

BMJ Open Farm environment during infancy and lung function at the age of 31: a prospective birth cohort study in Finland

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ABSTRACT

Objectives: Farming as an occupation is considered a risk factor for asthma and reduced lung function. By contrast, living on a farm during infancy has been reported to be associated with lower risk of asthma in adulthood. However, little is known about the association between farming environment during infancy and lung function in adulthood. We aimed to study the prospective longitudinal association between farming environment during infancy and lung function in adulthood.

Design: A prospective birth cohort study.

Setting: Northern Finland.

Participants: 5666 participants born in 1966 were followed up at the age of 31 years.

Primary outcome measures: Spirometry at the age of 31 years.

Results: To be born into a farmer's family was associated with higher forced expiratory volume in 1 s (FEV1) (36 mL; 95% CI 6 to 67 mL) and forced vital capacity (FVC) (40 mL; 95% CI 5 to 75 mL) at the age of 31 years. Contact with farm animals during infancy was associated with higher FEV1. No associations were seen with FEV1/FVC (FEV1/FVC ratio). Having dogs in childhood revealed similar associations. There was a suggestive dose-dependent association with the number of animal species during childhood and higher FEV1 and FVC at adulthood, especially among women.

Conclusions: Farming environment in early life may have a positive impact on lung function in adulthood.

INTRODUCTION

Farming environment during infancy, especially contact with farm animals, is associated with decreased risk of asthma and allergic diseases.^{1–3} Microbial exposure on a farm during infancy may inhibit the development of the allergic phenotype by influencing the development of the immune system.¹ On the other hand, respiratory diseases such as asthma, allergic rhinitis, organic dust syndrome and extrinsic allergic alveolitis are

Strengths and limitations of this study

- The prospective nature of the study allowed analysis of longitudinal associations between farming environment during infancy and lung function at the age of 31 years without possible recall bias.
- The information was comprehensive about the factors in infancy that may affect lung function, including birth weight and pregnancy information.
- Although work and home-based exposure to cold, dust, solvents and tobacco, as well as occupation at the age of 31 years, were taken into account, detailed post-childhood information about farming exposures was lacking.
- Owing to lack of information about physical activity during childhood, its effect on lung function at the age of 31 years cannot be estimated.

well-known occupational health problems among farmers.⁴ In a farming environment, especially with farm animals, constant exposure to dust (organic and inorganic), chemicals (eg, pesticides and fertilisers), gases, fumes and infectious agents,⁴ may irritate and induce inflammation in the respiratory system,^{5 6} lead to impairment of lung function^{7–12} and be a risk factor for respiratory diseases, for example, asthma.^{4–6} Therefore, living in a farm environment during infancy may reduce the risk of asthma and allergic diseases in adulthood, whereas exposure during adulthood may be a risk factor for respiratory diseases. There is a lack of longitudinal studies on the effect of farming environment during infancy and lung function in adulthood. The present prospective birth cohort study, with detailed questionnaire data regarding infancy and childhood environment, offered an excellent opportunity to

investigate the effect of farming environment in infancy, especially contact with farm animals, on lung function measured by spirometry, at the age of 31 years.

METHODS

The Northern Finland Birth Cohort 1966 (NFBC1966) is a prospective study of 12 058 live births from Oulu and Lapland, the two northernmost provinces of Finland, and covered 96% of the children born in that region between 1 January and 31 December 1966. In 1997, 8463 survivors still living in northern Finland or in the capital city area received a postal questionnaire and invitation to clinical examinations. A detailed description of the number of participants and flow charts of the 31-year follow-up study are shown on the study website.¹³ The current analyses included those 5666 participants who had complete spirometry data at the age of 31 years and who were not pregnant. The participants gave written informed consent.

Antenatal and childhood factors

Information about the farming environment, lifestyle factors, maternal factors and sociodemographic factors in infancy were collected from the mother during her pregnancy and/or immediately after delivery.² Parental professional farming was defined if the participant's mother, father or both were classified as professional farmers. Childhood information about having farm animals (species and counts), place of residence, residential density, maternal education, maternal age, maternal BMI, smoking during pregnancy from the second month, mother's age of menarche and parity number, gestational age at birth, birth weight and height were collected during pregnancy and/or immediately after delivery. Residential density was defined as number of participants in the household divided by number of rooms in the household. Data obtained from hospital discharge registry were used to identify patients with pneumonia before the age of 7 years. Information about smoking at the age of 14 years was collected, with questionnaires sent to participants and parents in 1980.

Assessment at the age of 31 years

During follow-up at the age of 31 years, participants underwent a clinical examination, spirometry and skin prick tests, and filled in a health questionnaire. Lung function was assessed by forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) using a Vitalograph P-model spirometer (Vitalograph Ltd, Buckingham, UK) with a volumetric accuracy of 2% or 50 mL, whichever was greater. The spirometer was calibrated regularly using a 1 L precision syringe. The spirometric manoeuvre was performed three times, but was repeated if the difference between two maximal readings for FEV₁ or FVC was >4%. The highest FEV₁ and FVC were used. Those in the skin prick test with a mean weal reaction ≥ 3 mm to one or more of the four

allergens tested were considered to be atopic. Participants with a positive reaction to the negative control or negative reaction to histamine (<3 mm) were excluded. At 31-year follow-up, participants also filled in questionnaires that included queries on health and lifestyle factors, ownership of a cat or a dog before the age of 7 years (retrospectively) and sociodemographic factors.² Doctor-diagnosed asthma ever at the age of 31 years was based on self-report.²

Statistical analyses

The final analyses included those 5666 participants who had complete spirometry data and were not pregnant. Multivariate linear models were used to analyse associations between farm environment, potential confounders and lung function. We identified, a priori, the list of potential confounders. At the age of 31 years, potential confounders were height, weight, physical activity, education, smoking, exposure to cold, dust, solvents and tobacco smoke at work/or at home, paternal asthma, maternal asthma, paternal allergy and maternal allergy. Potential childhood confounders were height, weight and gestational age at birth, residential density, pneumonia before the age of 7 years and smoking at the age of 14 years. Potential maternal confounders were mother's menarcheal age, parity number, age, education and smoking during pregnancy (after the second month of pregnancy). For the final models, we included all variables that were associated with outcome at $p < 0.1$ level and changed the estimate for the gender-adjusted association between farm animals during infancy and outcome (FVC, FEV₁) by more than 10%. Models for FEV₁ were adjusted for gender, along with height, weight, smoking, education, exposure to solvents and tobacco smoke at home, and physical activity, at the age of 31 years; and smoking at the age of 14 years, birth height and weight, maternal education, paternal asthma and maternal age. Models for FVC were adjusted for gender, height, weight, smoking, education, exposure to solvents and tobacco smoke at home and physical activity at the age of 31 years; and birth height and weight, maternal education and residential density during infancy. Models for FEV₁/FVC were adjusted with confounders selected for models for both FEV₁ and FVC.

Among included participants, the maximum percentage of missing data was 4.4% for diseases, 0.9% for farm characteristics collected during the mother's pregnancy, 4.6% for pet ownership collected at the 31-year follow-up, and 2.9% for data on current occupation. For statistical analyses, missing data for confounders were classified as a separate category. The highest percentage of missing information concerned allergic conditions of the father (12.8%). All analyses were conducted with IBM SPSS.

RESULTS

Characteristics and overall prevalence of allergic and respiratory diseases among study population at the age

of 31 years are described in table 1. Having a parent who was a professional farmer during one's infancy was significantly associated with increased FEV₁ and FVC at the age of 31 years (table 2). Furthermore, having farm animals during one's infancy was associated with significantly increased FEV₁ at the age of 31 years (table 2). Having dogs in childhood revealed similar associations (table 2). No associations were detected with FEV₁/FVC.

There was a suggestive association between the number of animal species during childhood and increasing lung function at the age of 31 years (table 2), especially among women (table 3). Further adjustment for current farming occupation at the age of 31 years had no impact on the size of the estimates of the observed significant associations on table 2 (data not shown). Although associations between farming environment and higher lung function at the age of 31 years were most evident among women, no significant gender interactions ($p < 0.05$) were observed. The smallest p value was observed for the interaction between gender and having cats in childhood (FVC, $p = 0.09$), reaching almost nominal statistical significance. Other p values for interaction between gender and having dogs during childhood, having farm animals, or family being involved in professional farming during infancy ranged between $p = 0.18$ and 0.92 .

To explore if the associations in table 2 are mediated via the protective effect of childhood farm life on atopy or asthma,² the models were further adjusted for atopy

and asthma (table 4). Atopy and doctor-diagnosed asthma reduced the size of the estimates in table 2 by 50% at the most. This suggests that although atopy and asthma probably mediate the effect on improved lung function, other pathways are also likely to be operational.

DISCUSSION

To the best of our knowledge, this is the first prospective birth cohort study on the association between a farming environment during infancy and lung function in adulthood. The results suggest that a farming environment during infancy is associated with higher FEV₁ and FVC at the age of 31 years. No associations with FEV₁/FVC were observed. Our findings suggest that farming environment in early life may have a positive impact on lung function in adulthood.

Respiratory diseases are well-known occupational health problem among farmers.⁴ Lowered lung function has been reported among farmers in occupational settings,^{7 8} and especially among those working with farm animals, in longitudinal studies.^{9 10} Furthermore, Eduard *et al* reported reduced FEV₁ among livestock farmers compared to crop farmers, however, with no association with FVC.¹¹ Environmental exposure to animal houses has also been reported to be associated with decreased FEV₁.¹² On the other hand, Omland *et al*¹⁴ reported that there were no associations between occupational farming and lung function, with similar findings being described between dairy farmers and controls, in a longitudinal study.¹⁵ The effect of an early farm life environment on lung function is less clear. Merchant *et al*¹⁶ reported that children born on farms had higher FVC compared with children not born on a farm. However, most studies have reported that living on a farm in childhood has no effect on lung function on childhood^{17 18} or adulthood.¹⁹ There is lack of prospective longitudinal studies on the matter.

By contrast, numerous reports have been published over the past decade concerning the association between farming environment during infancy and decreased risk of allergic diseases and asthma.¹⁻³ It has been hypothesised that high microbial exposure in a farming environment may affect development of the immune system during childhood and promote non-allergic phenotypes.¹ Some studies have reported that high microbial exposure, such as exposure to bacterial endotoxin (the Gram-negative bacterial cell wall component), may affect the development of the immune system^{20 21} and lead to reduced risk of asthma in childhood.^{1 20 22} On the other hand, high exposure to endotoxin may also irritate the airways, and be a source of airway inflammation and obstruction not only in the occupational setting,⁶ but also during infancy when exposure to endotoxin may be a risk factor for wheezing.²² So, microbial exposure during infancy may promote development of non-allergic phenotype and decreased risk of allergic diseases and asthma,¹ but it

Table 1 Characteristics of the study population at the age of 31 years, stratified by parental professional farming during infancy

	Parental professional farming during infancy			
	No		Yes	
	n	Mean	n	Mean
FVC (L)	4367	4.75	1299	4.73
FVC (% predicted)	4367	96.5	1299	97.4*
FEV ₁ (L)	4367	3.97	1299	3.97
FEV ₁ (% predicted)	4367	96.7	1299	97.7*
FEV ₁ /FVC (%)	4367	84.0	1299	84.3
Height (cm)	4367	171.5	1299	170.7*
Weight (kg)	4367	72.8	1299	72.9
	n	Per cent	n	Per cent
Female	2178	49.9	672	51.7
Current smoking	1350	30.9	327	25.2*
High school graduate	1785	40.9	369	28.4*
Atopy†	1395	33.5	254	20.4*
DD asthma†	364	8.5	94	7.3

Atopy: Participants with a weal reaction ≥ 3 mm to one or more of the four allergens tested were considered to be atopic.

* p Value < 0.05 .

†DD asthma $n = 5586$; atopy $n = 5416$.

DD, doctor-diagnosed ever; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2 Associations between farming environment during infancy and lung function at the age of 31 years

Farm-related factors during infancy	N	FEV ₁ difference (mL)			FVC difference (mL)		
		Crude	Adj	95% CI	Crude	Adj	95% CI
Parental professional farming							
No	4367	0	0		0	0	
Yes	1299	44	36	(6 to 67)	42	40	(5 to 75)
Family had farm animals							
No	3930	0	0		0	0	
Yes	1692	39	32	(3 to 61)	14	11	(-22 to 43)
Family had dogs*							
No	2478	0	0		0	0	
Yes	2995	34	36	(10 to 61)	37	37	(8 to 67)
Family had cats*							
No	2767	0	0		0	0	
Yes	2640	18	15	(-11 to 41)	16	14	(-16 to 44)
Number of animal species†							
0	1476	0	0		0	0	
1	1539	39	39	(6 to 73)	41	41	(2 to 79)
2	1046	53	56	(18 to 94)	32	30	(-14 to 74)
3	663	67	65	(20 to 109)	54	51	(0 to 103)
4 or more	485	55	44	(-6 to 94)	48	43	(-14 to 100)
Number of cows							
0	3970	0	0		0	0	
1-4	878	36	31	(-6 to 67)	17	12	(-30 to 53)
5 or more	767	46	35	(-3 to 73)	18	16	(-27 to 59)

Crude: adjusted for gender and height at the age of 31 years.

Adj: multivariate model, for more detailed information see Methods section.

*Before the age of 7 years.

†Includes cows, pigs, sheep, poultry, minks, cats and dogs.

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

may also be a risk factor for occupational asthma, and other occupational respiratory diseases such as organic dust syndrome and chronic bronchitis.⁴

In the present study, farming environment during infancy was associated with higher FEV₁ and FVC but not with FEV₁/FVC. These spirometric findings suggest that a non-farming environment is associated with lower lung volumes, not airflow limitation. This is an unexpected finding, since farming environment is mainly associated with obstructive disorders. However, as our lung function measurements consisted of FEV₁ and FVC, the type of lung function impairment cannot be definitely identified. One potential mechanism for the present findings suggesting lower lung volumes in a non-farming population may be obstruction in small airways caused by patchy collapse in early exhalation. In such a case, FEV₁ and FVC are decreased and FEV₁/FVC is normal.²³ However, the possible contribution of airway obstruction on the suspected restrictive-type impairment would require a bronchodilator test. Confirmation of a true restrictive abnormality would require total lung capacity measurement either with a body plethysmograph or using gas dilution methods.²⁴

We have previously shown, in this cohort, that an early farming environment is associated with reduced risk of atopic sensitisation, asthma and atopic diseases at the age of 31 years.² These associations are, therefore, potential

explanations for the present observations. However, in additional analyses, when we further adjusted for atopy and doctor-diagnosed asthma, the size of the estimates for the association between early childhood farming environment and current lung function were reduced by 50% at the most. This suggests that although atopy and asthma probably mediate the effects on improved lung function, other pathways are also likely to be operational. These results imply that an early farming environment may improve lung function, however, not simply by preventing development of atopy and asthma.

Differences in physical activity could also explain the observed differences in lung function. Physical activity is shown to be associated with higher lung function, measured with FEV₁ in adulthood, in men and women of all ages.²⁵ In the present study, analyses were adjusted for current, but not for childhood, physical activity. It is possible that children living on farms have a higher level of physical activity, as they may participate in physically demanding tasks on farms, as compared with their peers living in non-farming environments. Unfortunately, there is lack of information about levels of physical activity during childhood and, therefore, the effect of childhood physical activity on lung function at the age of 31 years cannot be estimated.

As the differences in the participant's current²⁶ or birth weight, as previously shown in this same setting,²⁷

Table 3 Associations between farming environment during infancy and lung function at the age of 31 years, stratified by gender

Farm-related factors during infancy	Women			Men		
	N	FEV ₁ difference (mL) Adj (95% CI)	FVC difference (mL) Adj (95% CI)	N	FEV ₁ difference (mL) Adj (95% CI)	FVC difference (mL) Adj (95% CI)
Parental professional farming						
No	2178	0	0	2189	0	0
Yes	672	38 (2 to 75)	37 (−4 to 78)	627	31 (−19 to 82)	44 (−12 to 100)
Family had farm animals						
No	1970	0	0	1960	0	0
Yes	858	49 (15 to 83)	26 (−12 to 65)	834	11 (−36 to 58)	−6 (−58 to 47)
Family had dogs*						
No	1248	0	0	1230	0	0
Yes	1513	41 (10 to 71)	48 (12 to 83)	1482	29 (−12 to 70)	24 (−23 to 71)
Family had cats*						
No	1340	0	0	1427	0	0
Yes	1403	32 (2 to 63)	40 (5 to 75)	1237	0 (−42 to 42)	−10 (−57 to 38)
Number of animal species†						
0	730	0	0	746	0	0
1	770	42 (2 to 82)	47 (1 to 94)	769	33 (−20 to 87)	29 (−32 to 91)
2	535	65 (20 to 110)	63 (10 to 115)	511	41 (−21 to 102)	−13 (−83 to 58)
3	351	93 (40 to 146)	78 (18 to 139)	312	22 (−51 to 96)	17 (−67 to 101)
4 or more	265	63 (5 to 122)	73 (7 to 140)	220	34 (−49 to 117)	22 (−73 to 117)
Number of cows						
0	1987	0	0	1983	0	0
1–4	441	50 (6 to 95)	16 (−33 to 66)	437	8 (−51 to 67)	9 (−57 to 75)
5 or more	397	50 (7 to 93)	37 (−14 to 88)	370	15 (−47 to 77)	−7 (−77 to 63)

Adj: multivariate model, for more detailed information see Methods section.

*Before the age of 7 years.

†Includes cows, pigs, sheep, poultry, minks, cats and dogs.

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

would offer a simple explanation for current findings, we adjusted all the models with both current and birth weight. We also ran the models adjusting for body mass index, instead of weight, at the age of 31 years, but the results were unchanged. Therefore, the associations between a farming environment during infancy and lung function in adulthood are unlikely to be explained by obesity.

Overall, there may be gender differences in respiratory responses to different environmental exposures. In a

recent meta-analysis, a higher risk of asthma was observed among women exposed to organic and inorganic dusts as compared with men. By contrast, exposure to organic dust was associated with lower lung function in men compared with women.²⁸ In the present study, the associations were mainly observed among women, but this difference between genders did not quite reach nominal statistical significance. These gender differences may be due to differences in biology or in exposure patterns.²⁹ In Finland, women and girls have traditionally

Table 4 To explore if the statistically significant associations in table 2 are mediated via the protective effect of childhood farming on atopy and asthma, the models were further adjusted for atopy and asthma

Farm-related factors during infancy	FEV ₁ difference (mL)			FVC difference (mL)		
	Adj	Adj+A*	Adj+A*+DDA	Adj	Adj+A*	Adj+A*+DDA
Parental professional farming	36	27	22	40	36	31
Family had farm animals	32	23	16	11	6	−1
Family had dogs†	36	33	30	37	36	33

Adj: multivariate model, for more detailed information see Methods section.

A: also adjusted for atopy at the age of 31 years.

DDA: also adjusted for doctor-diagnosed asthma ever at the age of 31 years.

*Participants with a weal reaction ≥ 3 mm to one or more of the four allergens tested were considered to be atopic.

†Before the age of 7 years.

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

taken care of cattle and other animals, which may partly explain these findings, and also underscores the importance of animal contact during childhood.

As the present study was prospective by nature, we were able to analyse associations between farming environment during infancy and lung function at the age of 31 years without possible recall bias. Because the present study lacked detailed information on farm environment after infancy, it was not possible to conduct detailed assessments of the effect of farm environment at different time points. However, in the analysis, we have been able to take work-based and home-based exposure to cold, dust, solvents and tobacco smoke at the age of 31 years into account, as well as current farming occupation. Selection among participants not participating in the 31-year follow-up might also misrepresent the observed associations, since almost 50% of participants attended follow-up, and no drop-out analyses were performed. Furthermore, even in our prospective cohort study, possible healthy worker effect is always a concern. There was no suggestion of healthy worker effect in adulthood as there was no change in the observed associations after adjustment for current farming occupation at the age of 31 years. However, it is possible that some parents of the present study subjects have avoided working in a farm environment due to respiratory problems, which could lead to differences in the genetic predisposition between those living and those not living on a farm in infancy. However, this was less likely in northern Finland in 1966 than it is today. In addition, in the statistical analyses, parental history of allergies and asthma was adjusted for. Therefore, we consider healthy worker effect an unlikely explanation for the present findings.

CONCLUSIONS

In conclusion, exposure to farming environment during infancy was associated with higher FVC and FEV₁, but not FEV₁/FVC, at the age of 31 years. This suggests that farming environment in early life may have a positive impact on lung function in adulthood, but this needs to be confirmed in future studies.

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Contributors JL wrote the manuscript and is the guarantor. He also performed the statistical analysis and made substantial contributions to the data interpretation and to the planning of the manuscript. HK made substantial contributions to the writing and planning of the manuscript, statistical analysis and data interpretation. A-LH, AR, ACA and M-RJ made substantial contributions to the writing of the manuscript and data interpretation. JP made substantial contributions to the writing and planning of the manuscript, statistical analysis and data interpretation. All the authors have critically revised and approved the final version of the manuscript.

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REFERENCES

1. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010;10:861–8.
2. Lampi J, Canoy D, Jarvis D, *et al*. Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland. *Clin Exp Allergy* 2011;41:987–93.
3. Remes ST, Iivanainen K, Koskela H, *et al*. Which factors explain the lower prevalence of atopy amongst farmers' children? *Clin Exp Allergy* 2003;33:427–34.
4. Linaker C, Smedley J. Respiratory illness in agricultural workers. *Occup Med (Lond)* 2002;52:451–9.
5. Bardana EJ Jr. Occupational asthma. *J Allergy Clin Immunol* 2008;121(2 Suppl):S408–11; quiz S421.
6. Radon K. The two sides of the "endotoxin coin". *Occup Environ Med* 2006;63:73–8, 10.
7. Heller RF, Hayward DM, Farebrother MT. Lung function of farmers in England and Wales. *Thorax* 1986;41:117–21.
8. Chatzi L, Prokopakis E, Tzanakis N, *et al*. Allergic rhinitis, asthma, and atopy among grape farmers in a rural population in Crete, Greece. *Chest* 2005;127:372–8.
9. Senthilselvan A, Dosman JA, Kirychuk SP, *et al*. Accelerated lung function decline in swine confinement workers. *Chest* 1997;111:1733–41.
10. Dalphin JC, Maheu MF, Dussaucy A, *et al*. Six year longitudinal study of respiratory function in dairy farmers in the Doubs province. *Eur Respir J* 1998;11:1287–93.
11. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. *Chest* 2009;136:716–25.
12. Radon K, Schulze A, Ehrenstein V, *et al*. Environmental exposure to confined animal feeding operations and respiratory health of neighboring residents. *Epidemiology* 2007;18:300–8.

13. Northern Finland Birth Cohort 1966, 31-year follow-up study. <http://www oulu.fi/nfbc/node/18097> (13 May 2015).
14. Omland O, Sigsgaard T, Hjort C, *et al.* Lung status in young Danish rurals: the effect of farming exposure on asthma-like symptoms and lung function. *Eur Respir J* 1999;13:31–7.
15. Gainet M, Thaon I, Westeel V, *et al.* Twelve-year longitudinal study of respiratory status in dairy farmers. *Eur Respir J* 2007;30:97–103.
16. Merchant JA, Naleway AL, Svendsen ER, *et al.* Asthma and farm exposures in a cohort of rural Iowa children. *Environ Health Perspect* 2005;113:350–6.
17. Fuchs O, Genuneit J, Latzin P, *et al.* Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide. *J Allergy Clin Immunol* 2012;130:382–8.e6.
18. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med* 2000;161:1563–6.
19. Schulze A, van Strien RT, Praml G, *et al.* Characterisation of asthma among adults with and without childhood farm contact. *Eur Respir J* 2007;29:1169–73.
20. Braun-Fahrlander C, Riedler J, Herz U, *et al.* Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–77.
21. Roponen M, Hyvärinen A, Hirvonen MR, *et al.* Change in IFN-gamma-producing capacity in early life and exposure to environmental microbes. *J Allergy Clin Immunol* 2005;116:1048–52.
22. Mendy A, Gasana J, Vieira ER, *et al.* Endotoxin exposure and childhood wheeze and asthma: a meta-analysis of observational studies. *J Asthma* 2011;48:685–93.
23. Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–68.
24. Flesch JD, Dine CJ. Lung volumes: measurement, clinical use, and coding. *Chest* 2012;142:506–10.
25. Nystad W, Samuelsen SO, Nafstad P, *et al.* Association between level of physical activity and lung function among Norwegian men and women: the HUNT study. *Int J Tuberc Lung Dis* 2006;10:1399–405.
26. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci* 2001;321:249–79.
27. Canoy D, Pekkanen J, Elliott P, *et al.* Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax* 2007;62:396–402.
28. Dimich-Ward H, Beking K, DyBuncio A, *et al.* Occupational exposure influences on gender differences in respiratory health. *Lung* 2012;190:147–54.
29. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010;118:167–76.