

## Original Article

# Association between maternal smoking during pregnancy and recurrent wheezing in infancy: evidence from a meta-analysis

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Received February 16, 2015; Accepted April 13, 2015; Epub May 15, 2015; Published May 30, 2015

**Abstract:** Background: Quantification of the association between the maternal smoking during pregnancy and recurrent wheezing in infancy is still conflicting. Thus, we performed a comprehensive meta-analysis to test the hypothesis that maternal smoking during pregnancy may increase the risk of recurrent wheezing in infancy. Methods: Pertinent studies were identified by a search in PubMed and Web of Knowledge up to October 2014. Random-effect model (REM) or fixed effects model (FEM) was used to combine study-specific results. Publication bias was estimated using Egger's regression asymmetry test. Results: Seven articles (3 cohort study and 4 cross-sectional studies) involving 8579 recurrent wheezing infant cases about maternal smoking during pregnancy and recurrent wheezing risk were used in this meta-analysis. The combined relative risks (RRs) of recurrent wheezing infants associated with maternal smoking during pregnancy was 1.491 (95% CIs = 1.329-1.672) overall. Significant associations were found both in Europe [RRs = 1.471, 95% CIs = 1.287-1.681] and other populations [RRs = 1.720, 95% CIs = 1.119-2.644] and cross-sectional studies [RRs = 1.474, 95% CIs = 1.306-1.663]. No publication bias was found. Conclusions: Our analysis indicated that maternal smoking during pregnancy could increase the risk of recurrent wheezing in infancy.

**Keywords:** Maternal smoking, recurrent wheezing, infancy, meta-analysis

## Introduction

Recurrent wheezing is common in young children, with a cumulative prevalence of up to 40% in the first 6 years of life [1]. It is an important cause of diminished health-related quality of life in infancy [2]. Many children are exposed to tobacco smoking, both before and after they are born. Maternal smoking during pregnancy is believed to affect the utero-placental flow, leading to an impaired foetal nutrition and consequent intrauterine growth retardation [3]. The foetus of smoking women is exposed from the time of conception to the same levels of nicotine as active smokers [4]. Smoking during pregnancy affects foetal lung development, reflected in spirometric flow in the neonate, especially when there is a family history of asthma and hypertension during pregnancy [5] and causes abnormal airway function [6, 7]. Up to date, a number of epidemiologic studies have been published to explore the relationship between maternal smoking during pregnancy

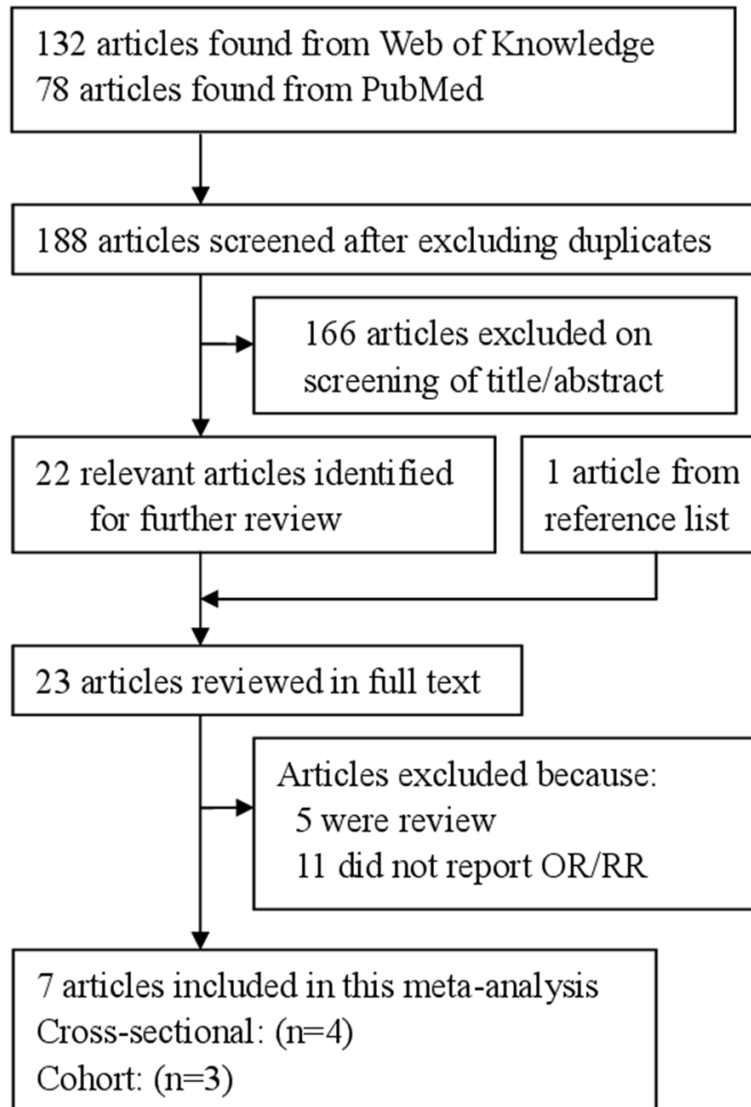
and risk of recurrent wheezing in infancy. However, the results are not consistent. Thus, to better characterize this issue, we conducted a comprehensive meta-analysis to evaluate the evidence from observational studies on maternal smoking during pregnancy with the risk of recurrent wheezing in infancy by summarizing it quantitatively with a meta-analysis approach.

## Methods

### *Search strategy*

A comprehensive search was conducted for available articles published in English using the databases of PubMed and Web of Knowledge up to October 2014 and by hand-searching the reference lists of the computer retrieved articles. The following search terms were used: 'recurrent wheezing' AND 'risk factor' AND 'smoking' AND 'pregnancy'. Two investigators searched articles and reviewed of all retrieved studies independently. Disagreements between

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**Figure 1.** The detailed steps of our literature search.

the two investigators were resolved by consensus with a third reviewer.

### *Inclusion criteria*

All relevant studies reporting the association of maternal smoking during pregnancy and recurrent wheezing in infancy were considered for inclusion. The inclusion criteria were as follows: (1) use a case-control, cross-sectional studies or cohort design; (2) the exposure of interest was maternal smoking during pregnancy; (3) the outcome of interest was recurrent wheezing in infancy; (4) report associations in the form of relative risks (RRs) with the 95% confidence intervals (CIs) for recurrent wheezing in

infancy or providing us sufficient information to calculate them. Accordingly, the following exclusion criteria were also used: (1) reviews and (2) repeated or overlapped publications.

### *Data extraction*

Two researchers independently extracted the following information: name of the first author, publication year, study design, ethnicity, the number of cases and controls or participants, sources of controls, the methods used for collection of data on exposure, exposure classification, confounders adjusted for and the RRs estimates with corresponding 95% CIs for the highest versus lowest level. From each study, we extracted the risk estimates adjusted for the greatest number of potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

### *Statistical analysis*

The pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RRs with 95% CIs for the highest vs. lowest levels to assess the association of recurrent wheezing in infancy risk. The Q test and  $I^2$  of Higgins and Thompson [8] were used to assess heterogeneity among included studies.  $I^2$  describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, and  $I^2$  values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively [9]. The DerSimonian and Laird random effects model (REM) was selected as the pooling method if substantial heterogeneity was present ( $I^2 > 50%$ ) [9]; otherwise, the fixed effects model

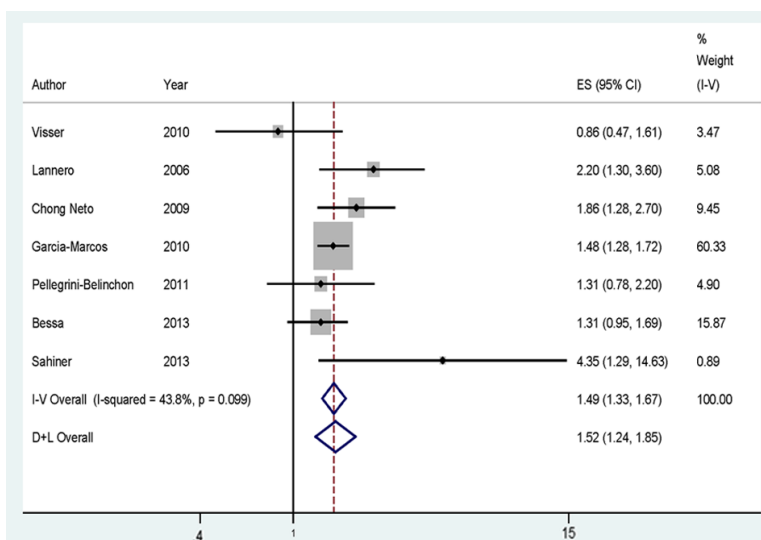
## Maternal smoking and recurrent wheezing in infancy

**Table 1.** Characteristics of studies on maternal smoking during pregnancy and recurrent wheezing risk

| First author, year               | Country     | Study design    | Cases | RRs (95% CIs) for highest versus lowest category | Adjustment or matched for   |
|----------------------------------|-------------|-----------------|-------|--|---|
| Visser et al. 2010               | Netherlands | Cohort          | 149   | 0.86 (0.47-1.61)                                 | Adjusted odds ratios compare those in the wheeze ever, recurrent wheeze, or severe wheeze group to children not having any wheezing.  |
| Lannero et al. 2006              | Sweden      | Cohort          | 321   | 2.2 (1.3-3.6)                                    | Adjusted for heredity, defined as asthma and/or allergic rhino-conjunctivitis diagnosed by a doctor and in combination with reported allergy to furred pets and/or pollen in one or both parents (reported asthma medication was required for asthma diagnosis), maternal age and length of exclusive breast feeding. |
| Chong Neto et al. 2009           | Brazil      | Cross-sectional | 679   | 1.86 (1.28-2.70)                                 | Na.   |
| Garcia-Marcos et al. 2010        | Europe      | Cross-sectional | 6369  | 1.48 (1.28-1.72)                                 | Adjusted for Male Gender, Asthma, Rhinitis, Infant eczema, Breast feeding, Mould stains, Pets at home.  |
| Pellegrini-Belinchon et al. 2011 | Spain       | Cross-sectional | 443   | 1.31 (0.78-2.20)                                 | Na.   |
| Bessa et al. 2013                | Brazil      | Cross-sectional | 89    | 1.31 (0.95-1.69)                                 | Adjusted for demographic, socioeconomic, family, and clinical characteristics.  |
| Sahiner et al. 2013              | Turkey      | Cohort          | 529   | 4.35 (1.29-14.63)                                | Adjusted for Gender, Asthma predictive index, Pet exposure at home during the first 3 years, Hospitalization during the first 3 years.  |

Abbreviations: Na: not available.

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**Figure 2.** The forest plot between maternal smoking during pregnancy and recurrent wheezing in infancy risk. White diamond denotes the pooled RRs. Black squares indicate the RRs in each study, with square sizes inversely proportional to the standard error of the RRs. Horizontal lines represent 95% CIs.

(FEM) was adapted. Publication bias was estimated using Egger's regression asymmetry test [10]. A study of influence analysis [11] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CIs of the combined analysis. All analyses were conducted using STATA software, version 10.0 (StataCorp LP, College Station, Texas). Two-tailed  $P \leq 0.05$  was accepted as statistically significant.

### Results

#### Search results and study characteristics

The search strategy identified 78 articles from Pubmed and 132 from the Web of Knowledge; 22 articles were reviewed in full after reviewing the title/abstract. By studying reference lists, we identified 1 additional article. Sixteen of these 23 articles were subsequently excluded from the meta-analysis for various reasons. In total, 7 articles [12-18] (3 cohort study and 4 cross-sectional studies) involving 8579 recurrent wheezing infants cases about maternal smoking during pregnancy and recurrent wheezing in infancy risk were used in this meta-analysis. The detailed steps of our literature search are shown in **Figure 1**. The characteris-

tics of these studies are presented in **Table 1**.

For maternal smoking during pregnancy and recurrent wheezing in infancy risk, data from 7 studies including 8579 recurrent wheezing infant cases were used. Significant association of maternal smoking during pregnancy and recurrent wheezing in infancy was reported in 4 studies, and no significant association of maternal smoking during pregnancy and recurrent wheezing in infancy was reported in 3 studies. Pooled results suggested that maternal smoking during pregnancy was significantly associated with the risk of recurrent wheezing in infancy [summary RRs = 1.491, 95% CIs = 1.329-1.672] with moderate heterogeneity ( $I^2 = 44.0\%$ ,  $P_{\text{heterogeneity}} = 0.098$ ) (**Figure 2**).

#### Subgroup analysis

For the subgroup analyses by study design, the association was significant in the cross-sectional studies [RRs = 1.474, 95% CIs = 1.306-1.663], but not in the cohort studies for the maternal smoking during pregnancy and recurrent wheezing in infancy risk. In subgroup analyses of geographic locations, when we restricted the analysis to Europe and Others, significant association was found both in Europe [RRs = 1.471, 95% CIs = 1.287-1.681] and Others [RRs = 1.720, 95% CIs = 1.119-2.644]. The main results are summarized in **Table 2**.

#### Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the association of maternal smoking during pregnancy and recurrent wheezing in infancy (**Figure 3**). Egger's test showed no evidence of significant publication bias between maternal smoking during pregnancy and recurrent wheezing in infancy ( $P = 0.592$ ).

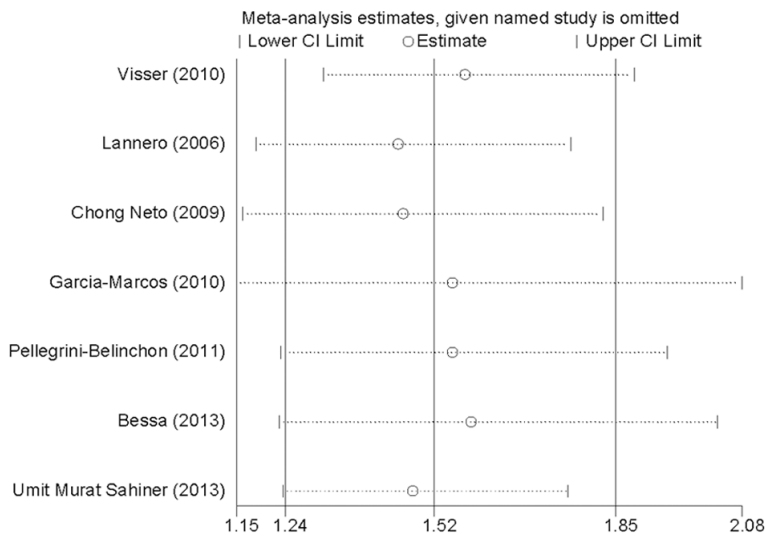
### Discussion

Finding from this meta-analysis suggested that maternal smoking during pregnancy could

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**Table 2.** Summary risk estimates of the association between maternal smoking during pregnancy and recurrent wheezing in infancy risk

| Sub-groups           | Cases | RR (95% CI)         |                     | I <sup>2</sup> (%) | P <sub>heterogeneity</sub> | Studies |
|----------------------|-------|---------------------|---------------------|--------------------|----------------------------|---------|
|                      |       | FEM                 | REM                 |                    |                            |         |
| All studies          | 8579  | 1.491 (1.329-1.672) | 1.516 (1.244-1.848) | 44.0               | 0.098                      | 7       |
| Study design         |       |                     |                     |                    |                            |         |
| Cross-sectional      | 7580  | 1.474 (1.306-1.663) | 1.474 (1.306-1.663) | 0.0                | 0.505                      | 4       |
| Cohort               | 999   | 1.663 (1.145-2.416) | 1.823 (0.796-4.174) | 75.0               | 0.018                      | 3       |
| Geographic locations |       |                     |                     |                    |                            |         |
| Europe               | 7282  | 1.471 (1.287-1.681) | 1.441 (1.092-1.900) | 45.6               | 0.138                      | 4       |
| Others               | 1297  | 1.549 (1.238-1.938) | 1.720 (1.119-2.644) | 60.4               | 0.080                      | 3       |



**Figure 3.** Analysis of influence of individual study on the pooled estimate in maternal smoking during pregnancy and recurrent wheezing in infancy risk. Open circle, the pooled RRs, given named study is omitted. Horizontal lines represent the 95% CIs.

increase the risk of recurrent wheezing in infancy. We also found significant association in cross-sectional studies, but not in cohort studies.

Maternal smoking during pregnancy might be an important risk factor for the recurrent wheezing in infancy. It is really a major problem to differentiate the effects of prenatal and postnatal smoke exposure since most mothers who smoke during pregnancy will continue to smoke after labor. Other studies have also shown that smoke exposure prenatally and postnatal were found to be related to the persistence of symptoms [19-21]. During the intrauterine period, smoke exposure by maternal smoking may affect the development of airways, which results in wheezing at an early age. A study

found that maternal smoking during pregnancy was especially related to transient wheezing [20]. It is probable that smoke exposure both causes a chronic inflammation in the airways and triggers the exacerbation of an ongoing inflammatory process.

We reported here the first comprehensive meta-analysis on maternal smoking during pregnancy and the risk of recurrent wheezing in infancy. Our study included a larger number of cases and participants, allowing a much greater possibility of reaching reliable conclusions about the association between maternal smoking during pregnancy and the recurrent wheezing in

infancy risk. However, our study has some limitations. First, as a meta-analysis of observational studies, we cannot rule out that individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Second, the included articles could not separate the RRs for the prenatal and postnatal smoke exposure. It is really a major problem to differentiate the effects of prenatal and postnatal smoke exposure since most mothers who smoke during pregnancy will continue to smoke after labor. Further studies with a separate report of prenatal and postnatal smoke exposure are wanted to confirm this association between maternal smoking during pregnancy and the recurrent wheezing in infancy risk. Third, we found a sig-

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nificant association between maternal smoking during pregnancy and the risk of recurrent wheezing in infancy in cross-sectional studies, but not in the cohort. Only 3 cohort studies with 999 cases were included in this meta-analysis, probably due to the small number of cases included. Further studies with cohort design are wanted to confirm this association between maternal smoking during pregnancy and the risk of recurrent wheezing in infancy. Fourth, moderate between-study heterogeneity was found in some analysis in this meta-analysis, and the between-study heterogeneity was not successfully explained by the subgroup analysis. The observed heterogeneity might arise from diversity in design quality, population stratification, characteristics of the sample, etc. Finally, publication bias should be concerned in meta-analysis because of small number of studies included. Nevertheless, we found no evidence of publication bias.

In summary, our analysis indicated that maternal smoking during pregnancy could increase the risk of recurrent wheezing in infancy.

### Disclosure of conflict of interest

None.

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### References

- [1] Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, de Jongste JC, Eber E, Everard ML, Frey U, Gappa M, Garcia-Marcos L, Grigg J, Lenney W, Le Souef P, McKenzie S, Merkus PJ, Midulla F, Paton JY, Piacentini G, Pohunek P, Rossi GA, Seddon P, Silverman M, Sly PD, Stick S, Valiulis A, van Aalderen WM, Wildhaber JH, Wennergren G, Wilson N, Zivkovic Z, Bush A. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096-1110.
- [2] Mohangoo AD, Essink-Bot ML, Juniper EF, Moll HA, de Koning HJ, Raat H. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. *Qual Life Res* 2005; 14: 1931-1936.
- [3] Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. *Paediatr Perinat Epidemiol* 1997; 11: 140-151.
- [4] Foundas M, Hawkrigg NC, Smith SM, Devadason SG, Le Souef PN. Urinary cotinine levels in early pregnancy. *Aust N Z J Obstet Gynaecol* 1997; 37: 383-386.
- [5] Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997; 10: 1774-1779.
- [6] Elliot JG, Carroll NG, James AL, Robinson PJ. Airway alveolar attachment points and exposure to cigarette smoke in utero. *Am J Respir Crit Care Med* 2003; 167: 45-49.
- [7] Gilliland FD, Berhane K, Li YF, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 2003; 167: 917-924.
- [8] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-1558.
- [9] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560.
- [10] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-634.
- [11] Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull* 1999; 47: 15-18.
- [12] Visser CA, Garcia-Marcos L, Eggink J, Brand PL. Prevalence and risk factors of wheeze in Dutch infants in their first year of life. *Pediatr Pulmonol* 2010; 45: 149-156.
- [13] Lannero E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res* 2006; 7: 3.
- [14] Chong Neto HJ, Rosario N, Sole D, Mallol J. Associated factors for recurrent wheezing in infancy. *Allergy* 2010; 65: 406-407.
- [15] Garcia-Marcos L, Mallol J, Sole D, Brand PL, Group ES. International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol* 2010; 21: 878-888.
- [16] Pellegrini-Belinchon J, Miguel-Miguel G, De Dios-Martin B, Vicente-Galindo E, Lorente-Toledano F, Garcia-Marcos L. Study of wheezing and its risk factors in the first year of life in the Province of Salamanca, Spain. *The EISL Study. Allergol Immunopathol (Madr)* 2012; 40: 164-171.
- [17] Bessa OA, Leite AJ, Sole D, Mallol J. Prevalence and risk factors associated with wheezing in the first year of life. *J Pediatr (Rio J)* 2014; 90: 190-196.

## Maternal smoking and recurrent wheezing in infancy

- [18] Sahiner UM, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Soyer O, Sackesen C, Tuncer A, Sekerel BE. Recurrent wheezing in the first three years of life: short-term prognosis and risk factors. *J Asthma* 2013; 50: 370-375.
- [19] Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A, Asthma NACM, Allergy Study G. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005; 171: 231-237.
- [20] Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003; 111: 661-675; quiz 676.
- [21] Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349: 1414-1422.