, Fenske N, Müller M, et al. Smoking during pregnancy increases the risk of overweight, but when does the risk emerge? (Poster und Vortrag). Meet the External Advisory Board des Kompetenznetzes Adipositas. FreisingMärz 2013.

3. Riedel C, Fenske N, Müller M, et al. Smoking during pregnancy increases the risk of overweight, but when does the risk emerge? (Poster und Vortrag). Jahrestagung der Deutschen Adipositas Gesellschaft (DAG). HannoverOktober 2013.

4. Riedel C, von Kries R, Buyken A, et al. Overweight in adolescence can be predicted at the age of 6 years (Poster). Meet the External Advisory Board des Kompetenznetzes Adipositas. FreisingMärz 2013.

5. von Kries R, Reulen H, Bayer O, Riedel C, Diethelm K, Buyken A. Increase in prevalence of adiposity between the ages of 7 and 11 years reflects lower remission rates during this period (Poster). Meet the External Advisory Board des Kompetenznetzes Adipositas. FreisingMärz 2013.

6. von Kries R, Reulen H, Bayer O, Riedel C, Diethelm K, Buyken A. Increase in prevalence of adiposity between the ages of 7 and 11 years reflects lower remission rates during this period (Poster und Vortrag). 29. Jahrestagung der Deutschen Adipositas-Gesellschaft e.V. StuttgartOktober 2012.

Eidesstattliche Versicherung

Sobotzki, Christina

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Mütterliches Rauchen in der Schwangerschaft als Risikofaktor für kindliches Übergewicht

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Ort, Datum

Unterschrift Doktorandin/Doktorand