行政院及所屬各機關出國報告

（出國類別：進修）

芬蘭赫爾辛基大學短期進修—環境職業衛生資料在Meta analysis分析之觀念與運用

服務機關：國防大學國防醫學院

出國人職稱：助理教授

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出國地區：芬蘭赫爾辛基

出國期間：92.3.17-92.8.27

報告日期：92.9.16

附件二

行政院及所屬機關出國報告提要

出國報告名稱：芬蘭赫爾辛基大學短期進修—環境職業衛生資料在 Meta analysis 分析之觀念與運用　　頁數 41 含附件：□是☑否

出國計畫主辦機關／聯絡人／電話

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出國類別：□1 考察　☑2 進修　□3 研究　□4 實習　□5 其他

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分類號／目

關鍵詞：職業環境衛生、meta-analysis、文獻收集

內容摘要：

本次出國短期進修選定之國家為北歐的芬蘭，芬蘭在職業環境衛生的成就，在世界上相當出名。然而國內較少學者前往進修，本次承蒙國防部暨國防醫學院核准職，前往芬蘭作為期半年的短期進修，個人深深感激及相當珍惜此次機會，到國外見識學習。這也是個人我第一次出國進行學術上的交流，初期懷著戒慎恐懼的心情，深怕生活的適應及語言上的隔閡，畢竟英文非我的母語，因此凡事戰戰兢兢認真學習，期望建立良好的互動，在未來的學術上能相互合作，並增進學術上的視野。所幸我的指導教授 Dr. Jaakkola 為人親切，非常有耐心的指導我研究設計與資料收集。並完全尊重我個人學習領域和興趣，亦鼓勵我旁聽博士班研究課程，希望我能充實既有的專業知識。

在此期間我和 Dr. Jaakkola 共同完成 meta-analysis 的研究方法、資料收尋選讀，與文章主題的撰寫。在文章的撰寫期間 Dr. Jaakkola 不斷的給予建議與相互討論，特別是在討論部分，當然也是文章最困難的部分，我們多次修正，直到我返國仍未間斷。最後成果應可在年底前完成文章的發表，這也是此次短期進修最感欣慰之處。

目次

摘要

本次出國短期進修選定之國家為北歐的芬蘭，芬蘭在職業環境衛生的成就，在世界上相當出名。然而國內較少學者前往進修，本次承蒙國防部暨國防醫學院核准職，前往芬蘭作為期半年的短期進修，個人深深感激及相當珍惜此次機會，到國外見識學習。這也是個人我第一次出國進行學術上的交流，初期懷著戒慎恐懼的心情，深怕生活的適應及語言上的隔閡，畢竟英文非我的母語，因此凡事戰戰兢兢認真學習，期望建立良好的互動，在未來的學術上能相互合作，並增進學術上的視野。所幸我的指導教授 Dr. Jaakkola 為人親切，非常有耐心的指導我研究設計與資料收集。並完全尊重我個人學習領域和興趣，亦鼓勵我旁聽博士班研究課程，希望我能充實既有的專業知識。在此期間我和 Dr. Jaakkola 共同完成 meta-analysis 的研究方法、資料收集，與文章主題的撰寫。在文章的撰寫期間 Dr. Jaakkola 不斷的給予建議與相互討論，特別是在討論部分，當然也是文章最困難的部分，經過我們多次修正，直到我返國仍未間斷。最後成果應可在國外期刊發表，這也是此次短期進修深感欣慰之處。

目的:學習新的觀念與研究設計、文獻收集、綜合分析及文章撰寫。

過程:學習過程：

(1).首先與指導教授(Dr. Jaakkola)討論學習目標，自己研究及興趣領域及指導教授研究領域，期望有所共通點及相互學習的機會。討論中，指導教授以最適合短期間學習能有所收穫之方式，即是我的專長研究領域，有關血鉛與健康危害研究，再結合指導教授已鑽研多年的生育危害研究領域，我們利用文獻收集方式進行統計分析，找出血鉛濃度與生育危害之相關性加以探討。

(2).接著進行文獻收集及如何利用挑選適合Meta-analysis統計分析方法之文章。本次學習主題即是：探討嬰兒臍帶血鉛濃度、母親懷孕時血鉛濃度、母親鉛工作與住家附近是否有鉛暴露源等，與嬰兒低出生體重(low birth weight)、早產(preterm delivery)、流產(spontaneous abortion)、死胎(stillbirth)之相關性研究。文章收尋時須先訂出所要納入(include)和排除(exclude)的標準，這也是這類研究中最困難的部分，我花了相當的時間與精力在文獻收集與閱讀上。期間與指導教授多次討論，找出文章的研究設計及結果，符合所選定探討目的相關文章。

(3).接著閱讀有關Meta-analysis的教課書，一遇不懂的地方就和指導教授討論，從中學習許多新的觀念。再此期間指導教授亦鼓勵我旁聽一些相關課程(meta-analysis, logistic regression)並取得學分(學分證

書如附件)。因為那是我第一次參與國外的課程且是英語講授，這是我想都沒想到的。這兩次的課程我努力讀教課書，我深信只有課前多準備才能降低語言的障礙，特別是不熟悉的課程。但對於體驗國外大學上課學習的心態經驗卻是一次難得的經驗。並體驗學習與國外同學一同參與討論活動。並於課程結束後，向授課教授請益，並邀請授課教授(Dr. Walter)明年到台灣來做學術訪問，已獲首肯。

(4).最後對綜合分析問題的解釋，先要彙整資料作表，將文獻呈現在同一表格中，並從文章中選出需加以分析變項，如何有效分類血鉛暴露濃度與健康危害比較。這部分與指導教授多次討論，經過多次修正找出最適合主題探討變相，加以列表，這無疑是一次深刻學習體驗。接著學習如何判讀Meta-analysis所分析的結果，整個進修過程中，我從中學習研究方法與學習態度。學習正確的文獻資料收尋，與資料取捨。閱讀文獻資料，製作表格，撰寫這類文章，這絕對是本次短期進修最大的收穫。

心得:

除了上述學習經驗與心得感想外，亦對芬蘭這個國家的風土民情亦有所了解，絕對值得與大家分享

(一)芬蘭國家簡介

芬蘭（Suomi in Finnish）是北歐五國中位置最東邊的國家，位於北緯 60－70 度之間，國土 338,000 平方公里（約台灣的十倍大），是歐洲中國土第七大的國家。位於瑞典與蘇俄兩國之間，北與挪威接壤，南臨芬蘭灣與愛沙尼亞相望，是東歐與北歐間交通橋樑，也是聖誕老人的故鄉，國土雖有三分之一在北極圈內，卻未直接瀕臨北極海。芬蘭素有千湖之國的美名，境內滿佈湖泊與森林。湖泊共有 187,888 個，佔總面積 10%，多集中於中、南部，Suomi 即芬蘭語「千湖之國」之意；森林面積佔 69%尤以中、北部最廣闊；另外有 8%耕作面積。由於擁有豐沛的水力林木資源，即使近年芬蘭的電子科技產品已大幅增加，但鋸木、造紙等森林工業製品仍佔出口總值 30%以上。

芬蘭的歷史，其實是一群最早由蘇俄中部遷移至波羅的海沿岸，再陸續往北遷移至此的移民他們為脫離瑞典和蘇俄的統治而奮鬥數個世紀的故事。最可惜的是，早期芬蘭的歷史是由瑞典以瑞典文寫成的，許多芬蘭的民族文化與重大事件都在外族的統治下被忽略而付之闕如。

芬蘭事實上與瑞典、挪威、丹麥和冰島等國有截然不同的歷史命運和

文化背景，就連語言、人種都和這些維京人(Scandinavian)全無瓜葛。芬蘭和匈牙利、愛沙尼亞同屬芬島語系，祖先來自歐亞交界的烏拉山區，據信原為遊牧民族，首先遷移至愛沙尼亞，然後往北遷移至今日的芬蘭。芬蘭人的祖先和最早來到這塊土地的北方原住民薩米人共同生活數千年，一直未發展為真正的國家形式。到了西元 1155 年，瑞典借傳教之名佔領芬蘭，從此芬蘭歷史展開急遽的變化。

再長達六百多年的瑞典統治期間，俄國這個東邊強鄰覬覦芬蘭的戰略位置，因此在 16 至 18 世紀之間，瑞典和俄國為搶奪芬蘭，甚至在芬蘭境內發生多次戰爭。1809 年，俄國終於如願以償，將芬蘭納入轄下的大公國。由於沙皇亞歷山大一世認為土庫太瑞典化，且赫爾辛基亦離聖彼得堡較近，在 1812 年將芬蘭首都遷至赫爾辛基。1835 年羅倫特（Elias Lonnrot）彙整芬蘭古代的口傳古詩歌民謠，出版「卡洛瓦拉」（Kalevala）史詩集，喚醒了芬蘭人的民族意識。1899 年西貝流士（Jean Sibelius）所做的「芬蘭頌」首度公開演奏，振奮當時抗俄的民心士氣，更成為現在的芬蘭國歌。1917 年 12 月 6 日宣佈獨立。1934~44 年為保衛國土與蘇聯陷入苦戰。1952 年赫爾辛基舉辦第十五屆奧運，全球矚目。1995 年加入歐盟。2000 年赫爾辛基獲得歐洲文化之都的殊榮。2002 年擔任歐盟主席。

芬蘭的人口約 520 萬，其中 92%說芬蘭語，6%說瑞典語。故第一官方語言為芬蘭語，第二為瑞典語。但芬蘭人也同時能說英語及法語或德語。

首都在赫爾辛基。由於芬蘭婦女是全世界最早獲得完整參政權，所以婦女參政的風氣很盛，目前總統與國會議長均為女性。

赫爾辛基大學是一棟棟分散在市區的建築，根本沒有校區。我們住的宿舍是古董級建築物，舊建築物的電梯都有一鐵門，內有一拉門，兩道們都關上，電梯才會動，裡面還有椅子可坐，是名符其實的坐電梯！芬蘭的治安很好，一切都採榮譽制，不但停車如此，搭公共交通工具也是如此。只要買了車票搭車，一小時內可無限次轉車。所以你上車不秀出車票是很平常的事，但如遇上查驗票時卻未持有效票則會被處以可觀的罰金。芬蘭為大陸型氣候，冬天長而冷，約七個月，即使在下雪的冬日，兒童不論在家中或學校，仍會有固定的戶外時間，以訓練兒童適應寒冷的氣候。由於冬天日照時間短，在此季節罹患憂鬱症的病人相當多。

赫爾辛基由於先後經歷瑞典和俄國的統治，也因此擁有俄國的建築風格及北歐的城市特色。市區內最重要的三個教堂為建築大師 C. L. Engel 設計的赫爾辛基大教堂、以炸藥炸開花崗岩而建成的岩石教堂和北歐最大的東正教教堂烏斯本斯基大教堂。其他像赫爾辛基火車站、國家劇院、國家美術館、國立博物館……等，均為不同時期的建築大師的傑作。適合戶外活動的地點有建在赫爾辛基外海的六座小島上的索門林納海上城堡、復活節和仲夏節在此稍大型營火的塞拉沙里露天博物館和紀念芬蘭最知名的音樂家西貝流士紀念公園。

赫爾辛基有一個很適合觀光客的措施:每一個月出一本 Helsinki This Week，裡面將赫爾辛基一個月內的活動巨細靡遺的介紹給觀光客知道。四月 18 日開始為復活節假期，持續了三天，從星期五到星期日，人們紛紛出城度假去了，星期五時，整個城市像睡著了似的，路上幾乎看不到行人。商店都關門去渡假了。星期六晚上我們在大教堂前的上議院廣場前欣賞了一年一度的復活節朝聖之旅的演出，將耶穌受難記分成四慕戲，精采演出吸引了大批觀光客。

五月一日勞動節，是當地的一個非常重要的節日。從前一天下午開始（May Day Eve）當地人便戴上白色的學生帽（必須年滿十八歲），帶著香檳、白酒或啤酒到市集廣場旁，為象徵赫爾辛基的波羅的海的女兒雕像旁看噴泉噴出泡泡水，為雕像洗個泡泡澡，再為她戴上學生帽。廣場上全是攤販和五彩繽紛的汽球。不論男女老少都戴著學生帽，未滿十八歲的少年少女及兒童則向萬聖節般的打扮自己。其中最大宗的族群卻是即將畢業穿著各色連身服的大學生，為了慶祝即將畢業，從昨晚便瘋狂慶祝，通宵達旦。所有人都是有備而來，注定要喝醉酒的人，早已穿上防寒的潛水衣在泡泡噴泉裡游泳，還爬出來跟我們握手，祝我們勞動節愉快！旁人見我們沒帶酒，還給我們酒杯並倒酒給我們喝，告訴我們這個節日的象徵意義：其實是芬蘭人為了冬天結束；迎接春天與陽光而狂歡，所以這時所見一切都不是平時的芬蘭人會有的舉動。到五月一日早上，全部的人就移往

Kaivopuisto Park 去野餐，沒想到飄著小毛雨的日子，公園裡依然人山人海，許多人早已搭好棚子擺好餐桌椅及烤肉架，甚至白色的籬笆、和美麗的盆景、沙發及電視，九點開始有合唱團和樂隊的演出，我們找個地方坐下，拿出爆米花、餅乾、葡萄和滷蛋，和大家一起野餐，孩子們開始冷得流鼻水，為了節省幾張昂貴的面紙，我們終於告別了這場盛宴。回程的路上，看見芬蘭國旗在每棟建築物前飄揚（芬蘭人動不動就掛國旗），突然覺得中華民國的國旗是那麼寂寞，心裡真是感觸良多啊！

一到五月芬蘭的冬天真的結束了，草皮都變綠了，樹木都開始生出嫩芽，鬱金香一下子就從土裡冒出十公分。這裡的小朋友戴墨鏡是很平常的事，小女生都穿的五彩繽紛，尤其喜歡綁頭巾或戴著美麗的帽子，連綁黑人辮子頭都顯得時髦又俏麗。最盛行的球類運動是足球（這是歐洲人的全民運動，幼稚園的小孩就很會踢了）和冰上曲棍球（他們是世界第一喲），也愛騎自行車和慢跑，雪融化之後，輪鞋族和滑板族就蜂湧而出，他們的身材大都維持的很好，為保持身材，芬蘭女性抽菸比例非常高。

五月九日是歐盟日，在 Esplanade Park 有辦一個嘉年華會，有表演各國音樂舞蹈，許多東歐國家大使館都派人來擺攤，有許多免費旅遊資料，有吃又有紀念品可拿，開心極了，我也認識不少東歐國家，覺得東歐國家也蠻適合旅遊的喔！

5 月 15 日是 Sofia Day，赫爾辛基最古老的街道 Sofiankatu 因市立

博物館亦位於此，故在這一天會舉行一年一度的春天化妝派對和市集，市博館和街道上店家的工作人員都穿上十八世紀以來的流行服飾。現場有管絃樂隊演奏、市博館導覽、兒童馬戲團、在上議院廣場上也有十八世紀是為對的操練及射擊表演，可以拿到一些免費的風景繪畫明信片以及特別便宜的芬蘭手工藝品及紀念品，也可和古裝人物們合照。

夏天在六月正式登場，赫爾辛基也開始為迎接陽光舉辦一系列的活動：婦女馬拉松在透樓湖畔展開，兒童奧運會、街舞日、森巴嘉年華、街頭流行秀及在露天博物館舉辦最重要的仲夏節慶典(Mid-summer festival)，可以在那裡看芬蘭人如何製作傳統手工藝，包括如何織蕾絲、從植物抽取纖維來紡織、製作木器……等，也有專為兒童設計的傳統童玩遊戲區，小朋友可以踩高蹺、丟馬蹄鐵、看人偶戲或騎馬。可以靜觀芬蘭傳統音樂舞蹈，也可與他們歡欣共舞。仲夏夜最高潮的活動是點燃一年一度的盛大營火(Bonfire)。自此夏天日照時間變的特別長，六月下旬起每天凌晨約一點鐘天才暗下來，約三點鐘天就和白天一樣了，睡眠時間自然也就縮短了許多。

七月是暑假的開始，大部份的人都到外地渡假去，暑假期間的機票價格幾乎是平時的一半，除了不間斷的音樂會，赫爾辛基變成一個相當乏味的城市。利用假日到芬蘭第二老的古都 Porvoo 走一趟，欣賞十五世紀的都市風貌，也可感受到一股濃厚的文化氣息。

建議:

短期進修對於曾經在國外修過學位者與未曾出國進修者而言，雖然在初期適應上，與研究探討深度上會有所不同，但是在學習的收穫上，我相信是一致的。尤其是在從事學術研究的領域上，更需不斷的精益求精，充實自我的專業知識。而短期進修絕對是一個寶貴的經驗，與學習的良機。

基於個人學習的經驗，建議國防部相關單位，持續鼓勵與支持短期進修的深造計畫，以強化國軍人才的本質學能。

附錄

檢附本次短期進修學習成果一份

全文完

Lead Exposure and Birth Outcomes: A Systematic Review and Meta-Analysis

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Abstract

To evaluate whether adverse pregnancy outcomes were caused by adverse effects of occupational or environmental exposure to lead. The authors used the Medline data retrieval system for 1966-2003 to identify and synthesize the epidemiological evidence for adverse effects of prenatal exposure to lead on birth defects. Exposure assessment constituted the principal difference among the studies. We classified the levels of exposure using a dichotomy among the studies according to cord blood lead levels, place of residence (exposed vs. unexposed community) and maternal occupation (lead exposure vs. no lead exposure. The authors calculated summary odds ratios and 95% confidence intervals using both fixed-effects and random-effects models. The results indicated that maternal occupational lead exposure would result in an increase risk in preterm deliveries and low birth weights. This study also found that using the cord blood lead level to investigate into the birth outcomes, low birth weight and preterm delivery, its results were inconsistent. Moreover, results indicated mother's occupational lead exposure and environmental lead exposure did not cause influence on spontaneous abortion and stillbirth. Differences in the susceptibility of populations, and different approaches in exposure assessment, may explain the heterogeneity of the results.

Key words: pregnancy outcomes, adverse effects, meta-analysis, lead exposure

Introduction

Lead is ubiquitous in the environment, and it is among the most studied elements. Lead has an extensive history as a reproductive toxin, which exerts its effect either directly on the developing fetus, after pregnancy begins, or indirectly on paternal or maternal physiology before and during the reproduction process (Silbergeld, 1983). Baltrop (1968) presented already in 1968 that lead can readily cross the placenta at about the twelfth to fourteenth week of gestation. Lead crosses the placenta throughout gestation. The correlation between maternal and umbilical cord blood lead levels has been shown to be strong in several studies, ranging from 0.55 to 0.92 (Wong et al., 1992; Klein et al., 1994; Odland et al., 1999; Ernhart, 1992). These findings suggest that lead freely crosses the placenta; therefore, it is plausible that maternal exposure to lead has adverse effects on fetal development and maternal health in pregnancy. Potential outcomes of lead exposure include low birth weight, preterm delivery, premature rupture of fetal membranes (PROM), small-for gestational age, spontaneous abortion, behaviors change, and congenital anomalies (Odland et al., 1999; Ernhart, 1992; Lockitch, 1993; Bellinger and Needleman, 1985; Angell and Lavery, 1982). A retrospective cohort study showed that less than adequate use of prenatal care might reflect

an increase in risk factors contributing to lead exposure in infancy. Low birth weight also was related to high blood lead levels (Recknor et al., 1997).

Most of the recent studies emphasized that adverse birth outcomes were caused by occupational or environmental lead exposure. Several studies (Irgens et al., 1998; Lindbohm et al., 1991; Andrews et al., 1994; Needleman et al., 1984; Min et al., 1996; Fahim et al., 1976; Savitz et al., 1989; Murphy et al., 1990; McMichael et al., 1986; Alexander et al., 1996; Factor-Litvak et al., 1991; Clark, 1977; Lin et al., 1998) have investigated the relation between parental occupational or environmental lead exposure and adverse birth outcomes. Although most of these studies found positive associations between lead exposure and pregnant outcomes, some results have failed to find evidence supporting these associations (Savitz et al., 1989; Murphy et al., 1990; McMichael et al., 1986; Alexander et al., 1996; Factor-Litvak et al., 1991; Clark, 1977; Lin et al., 1998).

We carried out a systematic quantitative review to identify and synthesize the evidence for adverse effects of occupational or environmental exposure to lead on adverse pregnancy outcomes including low birth weight, preterm delivery, small for gestational age, stillbirth, and spontaneous abortion.

Methods

Search strategy. We searched the Medline data retrieval system for the years 1966 to April 2003, using the following key words: (low birth weight or preterm delivery or gestational age or small for gestational age or spontaneous abortion or stillbirth) AND (lead exposure). In addition, we searched primary references from the identified publications. We considered all epidemiological studies that assessed the relation between exposure to lead, either directly or indirectly, and birth outcomes.

Inclusion criteria and study evaluation. Both authors reviewed the selected articles independently, extracted data, and assessed the validity of the studies. We applied inclusion criteria on the basis of the type of study, study population, exposure definition, and outcome definition. We accepted a priori all studies with the individual as the unit of observation – including cross-sectional, cohort, and case-control studies. We focused on parental occupational or non-occupational lead exposure, and evaluated the articles on the basis of the aforementioned criteria, as well as according to adjustment for confounding, and type of statistical analysis.

Definitions of outcomes. An infant was categorized as *low birth weight* (LBW) if birth weight was less than 2500g. *Preterm delivery* was defined as

delivery prior to the 37th weeks pregnancy. *Small for gestational age* (SGA) if birth weight was below the 10th percentile for infants of the same gestational age. *Spontaneous abortion* was a fetal loss prior to the 7th month of gestation, and *stillbirth* a fetal loss occurring in months seven through nine of gestation or when gestational age was missing, a weight of 1000g or more.

Statistical methods. For each study, odds ratios (OR) or relative risks (RR) and 95% confidence intervals (95% CI) by exposure category were extracted. We calculated summary odds ratios using both fixed-effects and random-effects models. The fixed-effects models were calculated using the Mantel-Haenszel method (OR_{MH}), with inverse variances of individual effect estimates as weights (Petitti, 1994). The random-effects models were calculated using the DerSimonian-Laird method (OR_{DL}) (DerSimonian and Laird, 1986). We attempted to explain the resulting heterogeneity according to differences between the studies, rather than considering the random-effects model as a conservative solution for heterogeneity. We calculated the summary odds ratios in 3 stages. First, we carried out a meta-analysis for each outcome by summarizing all the included studies that focused on the outcome of interest. Potential sources of heterogeneity were examined through the independent studies by plotting the measures of effect. A heterogeneity test based on the

Q-statistic, where $p<0.05$ indicates statistically significant heterogeneity. Second, in cases of heterogeneity between study-specific effect estimates, we used stratified analysis to determine the source of the heterogeneity. Third, we performed sensitivity analyses with, and without, the study that had the largest sample size, to identify the impact of this study on the results. We used the Stata 8.0 statistical package to perform the analyses.

Results

After searching the Medline system and searching references from the identified publications, the Medline search produced 28 articles. We finally included in the meta-analysis five cross-sectional studies (Satin et al., 1991; Bellinger and Needleman, 1985; Fahim et al., 1976; Irgens et al., 1998; Clark, 1977), three case control studies (Savitz et al., 1989; Min et al., 1996; Lindbohm et al., 1991), and four cohort studies (McMichael et al., 1986; Factor-Litvak et al., 1991; Recknor et al., 1997; Murphy et al., 1990). Six of the studies were carried out in different regions of the United States (Satin et al., 1991; Bellinger and Needleman, 1985; Fahim et al., 1976; Savitz et al., 1989; Min et al., 1996; Recknor et al., 1997), two studies presented results from Yugoslavia (Factor-Litvak et al., 1991; Murphy et al., 1990), other results from Norway, Finland, Zambia, South Australia, respectively (Irgens et al., 1998; Lindbohm et al., 1991; Clark, 1977; McMichael et al., 1986). The selected studies are summarized in Table1.

Preterm deliveries were evaluated in 7 studies (Satin et al., 1991; Bellinger and Needleman, 1985; Fahim et al., 1976; Savitz et al., 1989; Irgens et al., 1998; Factor-Litvak et al., 1991; McMichael et al., 1986), low birth weights in six of the studies (Bellinger and Needleman, 1985; Min et al., 1996; Recknor et al.,

1997; Irgens et al., 1998; Clark, 1977; McMichael et al., 1986), spontaneous abortions in 2 of the studies (Lindbohm et al., 1991; Murphy et al., 1990) and stillbirths in 2 of the studies (Savitz et al., 1989; Murphy et al., 1990). The outcome definitions were similar among the studies, and measurement was expected to be relatively accurate and valid.

Exposure assessment constituted the principal difference among the studies. We classified the levels of exposure using a dichotomy among the studies according to cord blood lead levels (Satin et al., 1991; Bellinger and Needleman, 1985; Recknor et al., 1997), community exposure (Fahim et al., 1976; McMichael et al., 1986; Factor-Litvak et al., 1991; Clark, 1977; Murphy et al., 1990) and maternal occupational lead exposure (Savitz et al., 1989; Irgens et al., 1998; Min et al., 1996; Lindbohm et al., 1991). When the individual studies were heterogeneous these categories were applied in the stratified analyses.

Seven studies used odds ratios as the measure of effect, and logistic regression analysis to calculate adjusted odds ratios (aORs) (Savitz et al., 1989; Irgens et al., 1998; Satin, Recknor et al., 1997; Min et al., 1996; Murphy et al., 1990; Lindbohm et al., 1991; Bellinger and Needleman, 1985). Four studies used prevalence ratio as the measure of effect and calculated unadjusted odds

ratios (Fahim et al., 1976; McMichael et al., 1986; Factor-Litvak et al., 1991; Clark, 1977). In all, the adjustment for confounding was relatively similar across all studies (see table 1).

The results of the meta-analysis are summarized in Table 2. Both the fixed-effects and random-effects summary odds ratios are given, as well as the magnitude of heterogeneity (Q-statistic). Figures 1-10 show tree plots of the study-specific and summary effect estimates for outcomes with several studies. The area of the plot indicates the relative amount of information and a horizontal line through the plot signifies the 95% confidence interval (95% CI).

Studies from Massachusetts (Bellinger and Needleman, 1985), California (Satin et al., 1991), Missouri (Fahim et al., 1976), South Australia (McMichael et al., 1986), Yugoslavia (Factor-Litvak et al., 1991), Unites States (Savitz et al., 1989), and Norway (Irgens et al., 1998) assessed preterm delivery as potential outcomes (Figure 1). All 7 studies applied different approaches to exposure assessment. (1) dichotomized cord blood lead level (Satin et al., 1991; Bellinger and Needleman, 1985), (2) exposed community vs. unexposed community (Fahim et al., 1976; McMichael et al., 1986; Factor-Litvak et al., 1991), and (3) maternal occupational lead exposure vs. non-lead exposure (Savitz et al., 1989; Irgens et al., 1998). Despite these differences, most of them

indicated a consistent effect (relative risks= 1.13 to 4.50). Our fixed-effects model was statistically significant (OR^{MH}=1.30, 95% CI=1.18, 1.43), with significant heterogeneity (Q-statistic=26.32, $p < 0.01$).

The study specific OR for preterm delivery and the cord blood lead levels exposure categories were shown in Figure 2 (OR^{MH}=0.94, 95% CI=0.67, 1.32), with some heterogeneity (Q-statistic=3.97, p=0.05). Figure 3 revealed the results of the 3 studies of preterm deliveries according to community exposure, which consistently pointed toward an increased risk (OR^{MH}=1.65, 95% CI=1.41, 1.92) (Q-statistic=4.54, p=0.10). Figure 4 displayed the results of 2 studies in the relationship between maternal occupational lead exposure and preterm deliveries were (OR^{MH}=1.14, 95% CI=1.00, 1.30) (Q-statistic=1.54, p=0.21). The studies on low birth weight (Fig 5) provide a summary odds ratio suggestive of increased risk (OR^{MH}=1.24, 95% CI=1.07, 1.43) (Q-statistic=8.49, p=0.13). The study specific OR for low birth weight and the different exposure categories, cord blood lead level, community exposure and maternal occupational lead exposure were shown in figure6, 7 and 8, respectively. Figure 8 displayed the results of 2 studies of low birth weights that pointed toward an increase risk (OR^{MH}=1.33, 95% CI=1.12, 1.59) (Q-statistic=0.36, p=0.55). The results for spontaneous abortions (Fig 9) (OR^{MH}=1.09, 95% CI=0.87, 1.37)

(Q-statistic=0.35, p=0.55), and stillbirths (Fig 10) (OR^{MH}=1.14, 95% CI=0.81, 1.61) (Q-statistic=1.41, p=0.24) were calculated combined for both maternal occupational lead exposure and exposed community exposure categories. Finally, the results of risk estimate for both preterm delivery and low birth weight according to maternal occupational lead exposure categories provided evidence of increase risk (OR^{MH}=1.14, 95% CI=1.00, 1.30, OR^{MH}=1.33, 95% CI=1.12, 1.59, respectively) (Fig 4 and 8). The results of risk estimate for both preterm delivery and low birth weight according to cord blood lead level categories provided no evidence of increase risk (OR^{MH}=0.94, 95% CI=0.67, 1.32, OR^{MH}=1.04, 95% CI=0.79, 1.37, respectively) (Fig 2 and 6), but with significant heterogeneity (Q-statistic=3.97, p=0.05, Q-statistic=4.19, p=0.04).

Discussion

Reports of reproductive problems attributed to high-dose occupational exposure to lead date back more than a century, with increased exposure associated with elevated rates of infertility, low birth weight, preterm birth, stillbirth and spontaneous abortion (Bellinger et al., 1991).

Lead transfer continues thereafter throughout fetal life and at the time of delivery a significant correlation between the lead concentration in the mother's blood and infant's cord blood is obtained (Barltrop, 1969; Harris and Holley, 1972).

Since lead passes through the placenta, offspring can be exposed in fetal life. Associations between high maternal blood level or environment with high lead level and low birth weight as well as preterm birth have been observed (Factor-Litvak et al., 1991). This investigation confirms that, even at raised levels, the infant's blood lead concentration at birth closely matches that of its mother. Therefore, we focused on maternal occupational or non-occupational lead exposure, exposed community or unexposed community, dichotomized umbilical cord blood lead levels to evaluate the association between lead exposure and birth outcomes (Irgens et al., 1998).

Although previously studies shown that most of these studies found positive associations between lead exposure and pregnant outcomes, some results have failed to find evidence supporting these associations (Clark, 1977; McMichael et al., 1986;

Savitz et al., 1989; Murphy et al., 1990; Factor-Litvak et al., 1991; Alexander et al., 1996; Lin et al., 1998).

In our study, two researches that used the cord blood lead level to discuss on the low birth weight (Bellinger et al., 1991; Recknor et al., 1997). Among them, the cord blood level category was dichotomized and divided into ≧100μg/L vs. <100μg/L and ≧50μg/L vs. <50μg/L. The research results of Recknor, 1997, indicated that those whose cord blood lead level ≧100μg/L, if the ratio is <100μg/L that will has a significant increase in the danger of low birth weight (RR=2.6 CI=1.04-6.52). Moreover, Bellinger, 1991, researched the ≧50μg/L vs. <50μg/L cord blood lead level category, yet, did not have significant statistical variation.

Furthermore, in another two researches that focused at the preterm delivery (Bellinger et al., 1991; Satin et al., 1991), the category standard is the ≧50μg/L vs. <50μg/L for cord blood lead level, and the result didn't have significant difference. Because this study found that using the cord blood lead level to investigate into the birth outcomes, low birth weight and preterm delivery, its results were inconsistent. The reason for this could be that the cord blood lead level in the research subjects was lower, the majority was lower than 100μg/L, and the influence on these two types of birth outcomes was, therefore, lower. In summary, our findings are generally consistent with the hypothesis that cord blood lead levels greater than 150 μg/L are associated

with a modest increase in risk of in utero growth impairment. Levels below 150 μ g/L do not appear to increase an infant's risk. (Bellinger et al., 1991)

Moreover, focused on using community exposure for exposure assessment to observe the influence on the two birth outcomes, preterm delivery and low birth weight, of them, community exposure caused significant influence on preterm delivery. However, it did not cause significant influence on low birth weight. When focused on investigating the two birth outcomes, spontaneous abortion and stillbirth, it was also found that community exposure had a relatively small influence on birth outcomes. This is a common problem for most researches when assessing the danger near lead contaminated areas. Exposure is not always directly proportional to residential distance and residential location may be a poor exposure proxy since exposure within communities is not homogeneous and substantial overlap of exposure distributions may occur. Sometimes the contamination to the air is often not caused by a single exposure, the exposure is also possibly caused by a contaminated water source, and the soil causes food to enter into contaminated material, these phenomena are more difficult to control in research studies. We conclude that at low current ambient levels, air-borne lead levels near the family residence are probably not the predominant source of fetal exposure. Air-borne and other routes of exposure that influence water and food supplies as well as maternal release of stored lead are probably more important for

adult women and their fetuses (Satin et al., 1991).

When focused on using maternal occupational lead exposure as an exposure assessment for the birth outcomes, preterm delivery and low birth weight, the results indicated that maternal occupational lead exposure would result in an increase risk in preterm deliveries and low birth weights. This may be related to maternal direct exposure to lead environments. Although in some studies (Savitz et al., 1989; Lin S et al, 1996), the majority was investigating on the paternal lead exposure and assumed that had larger influence on birth outcomes. Paternal exposure may be more accurately identified by industry than would maternal exposure because of men more likely to be operatives, however, in this study; it was evidently that maternal lead exposure also caused influence on fetuses.

Nevertheless, focused on the two birth outcomes, spontaneous abortion and stillbirth, maternal lead exposure did not cause influence on them. To synthesize the aforementioned maternal occupational lead exposure, although it would not cause spontaneous abortions or stillbirths, it still can influence the fetus and bring about preterm deliveries or low birth weights. In accordance with our study inclusion criteria, there were only two suitable researches, which were about the spontaneous abortion and stillbirth of birth outcomes, to be included into this analysis to investigate. Nevertheless, with considering the meta-analysis method of analysis, we integrated the

two categories of birth outcomes, maternal occupational lead exposure and community exposure, and reviewed these two types of exposure assessments, and we found that didn't reach any statistical significant difference from the meta-analysis results (spontaneous abortion: OR=1.09 CI=0.87-1.37 , stillbirth: OR=1.14 CI=0.81-1.61, see table2). It seemed that the results of these four papers that indicated mother's occupational lead exposure and environmental lead exposure did not cause influence on spontaneous abortion and stillbirth. Recent prospective studies have demonstrated how environmental chemicals, maternal smoking and drinking, and maternal nutritional status influence the risk of various adverse outcomes of pregnancy. There is also substantial evidence of deleterious effects of lead, and other heavy metals, upon pregnancy outcome. In epidemiological studies, therefore, there are methodological difficulties in apportioning the effects on pregnancy outcome between environmental lead exposure and the many other coexistent risk factors (McMichael et al., 1986).

Our meta-analysis provided consistent evidence of the effect of exposure to lead exposure on birth outcomes—in particular maternal occupational lead exposure for preterm delivery and low birth weight. Interpretation of the results of a meta-analysis is easiest when the specific effect estimates are homogeneous and have narrow confidence limits as an indication of good precision, as was the case for preterm delivery and low birth weight according to maternal occupational lead exposure. In this

situation, the contribution of meta-analysis is a more precise summary measure of effect, compared with estimates from the individual studies. However, homogeneous effect estimates do not eliminate the possibility that similar systematic errors and confounding appear in all of the individual studies.

The population-based studies reduced the possibility of selection bias in the individual studies, and consequently in the summary effect estimates. Systematic error in the outcome information is a possible source of bias for birth defects. Measures of most prominent birth defects, such as preterm deliveries and low birth weights, are less sensitive to information bias. In general, birth registration—and in some studies linkage to other sources—provided information on a number of maternal determinants of pregnancy outcomes, which were used to control for potential confounding.

A meta-analysis is difficult to interpret when the specific effect estimates differ substantially from one another, especially if estimates fall both below and above unity. The random-effects model has become a standard approach for incorporating heterogeneity. We elaborated on the heterogeneity between the specific effect estimates, but presented summary estimates from both the fixed- and random-effects models, to offer readers the opportunity to apply their own informed judgment. We also attempted to explain the observed heterogeneity, although the small number of studies in this meta-analysis limited the applicability of this approach.

The types of studies, study populations, and outcome assessments were relatively similar among the studies we examined, but the approaches to exposure assessment differed. We classified the preterm delivery and low birth weight studies into 3 categories on the basis of exposure assessment (table 2), and then conducted a stratified analysis. According to inclusion criteria and study evaluation, spontaneous abortion and stillbirth studies were combined together on the basis of exposure assessment in both community and occupational lead exposure.

This meta-analysis had several limitations because of the relatively small number of studies examined and the variability of exposure assessments during pregnancy. To date, exposure assessment in all published epidemiological studies has been based on routine monitoring of blood lead levels, and on information regarding the mother's place of residence, rather than information on the complex mixture of lead actually consumed during pregnancy. Random or systematic error in exposure assessment might have influenced the studied relationships. The summary odds ratio in a meta-analysis may be inaccurate when bias cannot be eliminated, or when there is insufficient adjustment for confounding factors. Also, publication bias is a concern for all meta-analyses. Our bibliographic search was limited to databases including published studies. There may exist other not published studies, for example, doctoral theses and congress communications. It is extremely difficult to identify such studies

(Villanueva CM et al., 2003). Furthermore, their inclusion could be questioned as quality criteria are difficult to apply. In addition, studies may assess effects on several birth outcomes, but only report the statistically significant results.

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Table1. Summary of Studies Included in the Meta-analysis

Author/ Year/ Location	Type of study	Study population	Outcomes in the meta-analysis	Exposure assessment	Adjustment for confounding
Irgens et al.1998 Norway	Cross-sectional; population-based	Total 37636 infants including: 1886 infants were born to mothers classified as lead-exposed, 35930 infants were classified as fathers lead-exposed, 180 infants had both parents exposed	Low birth weight, preterm delivery	Maternal occupational lead exposure vs. without occupational lead exposure	Maternal age and education, fathers education, gestational age
Bellinger et al. 1991 Massachusetts	Cross-sectional; population-based	Interviewing 4354 women within 2 days of delivery, complete data on all outcomes and covariates were available for 3503 infants including: 260 low birth weight, 243 preterm delivery	Low birth weight, preterm delivery	Umbilical cord lead ($\leqq$ 50 μ g/L, $>$ 50 μ g/L)	Maternal age, marital status, working status, education, race, ponderal index, parity, smoking status, beer wine spirit and coffee consumption during pregnancy, hematocrit at delivery, diabetes, mode of delivery
Clark AR. 1977 Kasanda, Zambia	Cross-sectional study population-based	5/122 exposed community (low birth weight prevalence), 3/31 unexposed community (low birth weight prevalence)	Low birth weight	Exposed community vs. unexposed community	Unadjusted
Fahim et al. 1976 Missouri	Cross-sectional study hospital-based	249 women unexposed community, 253 women exposed community (Including: 8 preterm deliveries in unexposed community, 33 preterm deliveries in exposed community)	Preterm delivery	Exposed community vs. unexposed community	Unadjusted
Satin et al. 1991 California	Cross-sectional; hospital-based	723 live births (Including: 14 preterm deliveries, 71 low birth weights)	Preterm delivery, low birth weight	Umbilical cord lead ($\leqq$ 50 μ g/L, $>$ 50 μ g/L)	Unadjusted

Min et al. 1996 Baltimore USA	Case control study, population-based	220 cases (low birth weight<2500g) 522 controls(≧ 2500g)	Low birth weight	Maternal occupational lead exposure vs. without occupational lead exposure	Infant race, marital status, maternal education, paternal education, maternal employment, paternal employment, household income, maternal height, pregnancy weight gain, maternal cigarette smoking during pregnancy, maternal health status, trying to become pregnant, previous pregnancy outcomes
Savitz et al. 1989 US	Case control study population-based	Case groups: Stillbirths (2096 mothers, 3170 fathers), preterm deliveries (363mothers, 552 fathers), vs. control groups: Live births (3668 mothers, 5669 fathers), Term (2624 mothers, 4038 fathers)	Preterm delivery, stillbirth	Maternal occupational lead exposure vs. without occupational lead exposure	Child's race, previous miscarriage, restricted to women who received prenatal care, mother's age<40yrs, alcohol consumption, no previous stillbirths, maternal smoking, mother's age≧20yrs, less than 2 previous miscarriages, no previous induced abortions
Lindbohm et al. 1991 Finland	Case-control study hospital-based	213 spontaneous abortions (cases), 300 births (controls)	Spontaneous abortion	Maternal occupational lead exposure vs. without occupational lead exposure	Wife age, paternal alcohol use, paternal exposure to cadmium and mercury, maternal exposure to organic solvents, mercury and alcohol, parity, contraception, previous spontaneous abortion and the index of missing information
Murphy et al. 1990 Kosovo, Yugoslavia	Cohort study population-based	A total of 639 women (304 exposed community, 335 unexposed community) had at least one previous pregnancy and lived at the same address	Spontaneous abortion, stillbirth	Exposed community vs. unexposed community	Maternal age, current smoking, ethnic group, maternal education

		since their first pregnancy. (Including: spontaneous abortion: 50 in exposed community, 47 in unexposed community. Stillbirths: 10 in exposed community, 13 in unexposed community)			
Factor-Litvak et al. 1991 Kosovo, Yugoslavia	Cohort study population-based	401 women in the exposed town and 506 in the comparison town were completed follow up (the analysis excludes cases with lengths of gestation less than 28 weeks or greater than 44 weeks)	Preterm delivery	Exposed community vs. unexposed community,	Unadjusted
McMichael et al. 1986 South Australia	Cohort study population-based	A total of 831 pregnant women (646 exposed community, 185 unexposed community)	Preterm delivery, low birth weight	Exposed community vs. unexposed community	Late fetal death
Recknor et al. 1997 Charleston, USA	Retrospective cohort population-bases	200 predominantly black infants between the ages of 6 and 22 months (Including: 22 low birth weight)	Low birth weight	Infants blood lead level $\geqq 100\ \mu$ g/L vs. $<100\ \mu$ g/L	Age at screen, race

Notes: Definitions of birth outcomes

Low birth weight (LBW): birth weight was less than 2500g

Preterm delivery: delivery prior to the 37 weeks pregnancy (Irgen, 1998; Bellinger, 1991; Savitz, 1989; Satin, 1991)

delivery prior to the 37 weeks pregnancy (stillbirths included) (McMichael, 1986)

delivery prior to the 37 weeks pregnancy and weighing less than 2500g (Fahim, 1976)

delivery <260 days gestation period (Satin, 1991)

preterm delivery excluded deliveries <28 weeks and deliveries >44 weeks (Factor-Litvak, 1991)

Spontaneous abortion: a fetal loss prior to the 7th month of gestation (Murphy, 1990)

no definition of spontaneous abortion (Lindbohm 1991)

Stillbirth: a fetal loss occurring in months seven through nine of gestation (Murphy, 1990)

a gestational age of 28 or more weeks or, when gestational age was missing, a weight of 1000g or more (Savitz)

Table2. Summary Odds Radios (ORs) for the Relationship between Exposure to Lead and the Risk of Birth Outcomes

Birth outcomes (Exposure category)	No. studies	OR^{MH}	95% CI	OR^{DL}	95% CI	Q-statistic	p
Preterm delivery	7	1.30	1.18, 1.43	1.47	1.11, 1.94	26.32	<0.01
(Cord blood lead level)	2	0.94	0.67, 1.32	1.38	0.43, 4.48	3.97	0.05
(Community exposure)	3	1.65	1.41, 1.92	1.78	1.28, 2.49	4.54	0.10
(Occupational exposure)	2	1.14	1.00, 1.30	1.29	0.75, 2.22	1.54	0.21
Low birth weight	6	1.24	1.07, 1.43	1.21	0.90, 1.64	8.49	0.13
(Cord blood lead level)	2	1.04	0.79, 1.37	1.42	0.54, 3.75	4.19	0.04
(Community exposure)	2	0.89	0.21, 3.78	0.94	0.15, 5.83	1.59	0.21
(Occupational exposure)	2	1.33	1.12, 1.59	1.33	1.12 1.59	0.36	0.55
Spontaneous abortion	2	1.09	0.87, 1.37	1.09	0.87, 1.37	0.35	0.55
Stillbirth	2	1.14	0.81, 1.61	1.17	0.76, 1.81	1.41	0.24

Notes: OR^{MH}=Summary OR using the Matel-Haenszel method for the fixed-effects model, OR^{DL}=Summary OR using the DerSimonian-Laird method for the random-effects model. $^{*}p<0.05$ indicated that a random effects model is more approprite.

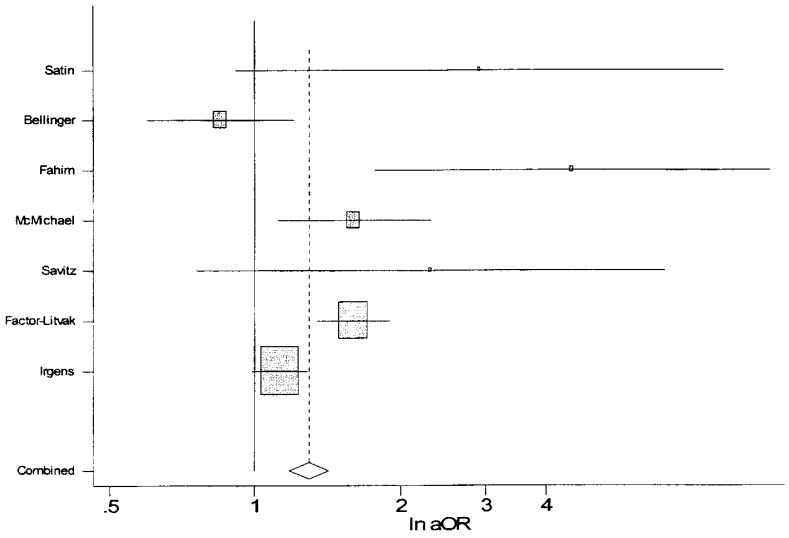

Figure1. Tree Plots of Study-specific and Summary Effect Estimates for Preterm Delivery.

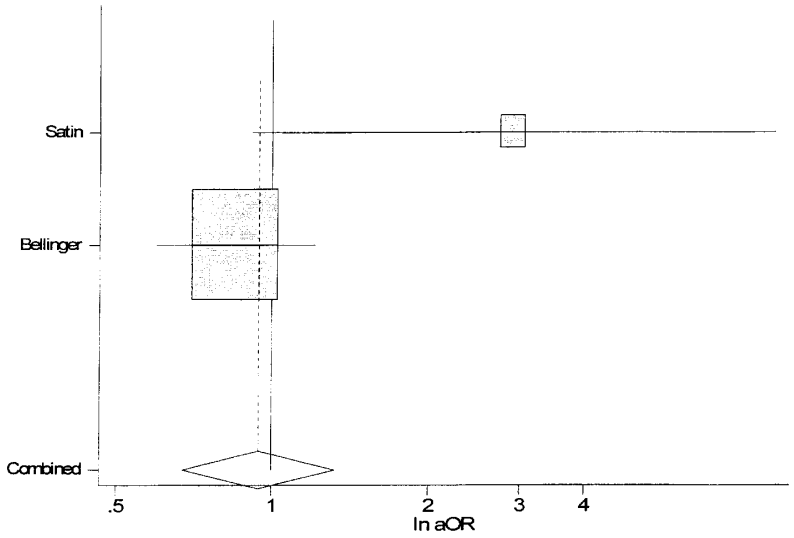

Figure1-1. Tree Plots of Study-specific and Summary Cord Blood Lead Level for preterm delivery.

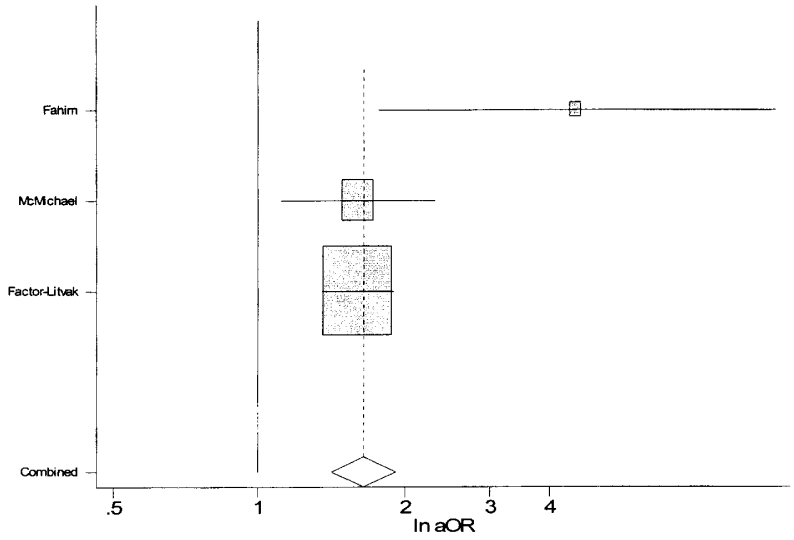

Figure1-2. Tree Plots of Study-specific and Summary Community Exposure for Preterm Delivery.

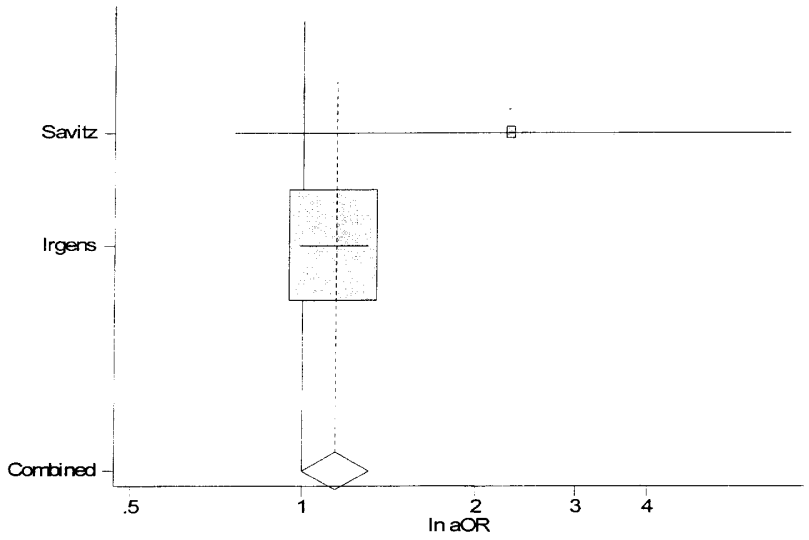

Figure1-3. Tree Plots of Study-specific and Summary Maternal Occupational Lead Exposure for Preterm Delivery.

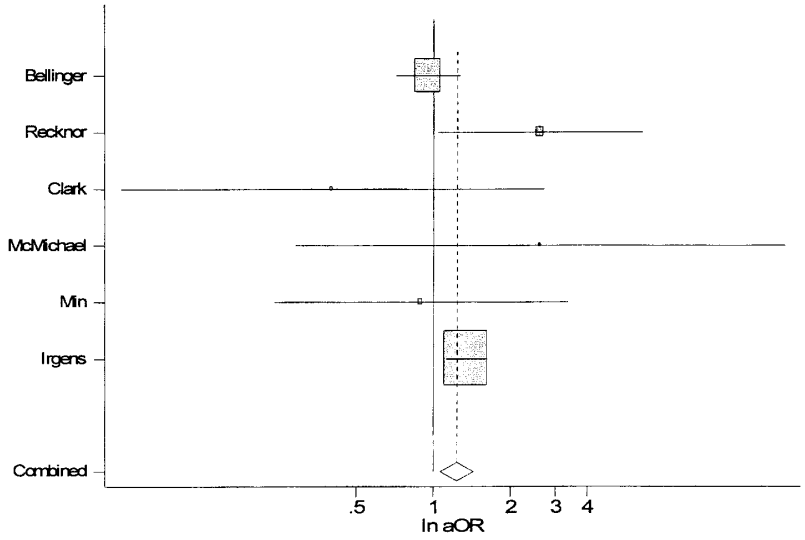

Figure2. Tree Plots of Study-specific and Summary Effect Estimates for Low Birth Weight.

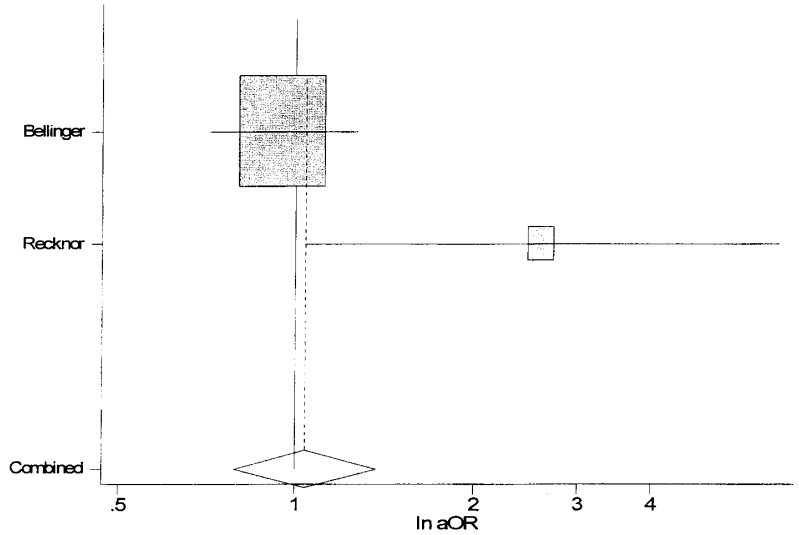

Figure2-1. Tree Plots of Study-specific and Summary Cord Blood Lead Level for Low Birth Weight.

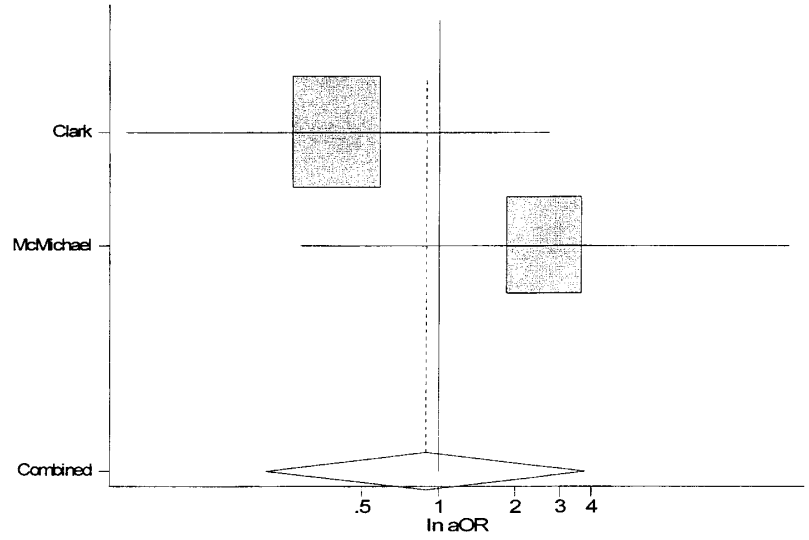

Figure2-2. Tree Plots of Study-specific and Summary Community Exposure for Low Birth Weight.

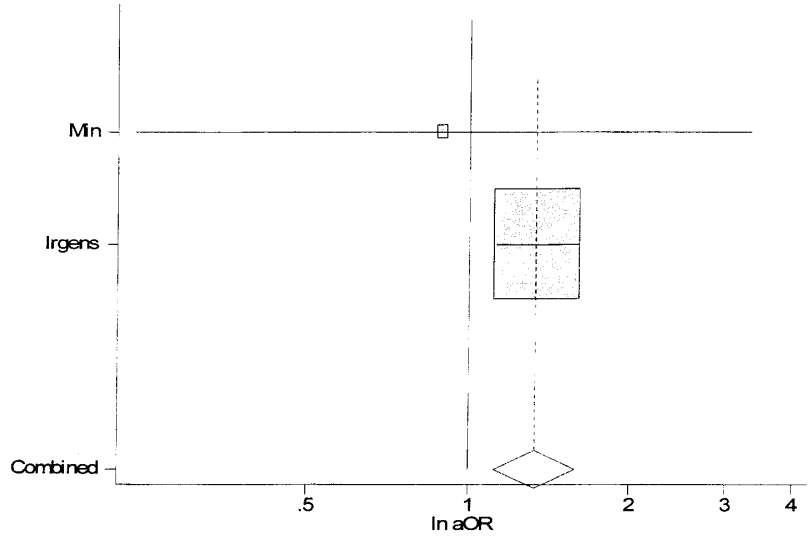

Figure2-3. Tree Plots of Study-specific and Summary Maternal Occupational Lead Exposure for Low Birth Weight.

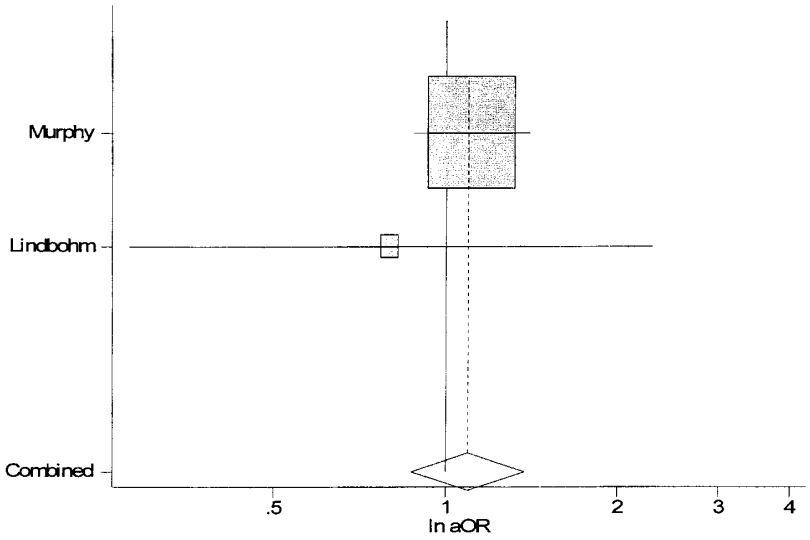

Figure3. Tree Plots of Study-specific and Summary Effect Estimates for Spontaneous Abortion.

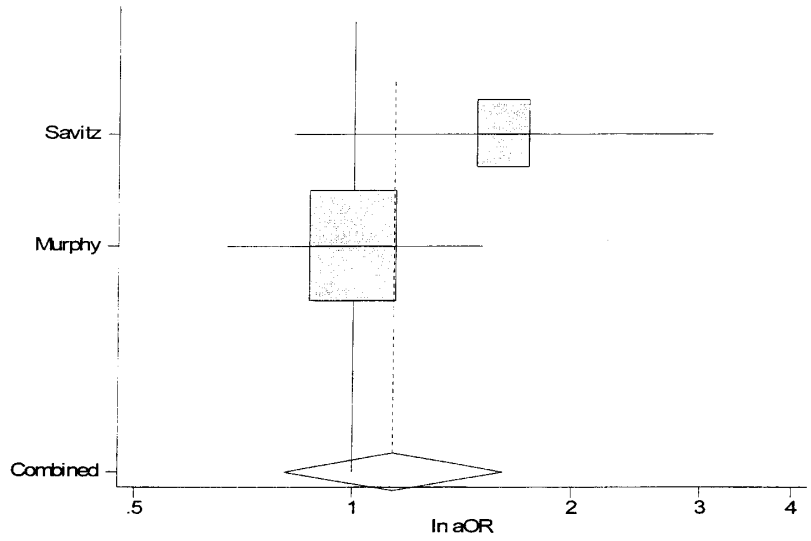

Figure4. Tree Plots of Study-specific and Summary Effect Estimates for Stillbirth.

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