THE INFLUENCE OF OCCUPATIONAL EXPOSURES ON RESPIRATORY HEALTH WITH A SPECIFIC FOCUS ON AGRICULTURE IN LOW- AND MIDDLE-INCOME COUNTRIES

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Statement of originality

I herewith certify that this dissertation is my original work and that all material included that is not my own work has been appropriately acknowledged or referenced.

Copyright declaration

Abstract

Chronic respiratory disease, particularly chronic obstructive pulmonary disease (COPD) is reported to be a major cause of morbidity and mortality worldwide. While smoking is the main cause of the disease, previous studies have shown associations between COPD and socioeconomic status and occupations. Many of the industries historically associated with occupational respiratory diseases have been transferred to low- and middle-income countries (LMICs) where workers' health protection is generally limited. As farming is a common economic activity in LMICs and has been associated in previous epidemiological studies with adverse respiratory health effects, I hypothesise that this occupation, and the underlying exposures in particular pesticide exposure, could be an important cause of chronic lung disease in these countries.

This doctoral thesis aims to examine the relationships between chronic respiratory disease (lung function and chronic respiratory symptoms) and occupational exposure specific to agricultural contexts especially in LMICs. It comprises: first, a systematic review and meta-analysis of pesticide use and lung function; second, a cross-sectional study in Nan province, Thailand examining the relationship between agricultural exposures and respiratory health; and third, a data analysis of the large multinational Burden of Obstructive Lung Disease (BOLD) study focusing on high risk occupational exposures, primarily farming, and respiratory outcomes.

The first study is a systematic review and meta-analysis exploring the available literature on the relationship between occupational exposure to pesticides and lung function. Of the 2,356 articles I retrieved, 56 were included in the systematic review and were pooled in meta-analyses of the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC), FVC and FEV_1. There was tentative evidence that exposure to cholinesterase (ChE) inhibiting pesticides reduced FEV_1/FVC but no evidence that paraquat exposure affected lung function in farmers.

The second study is a cross-sectional survey of adults aged 40 to 65 that I conducted in the agricultural Nan province, Thailand. The aim of this survey was to improve knowledge on the relationship of chronic airflow obstruction and respiratory health problems with several exposures related to farming activities, particularly pesticide use. I found that chronic airflow obstruction was uncommon in the studied villages; as with other studies in developing countries, farming villagers had a low smoking prevalence. Nan farmers had a high percentage of pesticide applicators but farming activities and pesticide use (duration, intensity and lifetime cumulative hours of spraying classified by pesticide types) were unlikely to be a major cause of respiratory problems there.

In the final study, I analysed data from the multinational population-based BOLD study of 28,823 adults aged ≥40 years. The aim of this analysis was to examine the relationship between occupational exposures and respiratory health in both high-income countries (HICs) and LMICs. I found that people working in any of three occupational exposure categories (organic dusts; inorganic dusts; and fumes) and 11 high-risk occupations (farming; flour, feed or grain milling; cotton or jute processing; hard-rock mining; coal mining; sandblasting; working with asbestos; chemical or plastics manufacturing; foundry or steel milling; welding; and firefighting) were more likely to report respiratory symptoms than those who did not work in any of

those occupations. There were no consistent associations of FEV_1/FVC or FVC with any high-risk occupations, particularly farming. The associations between occupational categories and lung function varied by gross national income.

Thesis Outline

This thesis is composed of five chapters. CHAPTER 1 provides a brief background to chronic respiratory disease, COPD, poor lung function and its non-smoking risk factors with specific focus on occupational exposures, particularly in LMICs, and the relationships between farming exposures and pesticide use and respiratory health and chronic respiratory disease. CHAPTER 2 is a systematic review and meta-analysis examining the association between various pesticide exposures and lung function parameters. CHAPTER 3 presents information on a small cross-sectional survey of adults aged 40 to 65 years in Nan province, Thailand, where farming is the main occupation. The aim of this study was to assess the associations between lung function and respiratory symptoms with farming and pesticide use. To scale up the analysis, I used data from a large (n=28,823) international population-based study evaluating a broader spectrum of occupational exposures. CHAPTER 4 describes this analysis, which explored the relationship between occupational exposures (organic dust; inorganic dust; fume and detailed 11 high-risk occupations) and respiratory health (respiratory symptoms and spirometric parameters), particularly in LMICs. CHAPTER 5 summarises the findings from my doctoral study and provides a series of conclusions based on these. This chapter also provides further perspectives on my work including potential future work and suggested public health implications.

Publications related to this thesis

Ratanachina J, De Matteis S, Cullinan P, Burney P. Pesticide exposure and lung function: a systematic review and meta-analysis. Occup Med (Lond). 2019.

Abstracts and prizes related to this thesis

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Ratanachina J, Amaral A, De Matteis S, Cullinan P, Burney P. Farming and respiratory health: a cross-sectional study in Thailand. Eur Respir J. 2020;56(suppl 64):656.

- presented as e-poster at ERS Virtual International Congress on 7-9 September 2020.
- recipient of a British Lung Foundation (BLF) Travel Award 2020

Ratanachina J, Amaral AFS, De Matteis S, Cullinan P, Burney P. T3 Occupational exposures and respiratory health: the burden of obstructive lung disease (BOLD) study results. Thorax. 2021;76(Suppl 1):A2.

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Abbreviations

2,4,5-T	2,4,5-trichlorophenoxyacetic acid
AChE	Acetylcholinesterase
BMI	Body mass index
BOLD	Burden of Obstructive Lung Disease
CAO	Chronic airflow obstruction
ChE	Cholinesterase
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DALY	Disability-adjusted Life Year
DAP	Dialkyl-phosphate
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
FAO	Food and Agriculture Organization of the United Nations
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in the first second
FEV_1/FVC	Forced expiratory volume in the first second to forced vital capacity of the lungs
FRAC	Fungicide Resistance Action Committee
FVC	Forced vital capacity
GIS	Geographic information system
GLI	Global Lung Function Initiative
GNI	Gross National Income
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPP	Gross Provincial Product
HIC	High-income country
HRAC	Herbicide Resistance Action Committee
HWE	Healthy worker effect
IRAC	Insecticide Resistance Action Committee
ISCO	International Standard Classification of Occupations

JEM	Job-exposure matrix
L	Litre
LLN	Lower limit of normal
LMIC	Low- and middle-income country
MMF	Maximum mid-expiratory flow
MRC	Medical Research Council
nAChR	Nicotinic acetylcholine receptor
NOS	Newcastle-Ottawa Scale
NHANES	National Health and Nutrition Examination Survey
NS	Non-statistically significant
OA	Occupational asthma
OR	Odd ratio
OSCAR	Occupational Self-Coding Automatic Recording
PEF	Peak expiratory flow
PIPAH	Prospective Investigation of Pesticide Applicators' Health
PPE	Personal protective equipment
RR	Relative risk
RSP	Restrictive spirometry pattern
SD	Standard deviation
SE	Standard error
SMD	Standardised mean difference
TCPN	Tetrachloroisophthalonitrile
THB	Thai Baht
TLCO	Transfer factor for carbon monoxide
UK	United Kingdom
USA	United States of America
VGDF	Vapour, gas, dust, or fumes
WHO	World Health Organization
£	British Pound

CHAPTER 1

General introduction

CHAPTER 1 General introduction

1.1 Chronic respiratory disease, COPD and poor lung function

The United Nations' Sustainable Development Goal (SDG) target 3.4 plans, by 2030, to reduce premature mortality from non-communicable diseases[1] (NCDs) including chronic respiratory disease among the global population aged 30 to 70 by 30% relative to 2015. (1, 2)

COPD is a chronic respiratory disease characterised by airflow limitation. The irreversible lung component of COPD is a result of diverse involvement of airway inflammation (i.e., chronic bronchitis) and lung parenchymal destruction (i.e., emphysema). (3, 4) The Global Initiative for Chronic Obstructive Lung Disease (GOLD) describes COPD as a common, preventable and treatable disease. (5)

COPD is a major cause of morbidity and mortality worldwide and remains a major public health problem in the 21st century. COPD has been the third most common cause of death since 2016 globally and has been estimated to cause three million deaths (5.3% of all deaths) a year. (6, 7) By 2030, COPD is forecasted to be the direct underlying cause of 7.8% of all deaths (8). The Global Burden of Disease Study (GBD) estimated 328 million people with COPD globally (9) of whom 65 million have moderate or severe disease. (2) The burden of COPD also challenges healthcare settings in many low- and middle-income countries (LMICs) where resource allocations are mainly designed for acute cases (i.e., communicable diseases), not for treating chronic diseases. (10) The severity and high prevalence of COPD cause both direct (e.g., healthcare resource utilisation) and indirect (e.g., loss of productivity) economic costs. (11, 12) The direct costs for respiratory diseases are relatively greater in countries with lower incomes. In India, for instance, the cost of treatment for COPD was about 28% of an average wage, whereas in South Korea and Singapore (high income countries (HICs)) it was between 2% and 4%. (13) Severe COPD impacts employment and the ability to work, (14) and accounted for 2.6% of global disability-adjusted life years in 2015. (15) In spite of the fact that COPD has high prevalence, morbidity and mortality, there is a lack of awareness among the public and even healthcare providers outside the field of respiratory medicine. (5)

Spirometry has played a major role in objectively assessing people's respiratory health at both individual and population scales. (16) Nowadays, a COPD diagnosis is mainly confirmed, monitored and its severity assessed by a forced expiratory manoeuvre from total lung capacity to residual volume using a spirometer, the most common lung function measurement tool. (17, 18) The frequent definition used for a diagnosis of COPD is the GOLD criteria introducing a fixed cut-point for the ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity of the lungs (FVC) below 0.70. (3) However, recent studies suggest that the use of a fixed ratio tends to overestimate the prevalence of obstruction among older and male subjects (19, 20) and underestimate it in younger people. (21) Several studies (e.g., Global Lung Function Initiative (GLI) and National Health and Nutrition Examination Survey (NHANES)) propose predicted values and the use of the lower limit of normal (LLN) of spirometric measures with published reference equations, which account for age, standing height and ethnicity. (18, 20, 22) Although the FEV_1/FVC ratio is generally independent of ethnicity, data from GLI found an exception among South East Asian subjects

[1] NCDs: cardiovascular disease; cancer; chronic respiratory disease; and diabetes

in whom FEV_1/FVC ratios were higher by 2.6% to 2.8%. (18) In the area of public health research, there are several limitations to available studies with lung function. A large number of studies assessed COPD by self-reported or from medical records which generally identify fewer cases of COPD than those based on spirometry. (23) Spirometry has not been extensively used as a quantitative evaluation in epidemiology studies in LMICs. Inadequate spirometry performance is also another problem. The use of only pre-bronchodilator spirometry in several studies might cause false positive cases of COPD due to an overlap with asthma. (23, 24)

In populations with a high prevalence of cigarette smoking, this is the predominant cause of COPD. (5, 25) However, smoking alone does not explain the overall distribution of COPD, particularly in LMIC contexts. (26) In HICs, the attributable fraction of COPD mortality from smoking is about 84% among men aged 30 to 65 years, and 77% in men aged 70 and over. The equivalent figures for women are 62% and 61%, respectively. In contrast, there are lower attributable fractions in LMICs: 49% and 45% for men, and 20% and 12% for women, respectively. Not all smokers develop COPD and not all COPD cases have been smokers. (27) A number of epidemiological studies reported that the never-smokers were also affected by COPD. (28, 29) Salvi and Barnes, for example, estimated that around 25% to 45% of COPD patients had never smoked. Furthermore, the regions with the highest rates of death from COPD are not those with highest smoking rates. (30) Therefore, more research to explain other attributable fractions of COPD, particularly among LMIC populations, is still needed.

Chronic airflow obstruction (CAO) is the main defining characteristic of COPD. For decades, associations of COPD and low lung function with early life factors such as low birth weight have been recognised. (31)

The multinational Burden of Obstructive Lung Disease (BOLD) survey of adults aged 40 and over, collected extensive information on lung disease in 41 centres in 34 countries across most regions of the world. This includes high quality spirometric measurements before and after bronchodilator. (32) The first phase of BOLD observed significant associations between COPD, defined by $FEV_1/FVC<LLN$, and age, body mass index (BMI), educational level, early life hospitalization due to respiratory illnesses, smoking, tuberculosis and a family history of COPD. (20)

COPD has been considered as a disease of poverty. (33) A number of current studies suggest that socioeconomic status, both at the individual and national levels, relates to COPD. Recently, the BOLD study found consistent associations between poor FEV_1/FVC and low socioeconomic status at both individual (using a wealth score) and community (using mean wealth scores between sites) levels. (34) Figure 1-1 presents findings on the relationship between COPD mortality rate and Gross National Income (GNI) per capita adjusted for purchasing power parity (PPP), the rate of currency conversion that equalises the purchasing power of different currencies. The chart illustrates higher rates in the countries with poorer socioeconomic status. Noticeably, the BOLD study found relatively low smoking rates among these developing regions. (35) In addition, a recent GBD study also found the highest age-standardized mortality rates from COPD among the two lowest income regions: South Asia and Sub-Saharan Africa, with at least 2.9 million deaths from COPD annually. (36) Although the previous findings between COPD (both morbidity and mortality) and low socioeconomic status are strong, their explanation is difficult. Several factors and confounders rather than poverty might explain the association. (33) The recent statement from the GOLD board of directors published in 2019 suggested that while smoking (including second-hand smoking) is the predominant risk of COPD in HICs, poverty and several environmental and early-life exposures are leading risk factors in LMICs. (37) However, most of the non-smoking causes in LMIC contexts are suggestive and need further research.

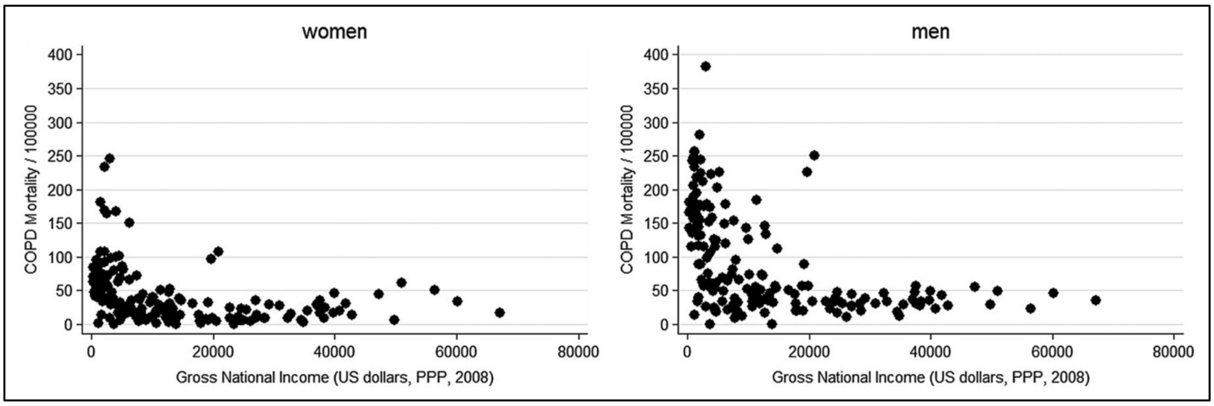


Figure adapted from Burney *et al.* (35); the Creative Commons CC BY 3.0

Figure 1-1 COPD mortality rates and Gross National Income

Research studies on restrictive spirometry patterns (RSP) have been emerging although the phenomenon remains poorly addressed in population research settings. Evidence indicates that the determinants of RSP include early life factors such as birth weight, nutrition and childhood infection, inhalational injury, genetics, systemic inflammation and the metabolic syndrome. (16, 33) The first findings of the BOLD study found that low-income countries with low smoking prevalences are prone to not only higher than expected COPD mortality rates but also, and paradoxically, a high prevalence of spirometric restriction. The prevalence of spirometric restriction was not associated with smoking but with GNI per capita lower than USD 15,000 (£9,477 in mid 2012) (38), mainly among Asians and Africans. (35) As poor FVC appears to be common in low-income populations, there is a need for more research to explain the characteristics and aetiologies of RSP.

Considering the pathogenesis of COPD, it is assumed to be the result of an abnormal lung response to chronic inhalation of toxic irritants, most commonly from cigarette smoke. (25, 39) which activates several immune responses leading to chronic inflammation. (40) Apart from tobacco smoking, the next most common potential factors of COPD are external risk factors including indoor and outdoor air pollution (i.e., noxious fumes and vapours) and occupational exposures from dusty work environments. (5, 41) A deeper understanding of these issues could significantly contribute to a reduction in the burden of COPD worldwide.

1.2 Occupational exposures

The GBD study estimated that occupational exposures accounted for 63.7 million DALYs and 1.16 million deaths globally in 2017. (42) Dusty jobs are common in workplaces worldwide (6) and several hazards in the workplace including dusts and fumes have a causal link with COPD pathogenesis. (43, 44) Occupational exposures have been previously associated with COPD risk. (45-47) An early BOLD analysis found a significant relationship between the number of working years in a dusty job and a decline in FEV_1/FVC ratio. (20) The most recent American Thoracic Society (ATS) and European Respiratory Society Statement (ERS) statement published in 2019 reported a relationship between COPD and occupational exposures, and estimated from available population-based studies that the occupational population attributable fraction (PAF) for COPD is 14%. Among never-smokers, the occupational PAF for COPD is 31% which suggest a stronger contribution of occupational factors to the burden of COPD in this group. Notably, there was very high heterogeneity between studies in the meta-analyses; and few have been able to identify consistent dose-response relationships. (48)

There is a wide variety of literature on the associations of occupational exposures with chronic respiratory health. To provide a broad overview of this, I focused on population-based studies with a range of occupational exposures (both specific occupations and industries e.g., farming and occupational categories e.g., those with exposures to organic dusts). First, I summarise the published systematic reviews of all occupational exposures (n=4); subsequently I examine those reviews that have concentrated on farming-related exposures (n=2); finally, and closest to the topic of my own review (Chapter 2), I describe the findings from the two reviews that have covered the literature on pesticide exposures. It is not my intention to provide a detailed dissection of each published review – that would be beyond the scope of this thesis - but I aim to provide a broad overview of the field and a setting for my work.

Table 1-1 summarises the 51 population-based studies on chronic respiratory disease and occupation included in four recent systemic reviews and meta-analyses: Omland *et al.* 2014 (49); Alif *et al.* 2016 (50); Sadhra *et al.* 2017 (47) and Blanc *et al.* 2019 (48). Fourteen (45%) of the 31 cross-sectional surveys, one ecological study, all six case-control studies, and seven (54%) of the 13 longitudinal studies found significant, positive associations of various occupational exposures with either COPD or poorer lung function. Within each review, different studies examined different exposures, used various exposure assessment techniques and applied different respiratory outcome standards, probably explaining much of the apparent heterogeneity. (51) Figure 1-2 illustrates the numbers of included studies in common among the four reviews; the lack of substantial overlap reflects in part the different aims and focuses of the reviews.

Two meta-analyses of the associations of occupational exposures assessed by job-exposure matrix (JEM) with COPD published in 2016-2017 showed diverse results. Alif *et al.* reported a significant association of COPD based on spirometry with low (but not high) mineral dust exposures but no statistically significant associations with biological dusts or fume exposures. (50) In contrast, Sadhra *et al.* found higher risks of COPD from biological dusts than mineral dust exposures. (47)

Many industries such as mining, shipbuilding and textile manufacture, historically associated with occupational respiratory diseases have been transferred to LMICs where workers' health protection is generally weaker. (46) In addition, large numbers of people in these countries are engaged in smaller-scale industrial work and agriculture, where workers' health protection may be less well supervised. (52) However, as shown in table 1-1, most of the available studies were undertaken in HICs. There were only a few studies in LMICs: five in Asia (53-57) and two in Africa (58, 59). Therefore, future studies should aim to identify occupational risk factors for COPD in the contexts of LMICs where exposures remain common. (46) Moreover, studies observing dose-response relationships will strengthen the evidence of the relationship between occupational exposure and chronic respiratory disease. (49)

Table 1-1 Fifty-one population-based studies on chronic respiratory disease and occupations included in recent systematic reviews

Author, year	Systematic review: Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)	Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment: Self-reported	JEM	Respiratory outcome: Respiratory symptoms	COPD diagnosed by a physician	Spirometry	Effect estimates (the association of occupational exposure with COPD or FEV_1/FVC)
Cross-sectional studies (*n*=31)															
Torén, 2017 (60)				✓	Sweden	HIC	1,052	-	Vapour, gas, dust, or fumes (VGDF)	✓		✓	✓	✓	VGDF (male): OR= 2.8, 95%CI 1.2 to 6.4
Paulin, 2015 (61)			✓	✓	USA	HIC	1,075	-	VGDF	✓	✓			✓	VGDF: OR=1.44, 95%CI 1.04 to 1.97
Würtz, 2015 (62)				✓	Denmark	HIC	4,717	-	VGDF, organic dust, inorganic dust, fume/gas & vapour	✓	✓			✓	high organic dust exposure: OR=1.56, 95%CI 1.09 to 2.24
Scholes, 2014 (63)				✓	UK	HIC	7,879	-	shown as 'routine occupations'	✓			✓	✓	routine occupations: OR=1.61, 95%CI 1.13 to 2.31
Dijkstra, 2014 (64)			✓		The Netherlands	HIC	1,479	-	biological dust, mineral dust, gases/fumes, all pesticides, aromatic solvents, chlorinated solvents, other solvents & heavy metals		✓			✓	n/a (The outcome of study was chronic mucus hypersecretion (CMH).)

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Cross-sectional studies (*n*=31)															
Doney, 2014 (65)			✓	✓	USA	HIC	3,667	-	VGDF		✓			✓	Self-reported (VGDF): OR=2.6, 95%CI 1.1 to 2.3; JEM: OR=2.4, 95%CI 1.1 to 5.0
Rodríguez, 2014 (66)			✓		Spain	HIC	338	ISCO-88 Job titles	biological dust, mineral dust & gases/fumes	✓	✓	✓		✓	biological dust >13years: OR= 0.4, 95%CI 0.2 to 1.0
Hansell, 2014 (67)		✓	✓	✓	New Zealand	HIC	1,017	18 occupations	biological dust, mineral dust, gases/fumes & VGDF	✓	✓	✓	✓	✓	biological dust (high): NS, OR=0.96, 95%CI 0.43 to 2.13; mineral dust (high): NS, OR= 0.96, 95%CI 0.43 to 2.16; gases or fumes: NS, OR=0.85, 95%CI 0.39 to 1.85; high VGDF NS, OR=0.92, 95%CI 0.47 to 1.79;
Darby, 2012 (68)			✓		UK	HIC	2,001	-	VGDF	✓	✓	✓	✓	✓	VGDF: OR=3.9, 95%CI 2.7 to 5.8

Table 1-1 *continued from previous page*

	Systematic review									Exposure assessment		Respiratory outcome			Effect estimates
Author, year	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)	Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV$_1$/FVC)
Cross-sectional studies (*n*=31)															
Melville, 2010 (45)				✓	UK	HIC	845	9 occupational groups	-	✓		✓		✓	any occupation: OR=3.53, 95% CI 1.58 to 7.89
Rodríguez, 2008 (69)			✓		Spain	HIC	185	-	biological dust, mineral dust & gases/fumes	✓	✓	✓		✓	n/a
Jaén, 2006 (70)	✓			✓	Spain	HIC	576	-	dusts, gases or fumes	✓		✓		✓	FEV$_1$/FVC ratio (β)= -1,7%, 95%CI -3.3 to -0.2
Matheson, 2005 (71)	✓	✓	✓		Australia	HIC	1,213	-	biological dust, mineral dust & gases/fumes	✓	✓	✓	✓	✓	biological dust: OR=3.19, 95%CI 1.27 to 7.97; mineral dust: NS; gases/fumes: OR=2.81, 95%CI 1.01 to 7.77
Hnizdo, 2004 (72)	✓				USA	HIC	9,120	17 occupations & 17 industries	-	✓				✓	Caucasians: PAF=22.2%, 95%CI 9.1 to 33.4; African-Americans: PAF=23.4%, 95%CI 2.2 to 40.0; Mexican-Americans: PAF= 49.6%, 95%CI 32.1 to 62.6

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Cross-sectional studies (*n*=31)															
de Meer, 2004 (73)			✓		The Netherlands	HIC	1,906	350 Job titles	organic dusts, mineral dust & gas/fume		✓	✓		✓	n/a
de Marco, 2004 (74)	✓				ECRHS* 13 countries in Europe, USA, Australia & New Zealand	HICs	14,855	-	VGDF	✓		✓		✓	VGDF: NS, relative risk ratios (RRRs): p=0.006
Trupin, 2003 (75)			✓	✓	USA	HIC	1,932	15 occupational exposures	VGDF	✓	✓		✓		VGDF: OR=2.0, 95%CI 1.6 to 2.5
Hnizdo, 2002 (76)	✓			✓	USA	HIC	9,495	14 occupations & 16 industries	-	✓				✓	armed force: OR=2.0, 95%CI 1.1 to 3.6; material handlers OR=2.2, 95%CI 1.3 to 3.7
Zock, 2001 (77)			✓		ECRHS I (11 countries in Europe, USA, Australia & New Zealand)	HICs	13,253	10 occupational groups	VGDF	✓	✓	✓		✓	n/a

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Cross-sectional studies (*n*=31)															
Sunyer, 1998 (78)		✓	✓		Spain	HIC	1,735	-	biological dust, mineral dust & gases/fumes	✓	✓	✓		✓	high mineral dust: OR=3.0, 95%CI 1.0 to 9.4
Fishwick, 1997 (79)	✓				New Zealand	HIC	1,132	21 occupations	VGDF	✓		✓		✓	VGDF: OR=3.13, 95%CI 1.07 to 9.12
Isoaho, 1994 (80)	✓				Finland	HIC	1,191	-	dust	✓		✓	✓	✓	dust: OR=2.3, 95%CI 1.1 to 4.8
Hsairi, 1992 (81)			✓		France	HIC	13,553	-	dust & gas or fume	✓	✓	✓			n/a
Bakke, 1991 (82)	✓		✓		Norway	HIC	714	asbestos, quartz, wood dust, metal gases, aluminium processing, welding & soldering	dust or gas	✓			✓	✓	asbestos: OR=2.8, 95%CI 1.1 to 7.3; quartz: OR=3.7, 95%CI 1.2 to 11.0
Viegi, 1991 (83)	✓				Italy	HIC	1,635	-	dusts, chemicals or gases	✓		✓		✓	OR=2.31, 95%CI 1.10 to 4.86
Lebowitz, 1977 (84)	✓				USA	HIC	1,195	silica, asbestos, smoke, auto exhaust & other compounds	-	✓			✓	✓	significantly increased prevalence: p<0.01

Table 1-1 *continued from previous page*

	Systematic review									Exposure assessment		Respiratory outcome			Effect estimates
Author, year	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)	Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Cross-sectional studies (*n*=31)															
Sinha, 2017 (56)				✓	India	LMIC	1,203	-	dust & fumes	✓				✓	OR=6.16, 95%CI 3.30 to 10.22
Obaseki, 2016 (58)				✓	Nigeria	LMIC	1,148	farming	dusty jobs	✓		✓		✓	dusty jobs: NS; OR=1.5, 95%CI 0.7 to 3.0
Lam, 2012 (53)				✓	China	LMIC	8,216	7 occupational groups	dust or gas/fume	✓		✓		✓	high gas/fume exposure: OR=1.48, 95%CI 1.03 to 2.12
Idolor, 2011 (57)				✓	The Philippines	LMIC	991	farm work	dusty jobs	✓		✓		✓	dusty jobs: NS; OR=1.16, 95%CI 0.79 to 1.69
Xu, 1992 (54)	✓				China	LMIC	1,094	-	dust & gas or fume	✓		✓		✓	n/a (dusts: significantly decreased in FEV_1: $p<0.05$)
Ecological analysis (*n*=1)															
Blanc, 2009a (85)	✓			✓	31 countries from BOLD, ECRHS II* & PLATINO**	HICs & LMICs	19,094	-	dusty jobs	✓	✓			✓	significantly increased prevalence per10% increase in dusty job exposures: p=0.003

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Case-control studies (*n*=6)															
Blanc, 2009b (86)	✓		✓	✓	USA	HIC	1,942	-	VGDF	✓	✓		✓	✓	VGDF: self-reported: OR=2.1, 95%CI 1.4 to 3.0
Blanc, 2009c (87)	✓		✓		USA	HIC	1,504	-	VGDF	✓	✓			✓	VGDF: OR=2.33, 95%CI 1.45 to 3.72
Weinmann, 2008 (88)	✓		✓	✓	USA	HIC	744	-	mineral dusts, metal dusts and fumes, organic dusts, irritant gases or vapours, sensitizers, organic solvents & diesel exhaust	✓	✓			✓	Occupational exposure: OR=1.5, 95%CI 1.1 to 2.1
Mastrangelo, 2003 (89)	✓		✓		Italy	HIC	429	16 occupations	biological dust, mineral dust & gas/vapour/fume	✓			✓		biological dust: OR=8.86, 95%CI 2.29 to 34.3; mineral dust: OR=3.80, 95%CI 1.21 to 12.0; gas/vapour/fume: OR=5.83, 95%CI 1.82 to 18.6

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV_1/FVC)
Case-control studies (*n*=6)															
Mak, 2001 (90)	✓				USA	HIC	517	-	dusts, gases or fumes	✓				✓	occupational inhalant: OR=1.79, 95%CI 1.12 to 2.85
Govender, 2011 (59)			✓		South Africa	LMIC	212	14 occupations	biological dust, mineral dust, chemicals, gases/fumes	✓	✓		✓		low dusts: OR=4.6, 95%CI 1.9 to 10.8; high dusts: 5.9, 95%CI 2.6 to 13.2
Longitudinal studies (*n*=13)															
Tagiyeva, 2017 (91)				✓	UK	HIC	237	-	vapors, gases, dusts, fumes, fibres, mists (VGDFFiM) & sub-fractions: biological dusts; minerals; diesel fumes		✓		✓	✓	any VGDFFiM: NS; OR=0.88, 95%CI 0.42 to 1.85
de Jong, 2014 (92)		✓		✓	The Netherlands	HIC	14,215	ISCO-88 Job titles	biological dust, mineral dust, gases/fumes & VGDF	✓	✓			✓	high VGDF: OR=1.41, 95%CI 1.16 to 1.70
Pallasaho, 2014 (93)			✓	✓	Finland	HIC	4,080	ISCO-88 Job titles	biological dust, mineral dust & gases/fumes	✓	✓	✓	✓		self-reported occupational exposure: OR=2.14, 95%CI 1.50 to 3.05

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates (the association of occupational exposure with COPD or FEV_1/FVC)
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	
Longitudinal studies (*n*=13)															
Mehta, 2012 (94)		✓		✓	Switzerland	HIC	4,267	-	biological dust, mineral dust, gases/fumes & VGDF	✓	✓			✓	mineral dusts: IRR=1.65, 95%CI 1.02 to 2.68
Skorge, 2009 (95)			✓		Norway	HIC	2,312	ISCO-88 Job titles	biological dust, mineral dust & gases/fumes	✓	✓	✓			n/a
Boggia, 2008 (96)	✓				Italy	HIC	2,019	-	welder smokes, gases or chemical irritants	✓			✓	✓	occupational exposure: OR=2.62, 95%CI 2.02 to 3.41
Harber, 2007 (97)	✓				USA & Canada	HIC	3,592	-	dust or fume	✓				✓	n/a (fumes, male: significantly associated with 0.25% reduction per year of post-bronchodilator FEV_1)
Sunyer, 2005 (98)	✓		✓	✓	ECRHS I 11 countries in Europe, USA, Australia & New Zealand	HIC	8,263	13 occupations	biological dust, mineral dust & gases/fumes	✓	✓	✓		✓	any occupational exposure: NS; high (male) RR=1.01, 95%CI 0.25 to 4.09; high (female) RR=1.13, 95%CI 0.15 to 8.78

Table 1-1 *continued from previous page*

Author, year	Systematic review				Country	Income	Sample size	Specific occupation data	Occupational exposure of study	Exposure assessment		Respiratory outcome			Effect estimates
	Omland, 2014 (*n*=24)	Alif, 2016 (*n*=5)	Sadhra, 2017 (*n*=22)	Blanc, 2019 (*n*=24)						Self-reported	JEM	Respiratory symptoms	COPD diagnosed by a physician	Spirometry	(the association of occupational exposure with COPD or FEV$_1$/FVC)
Longitudinal studies (*n*=13)															
Lindberg, 2005 (99)	✓			✓	Sweden	HIC	1,109	7 occupational groups (socioeconomic classes)	-	✓		✓		✓	manual workers: NS; OR=1.78, 95%CI 0.80 to 3.97
Humerfelt, 1993 (100)	✓				Norway	HIC	1,591	11 airborne agents	dusts, gases, vapours & fumes	✓				✓	high asbestos: $p<0.05$
Kauffmann, 1982 (101)	✓				France	HIC	556	metallurgy, chemistry, printing & flour-milling	dust, gases & heat	✓				✓	at least one occupational hazard: $p\leq0.01$
Zhong, 2007 (55)				✓	China	LMIC	20,245	-	dusts, gases or fumes	✓		✓	✓	✓	dusts/gases/fumes: OR=1.20, 95%CI 1.04 to 1.39
Krzyzanowski, 1986 (102)	✓				Poland***	LMIC	1,824	-	dusts or chemicals	✓		✓		✓	dusts, male (decline in FEV$_1$): $p<0.05$; chemicals, male (decline in FEV$_1$): $p<0.05$; COPD: NS (COPD using FEV$_1$ <0.65 or FEV$_1$ decline)

*ECRHS: European Community Respiratory Health Survey; **PLATINO: Latin American Project for the Investigation of Obstructive Lung Disease; ***Poland was a LMIC in 1986 according to the World Bank's classification. (103); NS: not statistically significant; n/a: neither COPD nor FEV1/FVC was reported.; OR: odd ratio; PAF: population attributable fraction

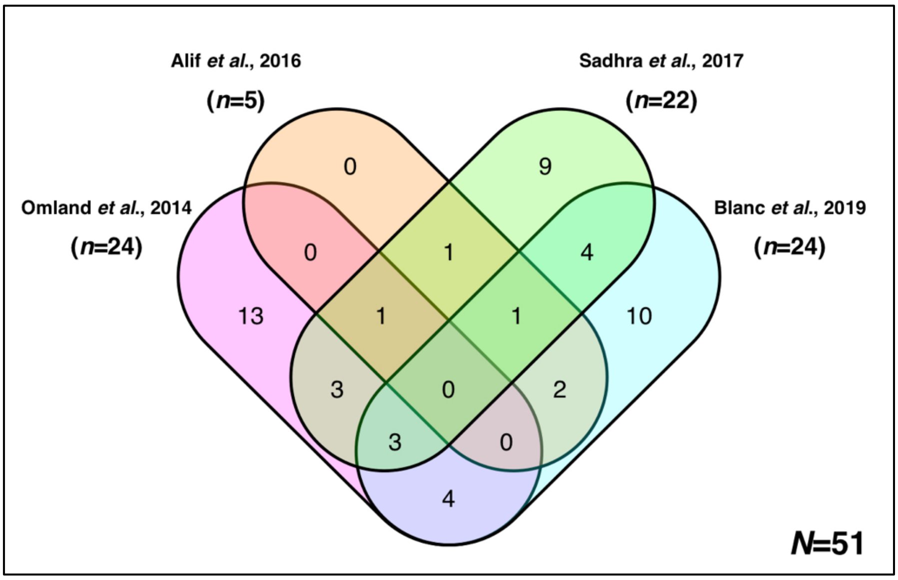


Figure 1-2 Overlap of studies on chronic respiratory disease and occupations included in four recent systematic reviews

1.3 Agriculture

Agriculture comprises a wide spectrum of activities including planting, harvesting, crop processing, gardening and nursery work, and livestock raising and breeding. (104) Worldwide, more than a billion labourers (about a third of the global workforce) work on farms. (105) Of the estimated 570 million farms in 161 countries, 83% of them are located in LMICs, (106) and account for almost 60% of the global agricultural workforce. A large majority of them work in the Asian and Pacific region (74%), followed by Africa (16%). (107) Figure 1-2 illustrates the proportion of agricultural workforces in each country in 2017. (108)

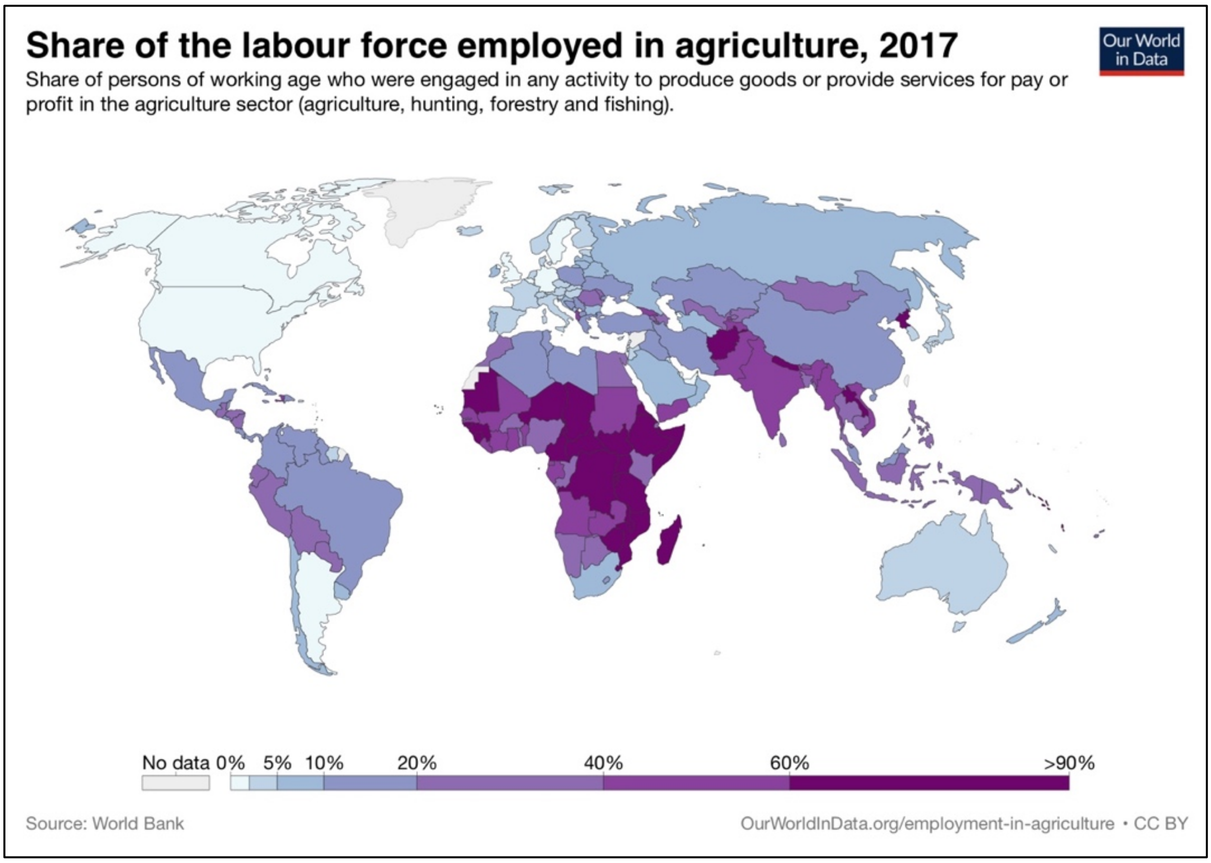


Figure was adapted from "share-of-the-labor-force-employed-in-agriculture.svg" on https://ourworldindata.org/grapher/share-of-the-labor-force-employed-in-agriculture. (109)

Figure 1-3 Global employment in agriculture in 2017

In most LMICs, agriculture plays a fundamental role as a way to earn an income as well as a way to subsist. (105, 110) Since the 1960s, many developing economies have transitioned from a traditional agrarian (for personal and family consumption) to an industrialised (for commercialisation) model. (111, 112) The growth of the global economy, with higher demand for agricultural products, resulted in an increase in both the number of farms and their densities. (106) Intensive agricultural workers are increasingly exposed to high levels of toxicants such as organic dusts (mostly from animal origins) and pesticides. (113, 114) Farming productivity has been associated with higher intensity usage of agrochemicals and manure exposures (104); and poor working conditions and inadequate personal protection remain an issue in several LMICs. (104, 115)

Farmers have some common characteristics worldwide. Most farming communities are located in rural areas where medical care resources are more limited. (116) A number of previous studies showed that farmers tend to smoke less compared to the general population. (51, 117-120) Furthermore, there are studies suggesting that the risks of COPD cases associated with agricultural occupational exposures are higher in non-smokers. (29, 121)

Agriculture is generally considered to be a hazardous occupation (116, 122) and an important cause of chronic respiratory disease. (46, 123) Bernardino Ramazzini, founder of occupational medicine, discussed the dangers of inhaling grain dust. (124) Agricultural exposures vary depending on the type of farm, region, climate, and season. While farmers in dry climates might be exposed to inorganic dusts (e.g., dry soil components) during soil preparation and harvesting, and those in humid farming conditions tend to be more exposed to bioaerosols (e.g., microorganisms), (115, 125) all farmers tend to be exposed to combinations of respiratory hazards. Some exposures can give rise to more than one respiratory symptom or disease. (116) Table 1-2 summarises the varieties of respiratory hazards on a farm from in-depth literature reviews. (104, 116, 125) Organic dusts (e.g., endotoxin found in grains and hays) are the main respiratory exposure among farmers; inorganic dusts are generally found in lower amounts. (122, 125, 126) Contaminants from farming activities affect not only farming workers but also family members and others in the neighbouring vicinity; there are thus relevant 'geographical' as well as occupational exposures of interest. (127)

Agricultural exposures have been associated with several chronic airway symptoms. (122, 128-132) In a farming environment, both organic and inorganic aerosols and fumes lead to lung inflammation, (104) one of the potential biological underlying mechanisms of an increased risk of lung disease among agricultural workers. (133) In intensive animal operations, biological dusts from bacterial products, gases (e.g. ammonia and hydrogen sulphide) and particulate matter have been associated with airflow obstruction. (122) Farm work potentially leads to several respiratory illnesses including rhinitis, asthma, hypersensitivity pneumonitis, pneumoconiosis and respiratory infection; however, it is unclear whether COPD is associated by farming. (51, 125, 127)

There are two recent systematic reviews of chronic respiratory disease in farmers, published by Fontana *et al.* in 2017 (134) and Guillien *et al.* in 2019 (135). Overall, both reviews reported a significant relationship between COPD and farming, particularly among livestock farmers. Fontana *et al.* reported COPD prevalences ranging from 3% to 68%; the risks of COPD were different according to farm categories (i.e., greenhouse, pesticides, dairy and multiple exposures). (134) Similarly, Guillien *et al.* found various associations of COPD and airflow limitation with different farming activities (i.e. cattle, swine, poultry, crop and mixed farming). (135) Both reviews suggested further epidemiological studies of different farm types/groups, farming practices, specific agents and factors, particularly in crop farmers. Further, there is a need for more quantitative measurements using appropriate definitions (i.e., post-bronchodilator spirometry using LLN specific to age, sex and ethnicity) to examine respiratory outcomes among farming populations.

Table 1-2 Agricultural respiratory hazards

Hazard categories	Exposure sources	Farming activities
Organic dusts	Grain dusts; hay; cotton; silage	Harvest; transfer; storage and processing; barn and silo operations; grain cleaning; cotton and flax industry
	Animal dander, urine and faeces	Animal confinement; livestock farming
	Endotoxins, bacterial	Animal confinement; livestock farming; animal feed industry; grain elevators; cotton and flax industry; potato processing; bedding chopper
	Mycotoxins, fungal	Contaminating the respirable fraction of airborne grain dusts
Inorganic dusts	Soil silicates	Soil preparation; plough; harvest
Chemicals, gases and fumes	Nitrogen oxides (NO_x); hydrogen sulphide (H_2S); ammonia (NH_3); carbon dioxide (CO_2); carbon monoxide (CO); methane (CH_4)	Slurry, manure and silage fermentation; silo operation; animal confinement
	Pesticides: herbicides; insecticides; fungicides; fumigant	Field working; application; mixing
	Fertilizers	Field working; application
	Disinfectants: chlorine	Dairy barn; animal confinement
	Diesel fuel	Agricultural machinery operations
	Welding fumes	Welding operations

Table 1-3 summarises the 22 studies included in these reviews that reported findings based on spirometry data. Of these, 19 studies used self-reported exposure assessments while two used a JEM for assessing farming exposures. There were various farming types (e.g., livestock vs crop) and farming activities in different regions which presumably lead to a variety in the types of exposure. Moreover, there were differences in COPD definition (i.e., FEV_1/FVC ratio cut-points: the fixed GOLD<0.70 vs LLN) and spirometry performance. To discriminate COPD from asthma, post-bronchodilator spirometry is necessary (136); however, among those studies with spirometry parameters reported, only ten of the 22 reported post-bronchodilator spirometry measures. Considering the relationships between exposure assessment techniques and respiratory outcomes, there were no obvious patterns whereby those with more sophisticated means of measurement produced systematically different findings from those with cruder methods. In addition there was a wide spectrum of study designs and population sampling methods. Eleven of the 20 cross-sectional surveys (five of mixed farming, three of dairy farming and one each of swine, green-house and crop farming) reported significant relationships between various farm exposures and poorer lung function. Findings from the longitudinal studies were less consistent. A study of mixed farming in the Netherlands reported a significant association of high herbicide exposure with poor lung function (FEV_1/FVC<70%), OR=2.11, 95%CI 1.03 to 4.30. (92) In contrast, Marescaux *et al.* reported that active dairy farmers in France had a decreased risk of COPD (LLN), OR=0.25, 95%CI 0.11 to 0.56. (137)

The majority of studies (16 of 22 studies) were undertaken in HICs in Europe and North America. Few studies were undertaken in LMICs: one in China (138); three from the same group of researchers in Macedonia (121, 139, 140); one in India (141) and one in Nigeria (58). The surveys in LMICs included 7,796 participants and those in HMICs 26,446, or 77% of the total. There have been no longitudinal studies in a LMIC. The same applies to a large pooling of research data on agricultural health (the Consortium of Agricultural Cohort (AGRICOH) study); fifteen of the 22 international cohort studies included an examination of respiratory health, all of them in HICs. (142)

Table 1-3 Twenty-two studies on farming and chronic respiratory disease with spirometry parameter results included in recent systematic reviews

Author, year	Systematic review		Country	Income	Farming types	Pesticide study included	Population		Overall sample size	Overall response rate (%)	Age (year)	Overall sex (%male)	Exposure assessment			Respiratory outcome		Effect estimates*
	Fontana, 2017 (*n*=14)	Guillien, 2019 (*n*=12)					Population -based	Farming -specific					Self-reported	JEM	Other	Spiro-metry test	Post-broncho dilator	
Cross-sectional studies (n=20)																		
Hansell, 2014 (67)		✓	New Zealand	HIC	crop	✓	✓		750 (with spiro-metry)	78%	25 to 74	54%	✓	✓		✓	✓	insecticides: NS; OR=0.69, 95%CI 0.29 to 1.68
Cha, 2012 (143)	✓		South Korea	HIC	mixed	✓		✓	2,882	n/a	classified into 4 age groups: <50; 50-59; 60-69; ≥70	68%	✓			✓		NS; OR=1.44 95%CI 0.50 to 4.16
Dalphin, 1998 (144)		✓	France	HIC	dairy			✓	414	76%		54%	✓			✓	✓	significantly lower %FEV_1/VC: p<0.025
Jouneau, 2012 (145)	✓		France	HIC	dairy			✓	147	n/a		59%	✓			✓	✓	foddering: significantly higher in COPD patients: p=0.02

Table 1-3 *continued from previous page*

Author, year	Systematic review		Country	Income	Farming types	Pesticide study included	Population		Overall sample size	Overall response rate (%)	Age (year)	Overall sex (%male)	Exposure assessment			Respiratory outcome		Effect estimates*
	Fontana, 2017 (*n*=14)	Guillien, 2019 (*n*=12)					Population -based	Farming -specific					Self-reported	JEM	Other	Spiro-metry test	Post-broncho dilator	
Cross-sectional studies (n=20)																		
Rimac, 2010 (146)		✓	Croatia	HIC	poultry			✓	86	42%		33%	✓			✓		NS; two-way ANCOVA showed no significant difference FEV_1/FVC between workers and controls.
Cushen, 2016 (147)	✓		Ireland	HIC	mixed			✓	372	n/a		76%	✓			✓		NS; livestock: p=0.77; arable: p0.25; mixed farm type: p=0.18
Eduard, 2009 (148)	✓		Norway	HIC	mixed			✓	4,735	79%		60%			environ-mental monitor-ing	✓		livestock: OR=1.9, 95%CI 1.4 to 2.6
Golec, 2014 (149)	✓		Poland	HIC	mixed			✓	64	n/a		50%	✓			✓		This study compared lung function measures between farmers with COPD and healthy farmers.

Table 1-3 *continued from previous page*

Author, year	Systematic review		Country	Income	Farming types	Pesticide study included	Population		Overall sample size	Overall response rate (%)	Age (year)	Overall sex (%male)	Exposure assessment			Respiratory outcome		Effect estimates*
	Fontana, 2017 (*n*=14)	Guillien, 2019 (*n*=12)					Population -based	Farming -specific					Self-reported	JEM	Other	Spiro-metry test	Post-broncho dilator	
Cross-sectional studies (n=20)																		
Guillien, 2016 (150)	✓	✓	France	HIC	mixed			✓	4,704	44%		59%	✓			✓	✓	significantly higher COPD prevalence in farmers compared to controls: p=0.005
Lamprecht, 2007 (151)	✓	✓	Austria	HIC	mixed		✓		1,258	57%		55%	✓			✓	✓	OR=1.5, 95%CI 1.1 to 2.0
Monsó, 2004 (152)	✓		Denmark, Germany, Switzer-land & Spain	HICs	mixed			✓	105	85%		80%			environ-mental monitor-ing	✓	✓	dust: OR=6.60, 95%CI 1.10 to 39.54
Bailey, 2007 (153)	✓		USA	HIC	mixed			✓ (veterans)	150	69%		99%	✓			✓		NS; Chi-square test (GOLD stage): p=0.25
Hnizdo, 2002 (76)		✓	USA	HIC	mixed		✓		9,823	n/a		47%	✓			✓		NS; OR=1.5, 95%CI 0.8 to 2.7
Dosman, 1988 (154)		✓	Canada	HIC	swine			✓	952	n/a		100%	✓			✓		significantly lower FEV_1/FVC (%): p<0.05

Table 1-3 *continued from previous page*

Author, year	Systematic review		Country	Income	Farming types	Pesticide study included	Population		Overall sample size	Overall response rate (%)	Age (year)	Overall sex (%male)	Exposure assessment			Respiratory outcome		Effect estimates*
	Fontana, 2017 (*n*=14)	Guillien, 2019 (*n*=12)					Population -based	Farming -specific					Self-reported	JEM	Other	Spiro-metry test	Post-broncho dilator	
Cross-sectional studies (n=20)																		
Liu, 2015 (138)	✓		China	LMIC	green-house			✓	5,420	92%		49%	✓			✓	✓	no control group; planting mushroom: OR=1.46, 95% CI=1.13 to 1.87; planting flowers OR=1.53, 95%CI 1.24 to 1.95
Stoleski, 2015a (121)	✓	✓	Macedonia	LMIC	dairy			✓	104	n/a		100%	✓			✓	✓	significantly lower FEV_1/FVC (%): p=0.01
Stoleski, 2015b (139)		✓	Macedonia	LMIC	crop			✓	150	n/a		58%	✓			✓		NS; t-test (FEV_1/FVC%): p=0.48
Stoleski, 2017 (140)		✓	Macedonia	LMIC	mixed			✓	250	n/a		74%			serum CRP	✓	✓	significantly different serum CRP levels between subjects with- and without COPD in each examined group: p=0.049 and p=0.040

Table 1-3 continued from previous page

Author, year	Systematic review		Country	Income	Farming types	Pesticide study included	Population		Overall sample size	Overall response rate (%)	Age (year)	Overall sex (%male)	Exposure assessment			Respiratory outcome		Effect estimates*
	Fontana, 2017 (*n*=14)	Guillien, 2019 (*n*=12)					Population -based	Farming -specific					Self-reported	JEM	Other	Spiro-metry test	Post-bronchodilator	
Cross-sectional studies (n=20)																		
Chakraborty, 2009 (141)	✓	✓	India	LMIC	crop	✓		✓	724	n/a		100%	✓			✓		significantly lower FEV_1/FVC (%): p<0.001
Obaseki, 2016 (58)		✓	Nigeria	LMIC	mixed		✓		1,148	74%		37%	✓			✓	✓	NS; OR=0.8, 95%CI 0.4 to 1.6
Longitudinal studies (n=2)																		
Marescaux, 2016 (137) (nested case-control)	✓		France	HIC	dairy			✓	575	98%		100%	✓			✓		active farmers: OR=0.25, 95%CI 0.11 to 0.56
de Jong, 2014 (92) (cohort)	✓		The Netherlands	HIC	mixed	✓	✓		14,215	n/a		43%	✓	✓		✓		high herbicide exposure: OR=2.11, 95%CI 1.03 to 4.30

*The association of farming with COPD or FEV_1/FVC
NS: not statistically significant; OR: odd ratio; CRP: c-reactive protein

1.4 Pesticide exposure

A pesticide is a substance or mixture of substances used for preventing, destroying, repelling, regulating or controlling pests. Pesticide consumption has grown by over 50% since the 1950s, and in 2012 global expenditure on pesticides was estimated to be £35 billion. (155) In LMIC regions, demand for pesticides has significantly increased; from 2004 to 2014, there was a 6.7% annual increase in Central and South America, and a 4% annual increase in Asia. (156)

There are three main categories of pesticide: herbicides; insecticides and fungicides. Other sub-categories are based on target pests e.g., rodenticides, nematicides and acaricides. (157) Herbicides makes up the largest proportion of total expenditure (45%), followed by insecticides, fungicides and other pesticides. (158)

Pesticides have different toxic effects to several organs causing various adverse health effects including neurodegeneration, cancers, endocrine disruption, inhibition of growth and development and toxicity to reproductive systems. Routes of pesticide exposures can be via ingestion, skin absorption and inhalation. (159) There are two main types of insecticides that affect the respiratory system. Organophosphorus compounds (organophosphate (OP) insecticides) primarily target acetylcholinesterase (AChE) which plays a major role in both the central and peripheral nervous systems. OP insecticides have acute toxicity and cause a 'cholinergic syndrome' reflecting overstimulation of cholinergic receptors. This mechanism affects the muscarinic cholinergic receptor resulting in increased respiratory tract bronchial secretions and bronchoconstriction. (160) Pyrethroids are insecticides that alter insect nerve action potential functions via voltage-gated sodium channels; they are efficiently absorbed by inhalation. (161) Acute pyrethroid poisoning is associated with respiratory symptoms including cough, mucous secretion, upper airway constriction and dyspnoea. (162) Paraquat, a bipyridyl herbicide, has been widely used for controlling weeds; it has the highest acute toxicity among herbicides. Paraquat can be transformed to a superoxide anion ($O_2^{\bullet -}$), which is toxic to alveolar type I and type II and Clara cells. Acute paraquat poisoning causes damage to alveolar epithelial cells with alveolar oedema resulting in anoxia. (163) In animal studies, more chronic exposure to paraquat damages the lung tissues. (164)

Occupational exposures to pesticides are varied, from manufacturing, transport, storage and direct or indirect use. In the agricultural field, several processes including mixing, loading, spraying, harvesting and equipment cleaning lead to exposures via skin, inhalation and ingestion. (165, 166) The degree of pesticide hazard relies not only on the toxicity of the pesticide but also on its preparation and formulation, the dimensions of the pesticide particle or aerosol, and the use of personal protective equipment (PPE). (167) The use of pesticides varies depending on the type of crops but most farmers tend to apply cocktails of pesticides with various inadequate practices. (168) Farmers in LMICs tend to have higher exposure levels to pesticides than those in developed countries due to inappropriate PPE use and poor pesticide application with lack of safety training. (104)

Several large studies in HICs report relationships between pesticide exposure and respiratory illnesses. For example, the AGRICAN study in France found pesticide use increased the risk of allergic asthma. (169) Similarly, in the USA, the Agricultural Health Study (AHS) cohort have reported a series of studies with significant associations between the use of various pesticides and asthma. (170, 171) Neither the AGRICAN nor AHS studies reported spirometric measurements and only the AHS study classified pesticide use, using generic names (e.g., coumaphos, heptachlor and parathion).

There are two recent systematic reviews that assessed the effect of pesticide exposure on a broad variety of respiratory health effects. (157, 172) Mamane *et al.* reported that occupational pesticide exposure associates with chronic respiratory symptoms: cough; phlegm; wheeze; breathlessness and chest tightness, chronic bronchitis and asthma; however, the relationships between pesticide exposures and COPD and lung function impairment were limited. (157) In addition, Doust *et al.* reported that the strength of available evidence for an association of pesticide exposure with COPD is much weaker than for asthma. Few studies reported spirometry data. (172)

Table 1-4 presents all articles reporting spirometry measures in the two systematic reviews. Together they reported on a total of seven articles with lung function as an outcome, but only Chakraborty *et al.* (141) was included in both reviews. Their different findings might be due to their diverse search terminologies and selection criteria. In general, the reviewed studies were small, seldom specified the pesticides used or the amount, frequency and duration of exposure and there was inadequate account taken of other potentially important exposures. Therefore, there is a need for better evidence on the risks to lung health and to lung function posed by pesticide use.

Table 1-4 Seven studies on pesticide exposure and respiratory health with spirometry parameter results included in recent systematic reviews

Author, year	Systematic review		Country	Income	Study design	Pesticide of study	Population	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Spirometric parameters	Effect estimates (the association of pesticide exposures with lung function: FEV_1/FVC; FVC; FEV_1)
	Doust, 2014 (*n*=4)	Mamane, 2015 (*n*=4)										
Cha, 2012 (143)		✓	South Korea	HIC	cross-sectional	paraquat	farmers	self-reported	✓		FEV_1/FVC, FVC & FEV_1	t-test: FEV_1/FVC: NS, FVC: NS, FEV_1: NS
Hernandez, 2008 (173)		✓	Spain	HIC	cross-sectional	unspecified	farmers	self-reported	✓		FEV_1/FVC, FVC, FEV_1, $FEF_{25-75\%}$ & TLCO	linear regression models: FEV_1/FVC: NS, FVC: NS, FEV_1:
Huang, 1995 (174)	✓		Japan	HIC	cross-sectional	TCPN	manufacturing workers	job title	✓		FEV_1/FVC, FVC, FEV_1, $FEF_{25-75\%}$ & PEF	t-test: FEV_1/FVC: $p<0.01$, FVC: NS, FEV_1: $p<0.05$
Chakraborty, 2009 (141)	✓	✓	India	LMIC	cross-sectional	ChE inhibiting (organophosphate & carbamate)	farmers	self-reported	✓		FEV_1/FVC, FVC, FEV_1, $FEF_{25-75\%}$ & PEF	t-test: FEV_1/FVC: $p<0.0001$, FVC: $p<0.0001$, FEV_1: $p<0.0001$
Schenker, 2004 (175)	✓		Costa Rica	LMIC	cross-sectional	paraquat	farmers	self-reported	✓		FEV_1/FVC, FVC, FEV_1, $FEF_{25-75\%}$ & TLCO	linear regression models: FEV_1/FVC: NS, FVC: NS, FEV_1: NS
Mekonnen, 2004 (176)		✓	Ethiopia	LMIC	cross-sectional	unspecified	farmers	job title	✓		FVC & FEV_1	F-test (decreased lung volumes): FVC: $p=0.009$; FEV_1:
Senanayake, 1993 (177)	✓		Sri Lanka	LMIC	cross-sectional	paraquat	farmers	job title	✓		FEV_1/FVC, FVC, FEV_1, $FEF_{25-75\%}$, MEF & PEF	ANCOVA: FEV_1/FVC: NS, FVC: NS, FEV_1: NS

NS: not statistically significant; TCPN Tetrachloroisophthalonitri

CHAPTER 2

Pesticide exposure and lung function: a systematic review and meta-analysis

CHAPTER 2 Pesticide exposure and lung function: a systematic review and meta-analysis

2.1 Introduction

Each year, two million tons of pesticides are used globally in agricultural and other sectors. (178) There is extensive evidence suggesting a link between occupational pesticide exposure and respiratory symptoms and illnesses including chronic bronchitis, chronic obstructive pulmonary disease and asthma. The evidence base has been summarized in two 'systematic' reviews. (157, 172) Both included articles published up to the end of 2013; they reported on a total of seven articles with lung function as an outcome, but only one of these studies (141) was included in both reviews. Thus, and furthermore, the quantitative impact of pesticide exposure on lung function is unclear. A preliminary screen of relevant articles published since 2014 revealed several new epidemiological reports of associations between pesticide exposure and lung function; here I reviewed all available literature on this topic and quantified, where appropriate, the effect of pesticide exposure on lung function.

2.2 Aim and objective

I aimed to examine the association between various pesticide exposures and decrements in lung function which are associated with chronic lung disease. The objective of this study is to review systematically all available published literature regarding the relationship between occupational exposures to pesticides (through farming, pesticide manufacture and any other relevant occupations) and lung function.

2.3 Methods

This systematic review was registered with the international prospective register of systematic reviews (PROSPERO) CRD42017078131 (appendix A-1). The search processes and reporting follow the Preferred Reporting Items for Systematic review and Meta-analysis protocols (PRISMA-P). (179)

2.3.1 Inclusion Criteria and Search Strategy

I searched MEDLINE, EMBASE, and Web of Science electronic databases through to 1 October 2017. The search strategy (table 2-1) included both free text and controlled vocabulary in MEDLINE and EMBASE but only free text searching in Web of Science. I considered only papers with adequate abstract information; there were neither date nor language restrictions. I included all experimental and observational (cohort, case-control and cross-sectional) studies that had assessed the relation between lung function outcomes and pesticide exposure and had included at least one unexposed control group. I included studies where pesticide was just one of several exposures studied; all pesticide exposure measures, including questionnaire, interview, job exposure-matrix, or biomarkers, were accepted.

Pesticide exposure assessments comprised pesticide type, duration, frequency of exposure and method of application.

Table 2-1 Search terms and number of articles retrieved in each database

	MEDLINE (Ovid)	EMBASE (Ovid)	Web of Science
Duration	Ovid MEDLINE® 1946 to 01/10/2017	Ovid Embase Classic + Embase 1947 to 01/10/2017	1970 to 01/10/2017
Search Term(s)	Controlled Vocabulary (CV): MeSH Free text (FT)	Controlled Vocabulary (CV): Emtree Free text (FT)	Free text (FT)
Exposure	CV: Pesticide FT: • Pesticide$ • Insecticide$ • Herbicide$ • Fungicide$ • Rodenticide$ • Fumigant$ • Biocide$ • Sheep dip$ • Avicide$ • Nematicide$ • Nematocide$ • Acaricide$ • Molluscicide$ • Molluscacide$ • Agrochemical$ • Agrichemical$	CV: Pesticides FT: • Pesticide$ • Insecticide$ • Herbicide$ • Fungicide$ • Rodenticide$ • Fumigant$ • Biocide$ • Sheep dip$ • Avicide$ • Nematicide$ • Nematocide$ • Acaricide$ • Molluscicide$ • Molluscacide$ • Agrochemical$ • Agrichemical$	FT: "Pesticide*" OR "Insecticide*" OR "Herbicide*" OR "Fungicide*" OR "Rodenticide*" OR "Fumigant*" OR "Biocide*" OR "Sheep dip*" OR "Avicide*" OR "Nematicide*" OR "Nematocide*" OR "Acaricide*" OR "Molluscicide*" OR "Molluscacide*" OR "Agrochemical*" OR "Agrichemical*"
Outcome	CV: Lung function test OR peak expiratory flow OR Oximetry OR provocation test FT: • Pulmonary function$ • Respiratory function$ • Lung function$ • Spiromet$ • FEV1$ • FVC$ • Forced Expiratory$ • Vital Capacity$ • Tiffeneau-Pinelli index$ • Expiratory flow$ • Expiration flow$ • Peak flow$ • PEEF • PEF • MEF • Oximet$ • provocation test$ • Bronchial challenge$ • Bronchial hyperresponsivenes$ • DLCO • TLCO • Diffusing capacity$	CV: Respiratory Function Tests FT: • Pulmonary function$ • Respiratory function$ • Lung function$ • Spiromet$ • FEV1$ • FVC$ • Forced Expiratory$ • Vital Capacity$ • Tiffeneau-Pinelli index$ • Expiratory flow$ • Expiration flow$ • Peak flow$ • PEEF • PEF • MEF • Oximet$ • provocation test$ • Bronchial challenge$ • Bronchial hyperresponsivenes$ • DLCO • TLCO • Diffusing capacity$	FT: "Respiratory Function*" OR "Lung function*" OR "Pulmonary function*" OR "Spiromet*" OR "FEV1*" OR "FVC*" OR "Forced Expiratory*" OR "Vital Capacity*" OR "Tiffeneau-Pinelli index*" OR "Expiratory flow*" OR "Expiration flow*" OR "Peak flow*" OR "PEEF" OR "PEF" OR "MEF" OR "Oximet*" OR "Provocation test*" OR "Bronchial challenge*" OR "Bronchial hyperresponsivenes*" OR "DLCO" OR "TLCO" OR "Diffusing capacity*"
Total	1,927	483	247

2.3.2 Data Extraction

After removal of duplicate records, I (JR) screened all the extracted titles and abstracts for eligibility. Two other reviewers composed of Dr De Matteis (SDM) and Professor Cullinan (PC) independently re-checked, on two occasions, a random sample of 200 articles. Inter-rater agreement showed kappa values between 0.66 to 1.00 indicating good to very good agreement. (table 2-2) In case of disagreement, consensus was reached by discussion between three reviewers (JR, SDM and PC).

Table 2-2 Inter-rater agreement measured as kappa coefficients

2a) Article No. 1 to 200 screening arranged by the most recent

	JR	SDM	PC
JR	1.00	0.81	0.71
SDM		1.00	0.66
PC			1.00

2b) Article No. 201 to 400 screening arranged by the most recent

	JR	SDM	PC
JR	1.00	1.00	0.80
SDM		1.00	0.80
PC			1.00

Kappa coefficients reflect inter-observer agreement (180): poor <0.20; fair 0.21-0.40; moderate 0.41-0.60; good 0.61-0.80; and very good 0.81-1.00

Inclusion and exclusion criteria were set for full-text screening. I chose only titles and abstracts including pesticide exposure, studies in humans, primary data with control groups and lung function test outcomes; we excluded studies of pesticide exposure by ingestion and those of agents not being used as pesticides. For each rejected article, I noted a reason.

I separated studies into those of long-term (lifetime) and short-term pesticide use, the latter undertaken pre- and post-exposure, between seasons or under experimental conditions. I undertook pre-specified subgroup analyses by national income using the World Bank Classification (181), by population of study (farmers, pesticide manufacturers, general populations, children and others), age and sex.

2.3.3 Quality Assessment

I assessed the quality of reporting in each study by applying a modified Newcastle – Ottawa Quality Assessment Scale (NOS). (182, 183)

2.3.4 Statistical analysis

Meta-analyses included only studies of long-term pesticide exposure, there being too few studies of short-term exposures. To limit inconsistencies between studies, I used only binary (yes/no) exposure data. I performed pre-specified subgroup analyses by the main categories of pesticides.

I included FEV_1/FVC (the forced expiratory volume in the first one second to the forced vital capacity of the lungs) ratio (%), reductions in which suggest an obstructive pulmonary pattern and FVC (either in litres or as a percentage of predicted value) suggesting pulmonary restriction as outcome measures. We also included studies showing binary outcome results of FEV_1/FVC ratio and FVC. I undertook further analyses of FEV_1 and peak expiratory flow (PEF) and other measures of Forced Expiratory Flow (FEF) and gas transfer. Where adjusted and unadjusted results were reported for an outcome, I selected the most completely adjusted estimate.

I converted differences in lung function, odd ratios and regression coefficients (β) into standardised mean differences (SMD) with their standard errors (SE). (184) I tested between-study heterogeneity using the Q test and estimated its magnitude using the I^2 statistic. A fixed effect model was primarily used. As recommended, a random effect model was then used in instances where no statistical significance was found in fixed effect models. I categorized 'high' heterogeneity as $I^2>50\%$ (185), We used Egger's test to check for publication bias. A p-value with a threshold of <0.05 was defined as statistically significant. I used the metan command in Stata 15 (StataCorp LP, College Station, TX) to perform the meta-analyses.

2.4 Results

2.4.1 Inclusion and exclusion of studies

A total of 2,356 articles were identified from the initial search; 2,266 were excluded. Of 90 articles reviewed in full, 71 studies were published in English and 19 in other languages. Of these, 50 articles in English and six in other languages (three in German, two in Polish and one in Russian) met our criteria and their details were extracted. (figure 2-1) Non-English articles were translated by Imperial College staff who were native speakers in the relevant language.

2.4.2 Pesticide exposure and metrics

Fifty studies presented findings of long-term exposure to pesticides, and eight of short-term exposures; two studies presented findings from both long- and short-term exposures. Most studies were conducted in farmers in low- to middle-income countries; studies of pesticide manufacturing workers and in general populations tended to be from high-income countries. (appendix A-2) Table 2-3 also shows lung function measures used in these studies. Most presented the results of FEV_1/FVC ratio, FVC and FEV_1 as their outcomes.

Table 2-3 Numbers of studies included in the review according to sampled population and length of exposure with numbers included in meta-analyses in parentheses

Sample	Long-term exposure studies				Short-term exposure studies
	FEV_1/FVC	FVC (L) or %predicted	FEV_1 (L) or %predicted	Other measures	
Farmers	14 (13)	21 (17)	20 (15)	21	4
Manufacturing workers	3 (2)	7 (3)	8 (4)	8	0
General populations	10 (5)	4 (1)	7 (2)	3	1
Children	2	2	2	2	1
Others	1	2 (1)	2 (1)	2	2

Twenty-eight of the 56 papers included did not specify the type of pesticide. Of the remainder, 14 specified a cholinesterase (ChE)-inhibiting pesticide, four pyrethroids, one dichlorodiphenyltrichloroethan (DDT) and one an unspecified household insecticide. Studies of herbicide exposures included eight with paraquat and four others. Overall, 25 articles defined the study and control groups by job title (e.g., pesticide sprayers and non-sprayers); 17 articles relied on self-reported pesticide exposure; four inferred exposure from a job exposure matrix (JEM) and four used biological markers of exposure. A geographic information system (GIS) was used in one article to evaluate exposure from distribution of a sulphur pesticide. The five remaining articles provided information on only short-term exposure studies. Of these, two articles presented pre- and post-exposure measurements, two stratified the analysis comparing exposed and unexposed areas and the last used an experimental chamber. (appendix A-2) I grouped pesticide exposures into four: 1) paraquat,

2) ChE-inhibiting pesticides, 3) other specific pesticides and 4) unspecified pesticides. I undertook meta-analyses for three outcome measures: FEV_1/FVC ratio, FVC and FEV_1.

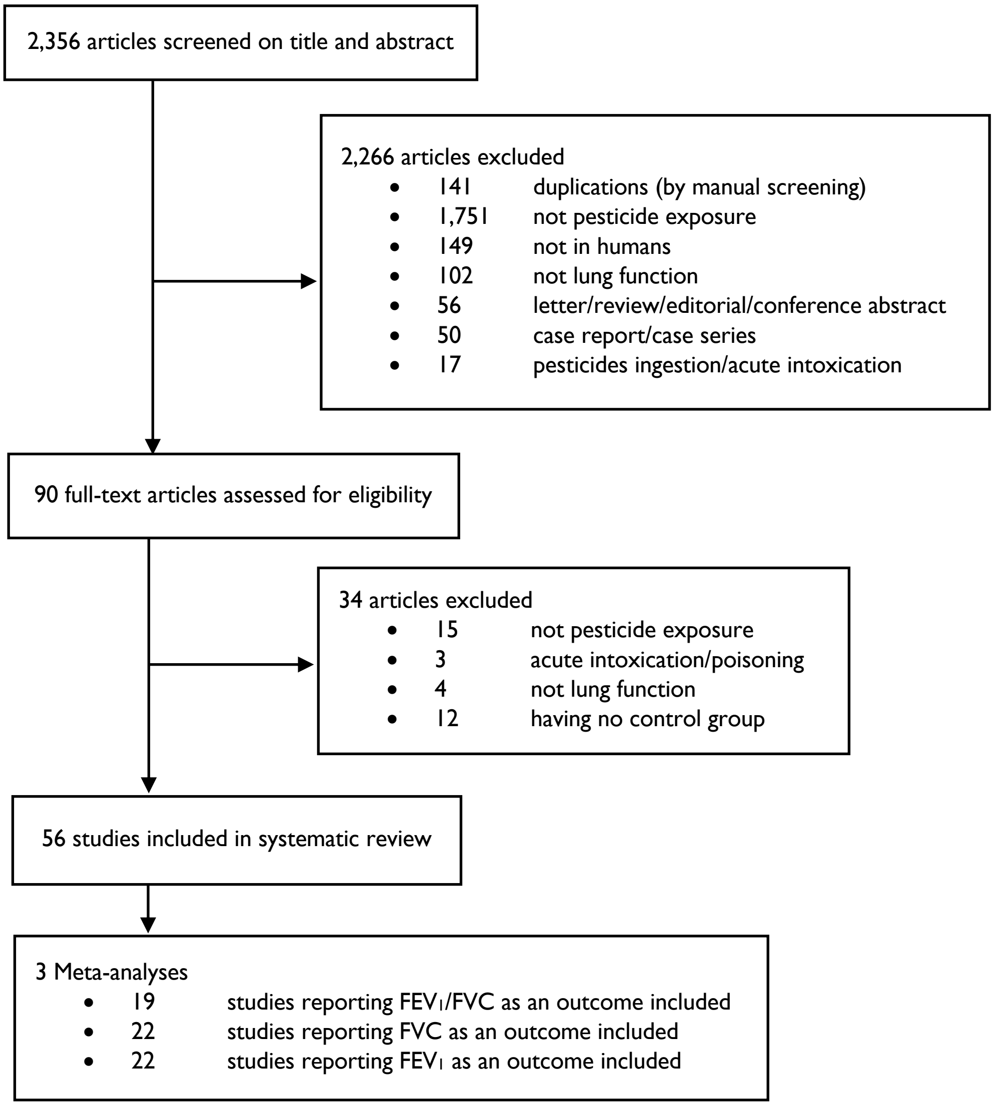


Figure 2-1 Systematic review and meta-analysis search results

2.4.3 Association of pesticide exposures with FEV_1/FVC

Nineteen studies were pooled in meta-analyses of the FEV_1/FVC ratio. Figure 2-2 illustrates a forest plot of the relationships between the FEV_1/FVC ratio and pesticide exposures classified by sampled populations. Pooled effect estimates (presented with diamonds) are shown only for subgroup analyses where there was not high heterogeneity. The sample sizes of all the included studies are shown in which appendix A-2.

Paraquat

In figure 2-2, four studies investigating the effects of paraquat exposure were included. All were conducted in farmers and none reported a significant relationship between paraquat exposure and the FEV_1/FVC ratio. (143, 175, 177, 186) There was no significant overall relationship between paraquat exposure and the FEV_1/FVC ratio (SMD=0.05, 95%CI -0.04, 0.15), with no evidence of between study heterogeneity (I^2=0%, p=0.85).

ChE-inhibiting pesticides

Four of seven studies of ChE-inhibiting pesticides were included in meta-analyses of the FEV_1/FVC ratio; results from Raanan *et al.* and Ye *et al.* were excluded because they used continuous units of exposure derived from urinary dialkylphosphate (DAP) concentrations. (187, 188) The estimated effect of ChE pesticides was highly heterogeneous (I^2=99%, p<0.001). (figure 2-3) On excluding the outlying result from Fareed *et al.* (189) which reported unfeasibly small SDs (0.01) for the FEV_1/FVC ratios in both the sprayer and control groups, heterogeneity diminished (I^2=46.3%, p=0.13) but the effect of ChE-inhibiting pesticides on the FEV_1/FVC ratio was not significant (SMD=-0.22, 95% CI -0.46, 0.01) using the random effects model but was significant using a fixed effects model (SMD=-0.27; 95% CI -0.39, -0.14). (141, 190-192) (figure 2-2)

Of the studies excluded from the meta-analysis, that by Ye *et al.* showed no significant relationships between FEV_1/FVC ratio and urinary metabolite concentrations at any age in a general population aged 12 to 79. (188) Raanan *et al.* measured urinary DAPs in children aged seven years, indicating organophosphate exposure, and reported no associated decrease in FEV_1/FVC with diethyl-, dimethyl- and total dialkyl-phosphate (DAP) concentrations. (187)

Other specific pesticides

Two studies related the FEV_1/FVC ratio to pyrethroid exposure. Ye *et al.* reported that a unit increase in log transformed urinary concentration of total pyrethroid metabolites was associated with a 0.3% increase in the FEV_1/FVC ratio (SE=0.1, p=0.01) among those aged 20 to 79 in a community population after adjustment for age, sex, race, height and weight. (193) Kilburn *et al.* studied flight attendants applying pyrethroid and found a significant increase of the FEV_1/FVC ratio in the exposed compared to the unexposed group (p=0.013). (194)

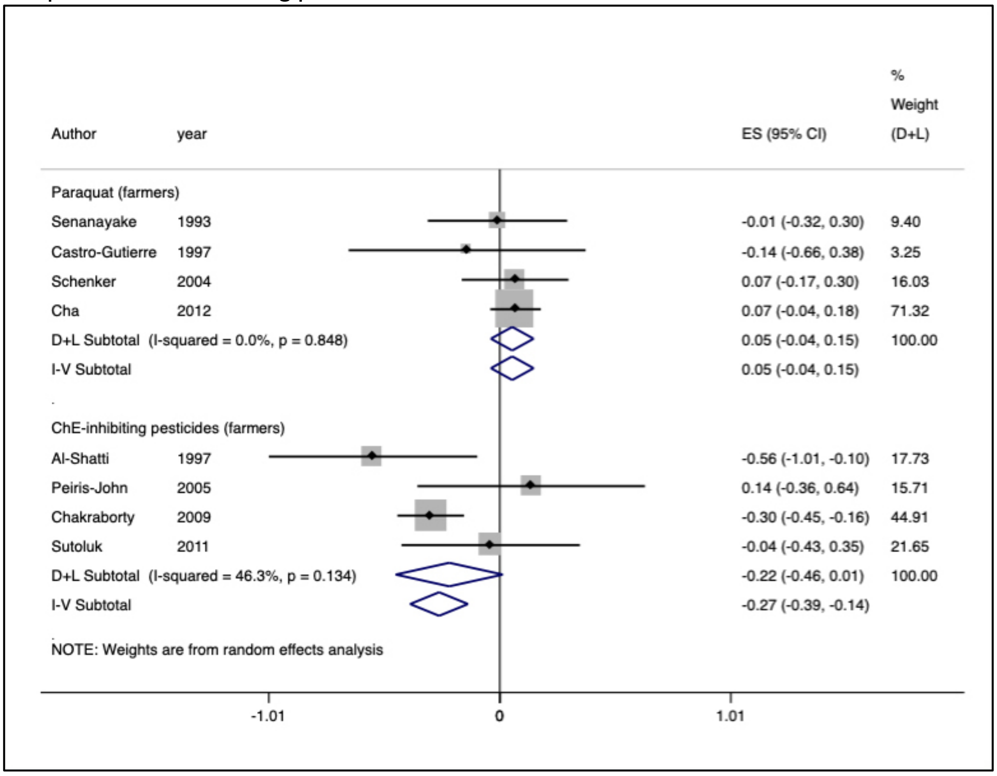
Suskind *et al.* studied 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) manufacturing workers and reported that the FEV_1/FVC ratio was significantly lowered in an exposed group (p=0.002) (195) Ye *et al.* reported no significant relationships between plasma DDT and dichlorodiphenyldichloroethylene (DDE) and the FEV_1/FVC ratio. (196) In Californian children, Raanan *et al.* showed no significant differences in FEV_1/FVC in relation to the distance of their home from areas where sulphur had been applied as an agricultural pesticide. (197)

Unspecified Pesticides

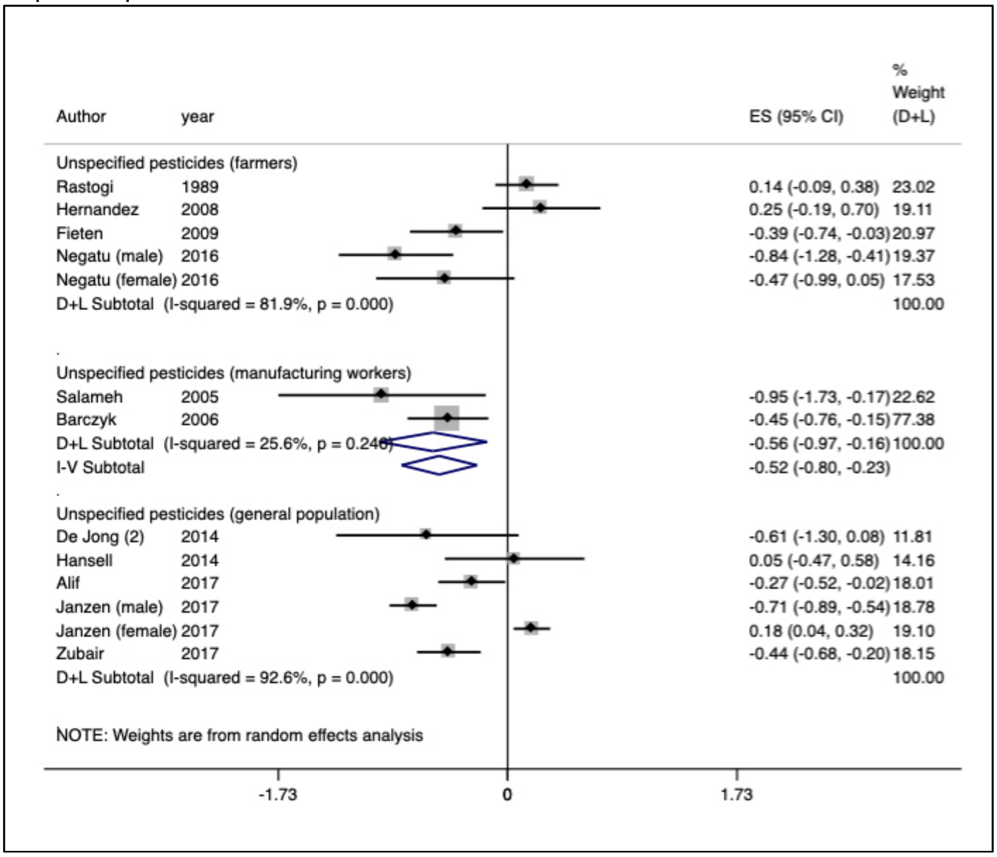
Eleven of 13 studies were included in a meta-analysis of FEV_1/FVC ratio and exposure to unspecified pesticides. There was high between-study heterogeneity in the studies in farmers (173, 198-200) (I^2=81.9%, p<0.001) and in general populations (67, 201-204) (I^2=92.6%, p<0.001). Two studies in pesticide manufacturing workers reported significantly reduced FEV_1/FVC ratios among exposed groups compared to controls (205, 206) with no significant heterogeneity. (I^2=25.6%, p=0.25) (figure 2-2) I do not report summary statistics for the groups with high levels of heterogeneity.

Two studies were not included in the meta-analysis, one because it presented the outcome as excess changes (percent per year), (201) the other because it presented non-parametric statistics. (207) ; the latter reported no significant relationship with FEV_1/FVC. (207) Two cohort studies in the Netherlands studied general populations. The Vlagtwedde-Vlaardingen Study reported that pesticide exposure was associated with an accelerated decline in the FEV_1/FVC ratio of -0.09 mL/year (95%CI -0.15, -0.03), (201) but this finding was not replicated in the LifeLines cohort, which was included in the meta-analysis, where high exposure to pesticides was not significantly related to FEV_1/FVC ratio. (208)

a) Paraquat and ChE-inhibiting pesticides



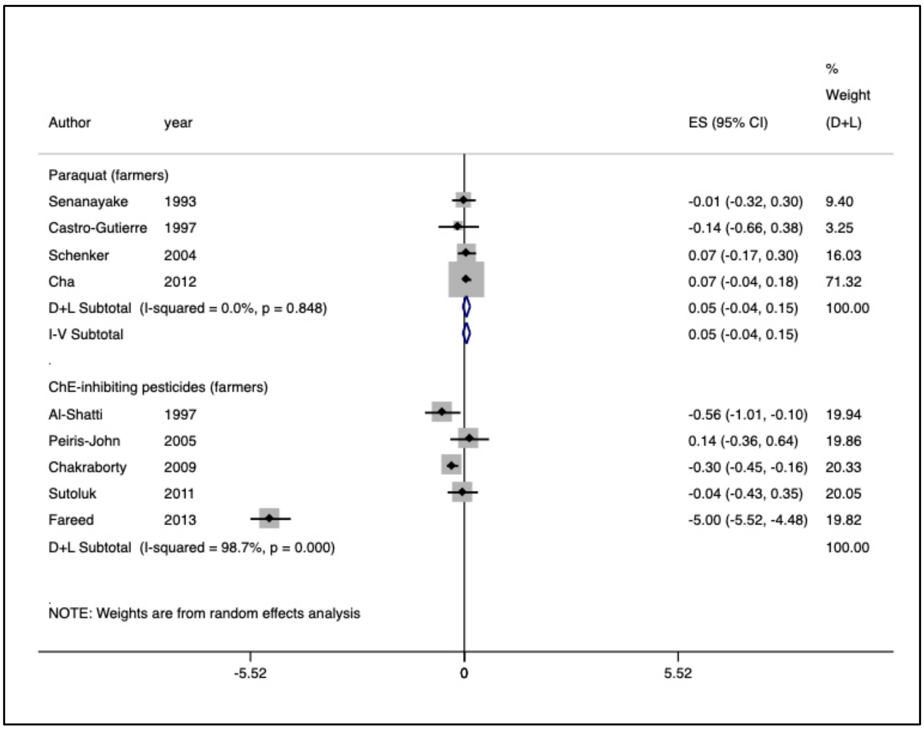
b) Unspecified pesticides



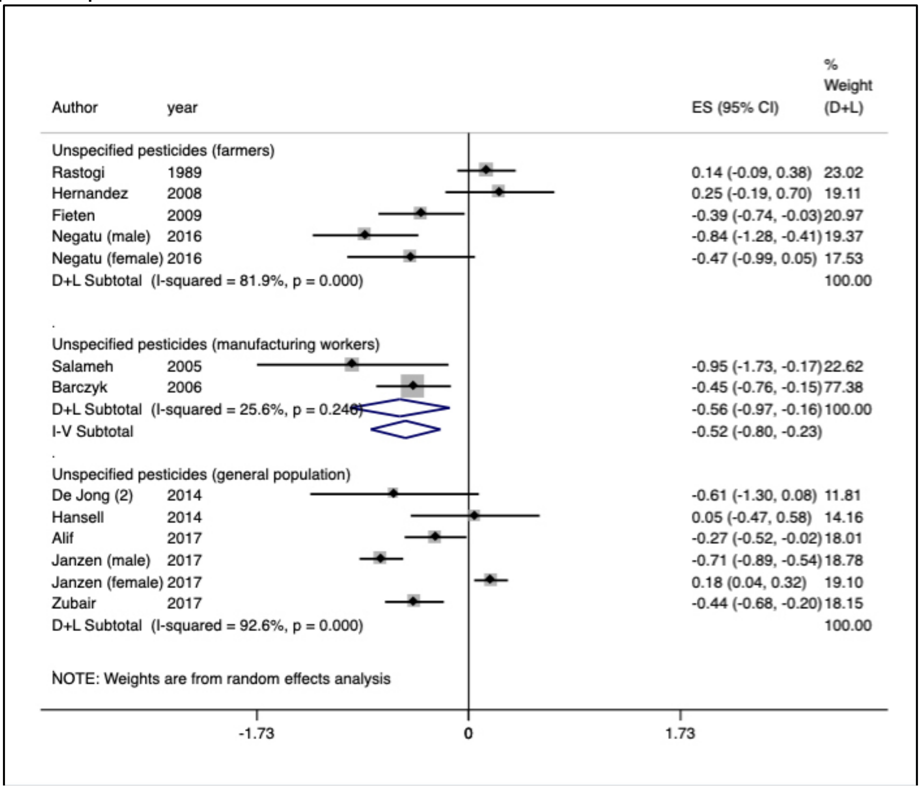
ES: standardised mean differences (SMD); D+L: random effects model; I-V: fixed effects model

Figure 2-2 Forest plot for FEV_1/FVC outcome (excluding Fareed *et al.*)

a) Paraquat and ChE-inhibiting pesticides



b) Unspecified pesticides



ES: standardised mean differences (SMD); D+L: random effects model; I-V: fixed effects model

Figure 2-3 Forest plot for FEV_1/FVC outcome (including Fareed *et al.*)

2.4.4 Association of pesticide exposures with FVC

Figure 2-4 illustrates the meta-analysis of associations of pesticide exposures with FVC. Twenty-two studies were included. Abu Sham'a *et al.* presented associations with exposure to both ChE-inhibiting pesticide (organophosphate) and other unspecified pesticide. (209) Fieten *et al.* showed results for all three main pesticide classes (paraquat, ChE-inhibiting (terbufos and chlorpyrifos) and other unspecified pesticides). (199)

Paraquat

All studies were conducted in farmers; five were included in the meta-analysis. (143, 175, 177, 186, 199) The forest plot demonstrates high heterogeneity in the group (I^2=59.7%, p=0.04). (figure 2-4) Only Cha *et al.* showed that paraquat exposure significantly worsened FVC. Howard *et al.*'s study was not included in the meta-analysis as standard errors were not reported; they found no significant difference in FVC in Malaysian paraquat sprayers. (210)

ChE-inhibiting pesticides

Nine of 12 studies presenting associations of ChE-inhibiting pesticide exposure with FVC including one in manufacturing workers were included in the meta-analysis. (141, 189-192, 199, 209, 211, 212) (figure 2-4) Two studies showed a significantly lower FVC in the exposed group and a further four showed an estimated reduction in lung function but there was high between-study heterogeneity (I^2=80%, p<0.001) and we are unable to provide an estimated effect overall. In excluded studies, Koilpakov *et al.* reported that 18.9% of a group exposed to ChE-inhibiting pesticide and 8.1% of an unexposed group had reductions in FVC ≤85% of predicted values. This is in agreement with the overall results of the meta-analysis, but as the paper did not provide numerators it could be not included in the meta-analysis. (213) Raanan *et al.* and Ye *et al.* were not included due to use of urinary biomarkers as continuous measures of exposure. In a general adult population, an increase in creatinine-corrected urinary concentration of DAP was significantly related to a lower FVC. (188) In a study of 7-year-old children Raanan *et al.* found a lower FVC with increase in DAP although the difference was not statistically significant. (187)

Other specific pesticides

Ye *et al.* reported a significant relationship between a unit increase in log transformed urinary concentrations of total pyrethroid metabolites and a 37.1 mL reduction in FVC in 12 to 19 years old after adjustment for age, sex, race, height and weight (p=0.05). (193) Kilburn *et al.* in their study of flight attendants showed no significant relationship between pyrethroid exposure and FVC. (194)

Suskind *et al.* showed significantly lower FVC in 2,4,5-T manufacturing workers (p=0.005). (195) Huang *et al.* showed no significant relationship between tetrachloroisophthalonitrile (TCPN) pesticide exposure and FVC in manufacturing workers. (174) Ye *et al.* measured plasma DDT and DDE in a general population and found significant relationships between both p,p'-DDT and p,p'-DDE concentrations and a lower mean FVC (-311 mL, p=0.003 and -18.8 mL, p=0.002, respectively). (196) Raanan *et al.'s* study of children found a decrease in

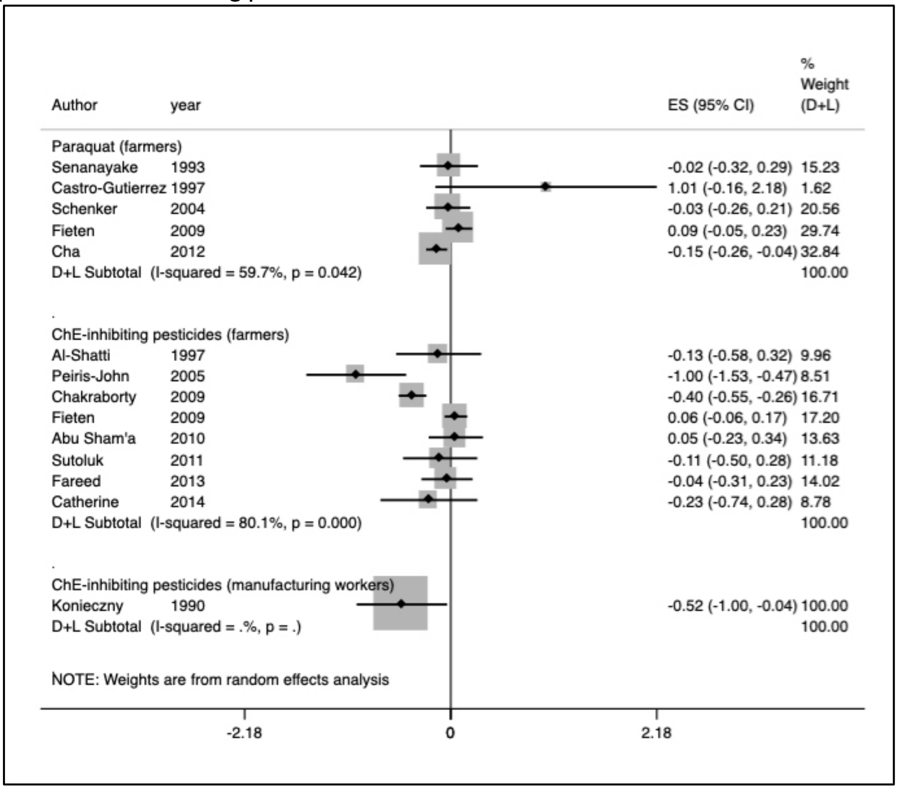
FVC (β=-0.127, 95%CI=-0.230, -0.024, p=0.003) in those living close to areas where sulphur pesticide sprays had been used. (197)

Unspecified Pesticides

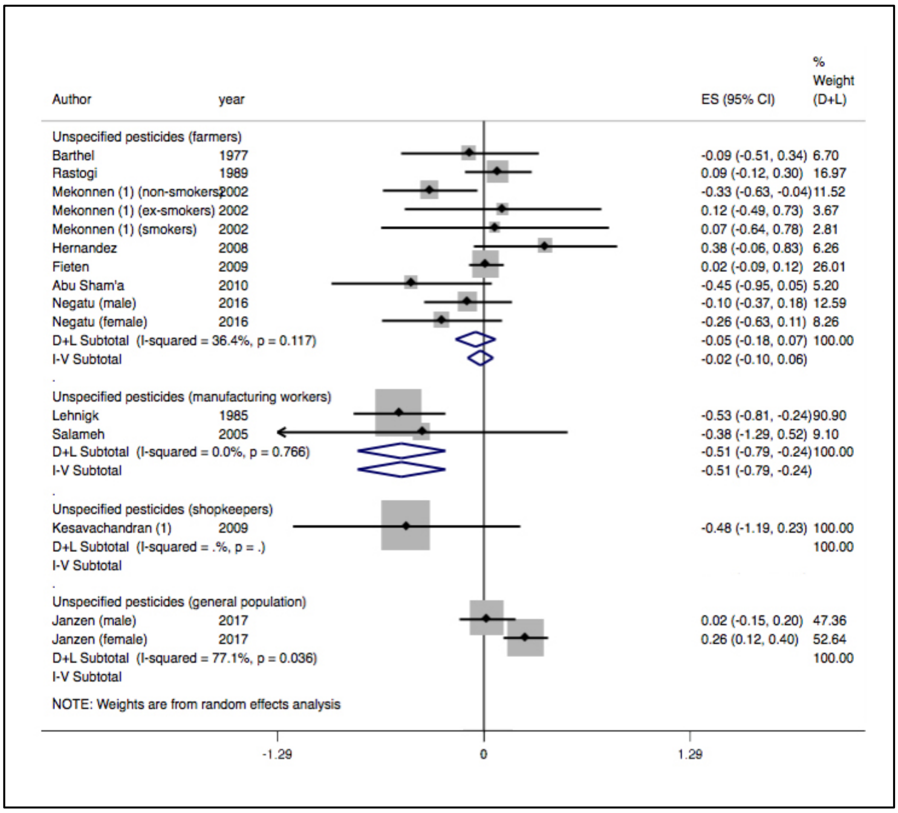
Eleven of 15 studies of the relationship between FVC and exposure to unspecified pesticide were included in a meta-analysis. I selected only one of the two papers by Mekonnen *et al*. reporting research in the same area and period of time. (176, 214) The one published in 2002 (214) was selected because it provided more detail on job titles (sprayers; supervisors; technicians and assessors) and I chose a group of sprayers as the exposed group. In the meta-analysis, six studies in farmers showed no overall effect on FVC with only moderate heterogeneity between studies which was not significant (I^2=36.4%, p=0.12). (173, 198-200, 209, 214, 215) Two studies in pesticide manufacturing workers showed a decrease in FVC compared to the controls with no evidence of between study heterogeneity (I^2=0%, p=0.77). (205, 216) Kesavachandran *et al.* reported no change of FVC in Indian pesticide shopkeepers. (217) Janzen *et al*. showed an increase of FVC in a female general population in Canada exposed to unspecified pesticides. (203) (figure 2-4)

Of the papers not included in the meta-analysis, Jones *et al*. analysed data using non-parametric statistics and showed a significantly higher FVC in crop sprayers using unspecified pesticides. (207) Zuskin *et al*. reported a significant reduction in FVC among the pesticide exposed group in both males and females, however, they performed lung function tests only in the study group and compared these with the results from a different study. (166) Thiele *et al.* presented percent of predicted FVC but no estimate of the variability of mean values and found no significant difference in FVC between a group exposed to unspecified pesticides and controls. (218)

a) Paraquat and ChE-inhibiting pesticides



b) Unspecified pesticides



ES: standardised mean differences (SMD); D+L: random effects model; I-V: fixed effects model

Figure 2-4 Forest plot for FVC outcome

2.4.5 Association of pesticide exposures with FEV_1

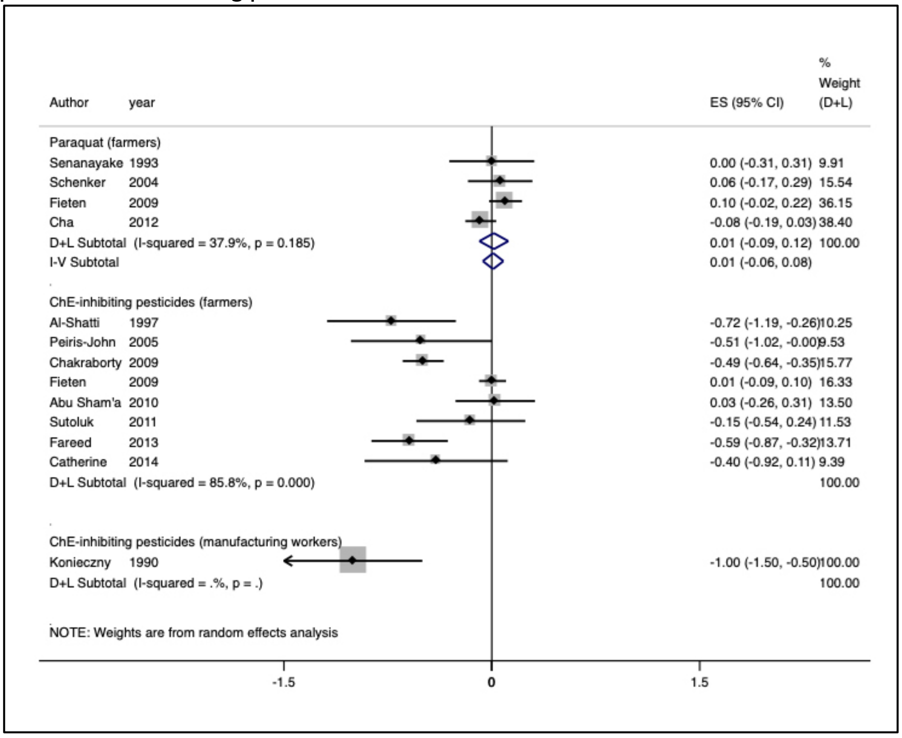
The results for FEV_1 are very similar to those for FVC, which might be expected in two measures that are highly correlated, although the meta-analysis of FEV_1 with paraquat exposure indicated only moderate between-study heterogeneity which was not significant (I^2=37.9%, p=0.19). In the studies of unspecified pesticide included in the meta-analysis, the studies in farmers showed high heterogeneity (I^2=68.2%, p=0.001). (figure 2-5)

2.4.6 Association of pesticide exposures with PEF and other FEF

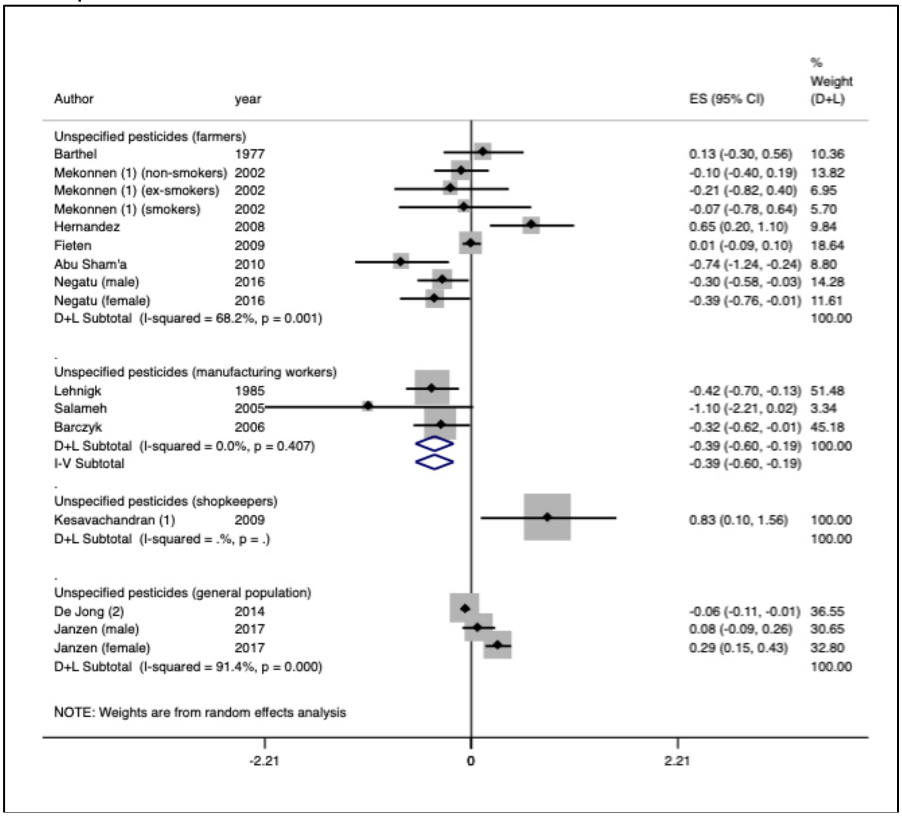
Senanayake *et al.* examined the effect of paraquat on PEF and showed no effect. (177) Four studies of the effects of ChE-inhibiting pesticides on PEF in farmers showed very high variability in effects between studies (I^2=98%, p<0.001). (141, 189, 192, 209) Seven other studies examined the effect of unspecified pesticides on PEF; one study showed a decrease in PEF in shopkeepers exposed to pesticides compared to controls (217) while six other studies in farmers showed either no or negative effects on PEF with high levels of heterogeneity between studies (I^2=53.7%, p=0.03). (209, 214, 219-222) The other study showed no significant effect of unspecified pesticides on PEF in farmers. (223)

Two studies reported no effect of paraquat on FEF25%-75%. (175, 177) Similarly, four of six studies of ChE-inhibiting pesticides reported no differences in FEF25%-75% (141, 187, 188, 209), whereas, two showed a significant decrease (191, 192). Three studies of unspecified pesticides reported significant associations with reduced FEF25%-75% (173, 200, 209) while two others revealed no effect. (205, 207) Other studies of specified pesticides including pyrethroid (194), 2,4,5-T (195) and DDT/DDE (196) showed no significant relationship to FEF25%-75%. In other FEF outcomes such as FEF25% (166, 211), FEF50% (166, 207, 211), FEF75%-85% (194) and maximum mid-expiratory flow (MMF) (174), I could not conclude much due to the small number of studies included and variation in study designs.

a) Paraquat and ChE-inhibiting pesticides



b) Unspecified pesticides



ES: standardised mean differences (SMD); D+L: random effects model; I-V: fixed effects model

Figure 2-5 Forest plot for FEV_1 outcome

2.4.7 Association of long-term pesticide exposures with other lung function measures

In farmers spraying paraquat, Dalvie *et al.* reported a significant relationship between long-term exposure and arterial oxygen desaturation ($\beta=0.194$, SE=0.008, $p=0.019$) despite there being no differences in spirometry. (224) Three studies found no association of paraquat exposure with the transfer factor for carbon monoxide (TLCO). (175, 177, 210) Examining unspecified pesticide exposure in farmers, Hernandez *et al.* showed no significant association with TLCO. (173) Barthel *et al.* showed no significant association with residual volume or total lung capacity. (215)

Kossmann *et al.* showed significant relationships between exposure to unspecified pesticides and both maximal inspiratory pressures (MIP) and maximal expiratory pressures (MEP) in both male and female production workers. (225) In other production workers, Lehnigk *et al.* showed a significant relationship between unspecified pesticide exposure and a decline in partial pressure of oxygen (P_aO_2) but not that of carbon dioxide (P_aCO_2). (216)

2.4.8 Association of short-term pesticide exposures with lung function

Eight studies were of short-term pesticide exposures; five reported differences between pre- and post-exposure lung function while three reported seasonal changes. Of three studies of unspecified pesticide exposures in farmers, two showed a reduced FEV_1 during the spraying period. (226, 227) Jones *et al.* however reported an improvement in FEV_1 and PEF and a decline in the mean daily variation in peak expiratory flow. (207) Two studies of ChE-inhibiting pesticides reported no change in lung function during exposure to chlorpyrofos (212) or fenthion. (228) Salome *et al.* showed a significant fall in FEV_1 when exposing patients with asthma to alletrin ($p=0.04$), but not pyrethrin ($p=0.08$). (229) Satpathy *et al.* showed no evidence of either obstructive or restrictive patterns of respiratory impairment in five mosquito net impregnators using cyfluthrin. (230) Pearce *et al.* found no significant changes between pre- and post-exposure PEF in children during spraying with *B.thuringiensis*. (231)

2.4.9 Reporting Bias

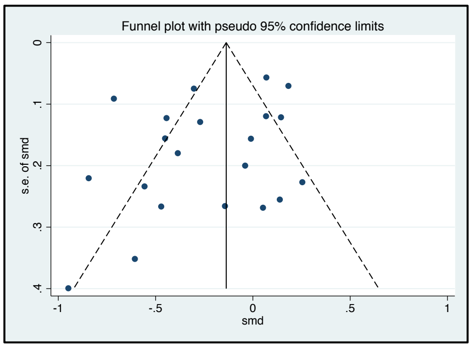
I also presented reporting quality and publication bias. Table 2-4 shows the modified NOS scores. As the studies included were not longitudinal, the length of follow-up was not included in the score from the modified NOS scale used by Saad *et al*. (183) Twenty eight of 56 studies reported the use of the American Thoracic Society and European Respiratory Society (ATS/ERS) acceptability and reproducibility criteria for their spirometric measurement. More recent publications tended to have higher modified NOS scores. There was no obvious pattern of modified NOS scores by countries, regions and national incomes. There was no evidence of publication bias, conclusions confirmed by Egger's test. (figure 2-6)

Table 2-4 Modified Newcastle-Ottawa Scale assessment

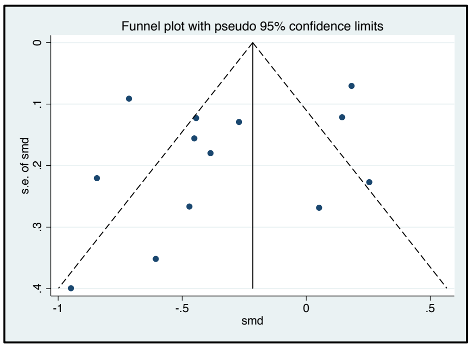
Author*	Selection			Compatibility		Outcome/Exposure		Modified NOS Score
	(1)	(2)	(3)	(1a)	(1b)	(1)	(3)	
English (50 articles)								
Taylor, 1963 (228)	1	0	0	0	0	0	0	1
Werner, 1969 (232)	1	1	1	0	0	0	0	3
Howard, 1981 (210)	1	1	1	1	1	0	0	5
Lings, 1982 (223)	1	1	0	0	0	0	0	2
Suskind, 1984 (195)	1	1	1	0	0	0	0	3
Rastogi, 1989 (198)	1	1	0	0	0	1	0	3
Senanayake, 1993 (177)	1	1	1	1	0	0	0	4
Huang, 1995 (174)	1	1	1	0	0	0	0	3
Al-Shatti, 1997 (190)	0	1	1	0	0	0	0	2
Castro-Gutierrez, 1997 (186)	1	1	1	0	1	1	0	5
Kossmann, 1997 (233)	1	1	0	0	0	0	0	2
Satpathy, 1997 (230)	1	1	0	0	0	0	0	2
Dalvie, 1999 (224)	1	1	1	1	1	1	1	7
Salome, 2000 (229)	1	1	1	0	0	1	0	4
Mekonnen (1), 2002 (214)	1	1	1	0	0	1	0	4
Pearce, 2002 (231)	1	1	1	0	0	1	1	5
Jones, 2003 (207)	1	1	1	0	0	1	0	4
Kilburn, 2004 (194)	1	0	1	1	1	0	0	4
Mekonnen (2), 2004 (176)	1	1	1	0	1	1	0	5
Schenker, 2004 (175)	1	1	1	0	1	1	0	5
Peiris-John, 2005 (191)	1	1	0	0	0	0	0	2
Salameh, 2005 (205)	1	1	1	1	1	1	0	6
Kesavachandran (2), 2006 (219)	1	1	0	0	0	0	0	2
Hernandez, 2008 (173)	1	1	1	1	0	1	0	5
Zuskin, 2008 (166)	1	1	1	0	1	0	0	4
Chakraborty, 2009 (141)	1	1	1	0	0	1	0	4
Fieten, 2009 (199)	1	0	1	0	0	0	0	2
Kesavachandran (1), 2009 (217)	1	1	1	1	0	0	0	4
Abu Sham'a, 2010 (209)	1	1	1	0	0	1	0	4
Sutoluk, 2011 (192)	1	1	1	0	0	1	0	4
Cha, 2012 (143)	1	1	1	1	1	1	0	6
Fareed, 2013 (189)	1	1	1	0	0	1	0	4
Pathak, 2013 (226)	1	1	1	0	0	1	0	4
Catherine, 2014 (212)	1	1	1	0	0	1	0	4
De Jong (1), 2014 (201)	1	1	1	0	0	1	0	4
De Jong (2), 2014 (208)	1	1	1	0	0	1	1	5
Desalu, 2014 (220)	1	1	1	0	0	0	0	3
Hansell, 2014 (67)	1	1	1	0	1	1	0	5
Abu Sham'a, 2015 (227)	1	1	1	0	0	1	0	4
Mathew, 2015 (221)	1	1	1	0	0	0	0	3
Ye (1), 2015 (196)	1	1	1	1	1	1	0	6
Garcia-Garcia, 2016 (222)	1	1	1	0	0	0	0	3
Negatu, 2016 (200)	1	1	1	0	0	1	0	4
Raanan (1), 2016 (187)	1	1	1	1	1	0	0	5
Ye (2), 2016 (193)	1	1	1	1	1	1	0	6
Ye (3), 2016 (188)	1	1	1	1	1	1	0	6
Alif, 2017 (202)	1	1	1	0	1	1	0	5
Janzen, 2017 (203)	1	1	0	1	1	0	0	4
Raanan (2), 2017 (197)	1	1	1	1	1	0	0	5
Zubair, 2017 (204)	1	0	1	0	0	1	0	3
Non-English (6 articles)								
Thiele, 1973, in German (218)	1	0	0	0	0	0	0	1
Barthel, 1977, in German (215)	1	0	0	0	0	0	0	1
Lehnigk, 1985, in German (216)	1	1	0	0	0	0	0	2
Koilpakov, 1987, in Russian (213)	1	0	0	0	0	0	0	1
Konieczny, 1990, in Polish (211)	1	0	1	0	0	0	0	2
Barczyk, 2006, in Polish (206)	1	1	1	0	0	0	0	3

*arranged by publication year

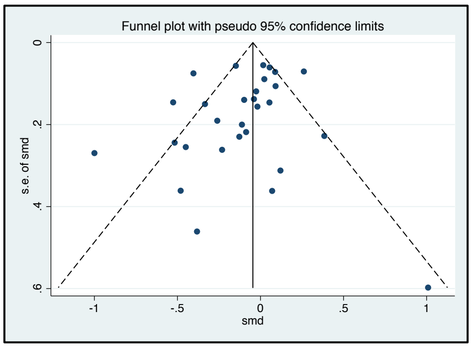
(1a) All included papers with FEV_1/FVC, p=0.162



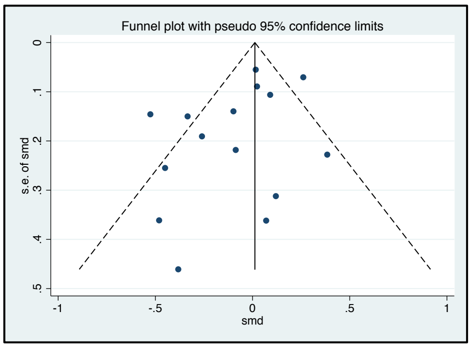
(1b) Only unspecified pesticides with FEV_1/FVC, p=0.278



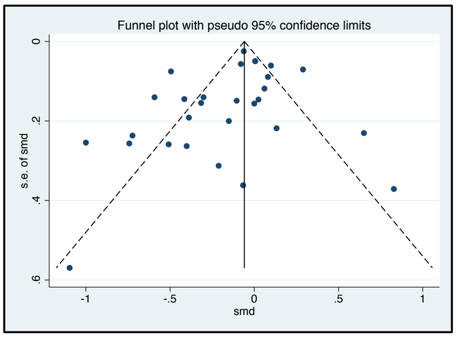
(2a) All included papers with FVC, p=0.195



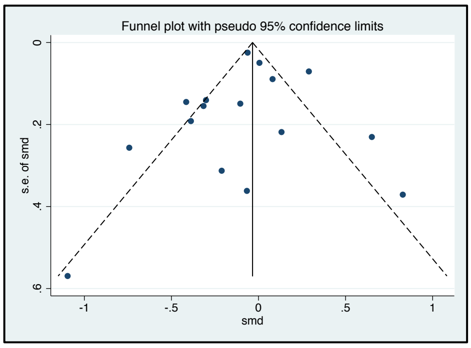
(2b) Only unspecified pesticides with FVC, p=0.104



(3a) All included papers with FEV_1, p=0.126



(3b) Only unspecified pesticides with FEV_1, p=0.719



p-values are derived from Egger's test.

Figure 2-6 Funnel plots

2.5 Discussion

This systematic review shows wide variation in the relationships between pesticide exposures and lung function. Overall, I found that paraquat has no effect on lung function but ChE-inhibiting pesticides were associated with a reduction in FEV_1/FVC ratio.

Paraquat exposure had no significant association with FEV_1/FVC with little heterogeneity and a very narrow confidence interval. This may be explained by the fact that paraquat has a low volatility; although it has high toxicity to lungs, the routes of paraquat exposure which injure lung tissues are mainly via oral ingestion, minimally via dermal absorption but not by inhalation. (163)

The meta-analysis showed a negative association between exposure to ChE-inhibiting pesticides and FEV_1/FVC; this was not statistically significant using a random effects model (SMD=-0.22, 95%CI=-0.46, 0.01, I^2=46%, p=0.134). The protocol stated that I would explore a fixed effects model if the I^2 statistic was less than 50% which has been suggested as a level of acceptable heterogeneity (185), and the effect was significant using a fixed effects model (SMD=-0.27, 95% CI -0.39, -0.14). (figure 2-2) One study, of short-term exposures to a ChE-inhibiting pesticide (chlorpyrifos), reported no association with either FEV_1 or EVC. (212) ChE-inhibiting pesticides such as organophosphate have cholinergic effects when ingested resulting in increased bronchial secretion and bronchoconstriction, (234, 235) suggesting that they might also have effects via inhalation. However, I suggest that the findings are interpreted with caution because of the heterogeneity arising from different study designs and populations.

In my review, exposure to ChE-inhibiting pesticides, particularly organophosphate was associated with significant reductions in FEV_1 and FVC. However, in each case there was a high degree of variability between studies, making the pooled value difficult to interpret. (figures 2-4 and 2-5) The possible causes of heterogeneity are variabilities of types of ChE-inhibiting pesticide exposures, durations of exposure and length of time since the last exposure. This suggests that more specific and better standardized exposure metrics ought to be collected in future.

In studies of lung function and exposure to unspecified pesticides (shown in figures 2-2, 2-4 and 2-5) most of my analyses of outcomes also showed excessive heterogeneity except only three studies in manufacturing workers which showed negative effects on lung function. (205, 206, 216) The most likely explanation is that there are significant differences in populations in each study design, but other possible reasons include the different types of pesticides of study and duration and intensity of pesticide exposure.

This is the first systematic review with meta-analysis of the effects of pesticides on lung function. The search terms are given in table 2-1 and the extraction form in appendix A-3. I used a standard method to evaluate the quality of publications (182, 183) (table 2-4), and I have been able to provide quantitative estimates of the effects of different classes of pesticides.

This review examines magnitudes and directions of relationships by the standardised mean difference (SMD) which can combine effect estimates from different studies, but does not give absolute estimates of effect size. However assuming, for instance, the standard deviation in the FEV_1/FVC expressed as a percentage to be 15%, the effects in figure 2 would represent for paraquat a difference of 0.75% (95%CI -0.60%, 2.25%) and for ChE-inhibiting pesticides -4.1% (95%CI -5.9%, -2.1%). This compares with a difference of -0.65 in ex-smokers and -3.82 in smokers compared with non-smoking men with mild symptoms in one study. (236)

Since FEV_1 does not add further information to the FEV_1/FVC ratio and FVC alone, and is difficult to interpret when unadjusted for a measure of lung size such as FVC, I did not comment further on FEV_1 in the meta-analysis. Moreover, I focused on FVC instead of FEV_1 as previous large studies (i.e., the Framingham Study (237), the Cardiovascular Health Study (238) and the Atherosclerosis Risk in Communities (ARIC) study (239)) reported clear associations between FVC and other health outcomes.

I acknowledge a number of limitations. The studies included are heterogeneous in terms of study designs, pesticide exposure metrics, lung function outcome measures and sampled populations. Most of the findings were from cross-sectional studies (appendix A-2), these give only weak evidence for causal relationships and selective survival or recruitment into an exposed force or a healthy worker effect could explain some lack of association between exposure and effect. (240) Regarding pesticide exposure metrics, twenty-five of the 56 articles included job titles, 17 used self-reported exposure and only four articles inferred exposure to pesticides from a job exposure matrix (JEM). (appendix A-2) Most long-term studies did not show specific ranges of exposure durations and failed to report routes of exposure. Only a few studies presented dose-effect relationships. Inconsistencies in the measurement of exposure and lung function outcomes makes summarising results across studies difficult. Just half of the reviewed studies mentioned the use of the ATS/ERS acceptability and reproducibility criteria for spirometric measurement. Moreover, the modified NOS score (table 2-4) reveals a number of studies with poor scores that reflect on their low reporting quality. These deficits might cause heterogeneity across studies and affect the accuracy of the individual and pooled associations between pesticide exposures and spirometric outcomes.

The study populations included in this review were also variable, including farmers, pesticide manufacturers, shopkeepers, flight attendants and general populations of both children and adults. The majority of studies reported associations without adjustments for potential confounders such as smoking, height and age. The percentage of males recruited to the different studies varied from 0% to 100% but most of the studies did not adjust for gender. As Negatu *et al*. and Janzen *et al*. stratified men and women in their analyses (figures 2-2, 2-4 and 2-5) and showed that associations appeared to differ by sex, (200, 203) this is a potentially important weakness in the current literature. When I considered only the studies that controlled for the main confounding factors, there were too few to perform meta-analyses (only seven for FEV_1/FVC, seven for FVC and nine for FEV_1). (appendix A-2)

In 2019, Pourhassan *et al*. published a similar systematic review of the relationships between pesticide exposure and chronic obstructive pulmonary disease (COPD) and chronic bronchitis. (241) The review included studies published before 13 June 2018, while my review was of articles published up to 1 October 2017. Eight studies were included in the Pourhassan *et al.* meta-analysis with a significant association between unspecified pesticide exposure and

COPD (OR=1.33, 95%CI 1.21 to 1.47; I^2=68.7%). Of these eight studies, only three (202, 208, 242) used lung function parameters; the other five studies (243-247) had no lung function reported. Just one (242), a European Community Respiratory Health Survey (ECRHS) population-based cohort study, was not included in my systematic review due to it being published in 2018. This additional article reported a significant association of unspecified pesticide exposure with a higher incidence of COPD (FEV_1/FVC<LLN); RR=2.2, 95%CI 1.1 to 3.8. (242)

There are several reasons why my systematic review included a larger number (fifty-six) of studies. First, I used search terms and controlled vocabularies that covered a wide range of 'lung function' outcomes (table 2-1), while the Pourhassan *et al.* used rough search terms covering only the domains of 'airflow obstruction', 'COPD' and 'chronic bronchitis'. Second, I did not limit the languages used in the literature search while the other included only English-language publications. Furthermore, Pourhassan *et al*. searched on only MEDLINE and Scopus databases, while I included all available studies in more electronic databases including MEDLINE, EMBASE (including all Scopus content with extensive biomedical, drug and chemical research (248)) and Web of Science.

2.6 Conclusion

The majority of the papers included in this review were studies among farmers. My study may partly explain previous reports of the relationship between agricultural exposure and respiratory disease. (116, 125, 134) Although there was a significant reduction in FEV_1/FVC among those exposed to ChE-inhibiting pesticides, there was a high degree of variability between studies which limits interpretation in terms of causal association. Evidence on exposure to unspecified pesticides also showed high heterogeneity. The findings of this systematic review suggest that further and better standardised evidence is required. I also suggest further studies with better and more comprehensive adjustments for potential confounders and co-exposures, particularly the effects of other occupational factors in each working environment. (122) Meanwhile respiratory surveillance should be enhanced in farmers exposed to ChE-inhibiting pesticides and in those manufacturing pesticides.

CHAPTER 3

Farming and respiratory health: a cross-sectional study in Nan province, Thailand

CHAPTER 3 Farming and respiratory health: a cross-sectional study in Nan province, Thailand

3.1 Introduction

Farming exposures have the potential to increase the risk of several respiratory illnesses including rhinitis, asthma, hypersensitivity pneumonitis, pneumoconiosis and respiratory infection. (104, 122) Whether farming has a role in chronic obstructive pulmonary disease (COPD) remains unclear. (125, 134, 135) Farming is a common occupation in developing countries and any adverse effects are likely to have a high impact on public health and economic growth. (249) The techniques of agriculture in these countries are often substantially different from those in high-income countries, (112, 250) yet a recent meta-analysis on respiratory illnesses in farmers has shown a scarcity of studies from low- and middle-income countries, these representing only five of 22 studies (three in Macedonia, one in Nigeria and one in India). (135) Analysis of the Burden of Obstructive Lung Disease (BOLD) study in the Philippines showed that farming exposure was associated with COPD; the probable responsible exposures included dusts, both organic and inorganic, pesticides and other chemicals. (57)

Thailand is one of the largest rice exporters in the world. (113) Thirty percent (11.3 of 37.3 million) of its working population is in the agricultural sector (251), accounting for 11% of gross domestic product and 40% of land use. The poorer, lower 40% of the population, are more likely to work in agriculture. (110) There has been a substantial increase in agricultural pesticide use in Thailand overtime. (252) Yet, there is little published literature regarding the health, and particularly the respiratory health, of farm workers in Thailand. (168)

Nan province is one of the largest farming communities in northern Thailand; more than a half of the population works in the agricultural sector. (253) Previous statistics show that this province has one of the largest numbers of pesticide importers and users in Thailand. (254) In 2016, Nan province reported the highest number of chronic bronchitis, emphysema and COPD death and hospital admission rates in the country; COPD was the commonest recorded cause of death in adults in the provincial hospital. (255, 256) Based on these figures, Nan province seemed a suitable place to undertake a population-based cross-sectional study focusing on farming.

3.2 Aim and objectives

In this study, the main aim was to improve our knowledge on the relationship of chronic airflow obstruction and respiratory health problems with several exposures related to farming. In addition, I aimed to provide a reliable estimate of the prevalence of chronic lung disease in Nan, as representative of a low-income province in Thailand. Nan is the third poorest Northern province in Thailand with, in 2016, a Gross Provincial Product per person (GPP) of THB 68,285 (£1,296) compared with the national GPP per person of THB 215,455 (£4,089). (257, 258)

The specific objectives were:

1) to estimate the prevalence of chronic airflow obstruction in this community

2) to assess the association of spirometric measurements with exposure to occupational exposures, including farming and pesticide exposures and practices.

3.3 Methods

3.3.1 Study preparation and design

To undertake this study, I first prepared all the necessary documents, including the protocol, questionnaires, ethical approval application, participant information sheet and consent form. I was trained on how to collect data and how to use a portable handheld spirometer (ndd EasyOne) by two of my supervisors (Dr Amaral, Professor Burney) between 25 February and 1 March 2019, at the National Heart and Lung Institute (NHLI), Imperial College London.

Prior to the start of my PhD project in 2017, I contacted the head of the occupational health section of Nan provincial hospital, Ms Wilawan Mormoon, to discuss study arrangements. In April 2019, I discussed these further with local stakeholders consisting of the heads of local communities, local healthcare workers, healthcare volunteers, and villagers. These discussions included information on local health concerns, particularly related to respiratory symptoms and diseases in the local area. I also conversed with them about the study visit, recruitment and schedule.

I had the first meeting with the local team, including Nan provincial hospital executives, nurses, public health officers, and two research assistants on 22 April 2019. I organised a training workshop for my local research team, on 7 to 8 May 2019. This covered the protocol, data collection using PC tablets (Huawei MediaPad T3 7, Huawei Technologies, Shenzhen, China), blood pressure and anthropometric measurements. To guarantee a high standard of spirometry measurements, given my training in spirometry testing, I was the person who performed pre- and post-bronchodilator spirometry on all participants.

Prior to the fieldwork study, I took an online Introduction to Good Clinical Practice (GCP) course provided by the National Institute for Health Research (NIHR) and a General Data Protection Regulation (GDPR) course provided by Imperial College London. The research protocol was approved by the local Faculty of Medicine, Chulalongkorn University Institutional Review Board (Med Chula IRB no.766/61) in Thailand and by Imperial College Research Ethics Committee (ICREC reference: 19IC5098). All ethical approval letters are shown in appendices B-1 and B-2. The expenses of the study were met by departmental research funds.

Participants fulfilling the study criteria, including an age between 40 and 65 years, were contacted and sent an information sheet at least two weeks prior to the visit. Local public health volunteers helped me make their appointments in advance. At the fieldwork site:

1) on the day of survey, each participant was registered and voluntarily signed a consent form. Histories of drug allergy and contraindications for spirometry tests were recorded and evaluated according to the research protocol.

2) participants had their body measurements taken and lung function measured. All participants' responses to questionnaires were collected using electronic forms and Open Data Kit technology on PC tablets (https://opendatakit.org/). (259)

All participants were given an information sheet and a consent form. Participants were allowed to ask questions until they were satisfied. I respected the right of each participant to refuse to participate without giving reasons. Exemplars of the information sheet and the consent form can be seen in appendices B-3 and B-4. This study did not include vulnerable populations such as prisoners, pregnant women, cancer and terminally ill and mentally ill patients. Data and all appropriate documentation will be stored at least until 2029 (minimum of 10 years after the completion of the study).

I have not revealed any identifiable individual data. The names and addresses of participants have been kept separate from the research record in a different location (a locked filing cabinet at my office in Bangkok, Thailand). Only study number (ID number) is used to link questionnaire data with spirometry data in the database. Only pseudo-anonymised information has been stored at Imperial College London. Only co-investigators including my supervisors, the group's data managers and I can access the data sets collected.

3.3.2 Study area

Nan province has 15 districts (Amphoe) and a population of around 480,000 people (table 3-1), being composed of local northern Thai people, hill tribes and minorities such as the Hmong, Khamu, Mabri, and Mein people. (253) In the province, there is one tertiary care (provincial) hospital, 14 community (district) hospitals, and 126 primary care units (PCU), currently known as health promoting hospitals. Nan has an area of about 11,472 km^2 and is adjacent to the border with Laos PDR, and is 670 km from Bangkok, the capital city of Thailand. Its geography includes plains, highlands and mountains.

3.3.3 Sample size and sampling method

Tha Wang Pha district was selected purposely for a cross-sectional study site as, according to a recent census, 47% of its total population were farmers. (253) In addition, compared to other appropriate districts with a similar proportion of farmers (Na Noi and Thung Chang), Tha Wang Pha was the most convenient district to travel to the field site from Nan provincial hospital (a temporary research office). (table 3-1)

Tha Wang Pha has 10 subdistricts (Tambon) composed of 88 villages in total. According to the Thai Department of Provincial Administration there were 18,597 (9,128 men; 49.08%) villagers aged between 40 and 65 years old in the district in 2018. (table 3-2) (260)

Table 3-1 Nan province population statistics in 2017

District (Amphoe)	Subdistricts (Tambon)	Villages	Population	Males	% Male	Farming Population	% Farming Population*
1. Mueang Nan	16	78	82,213	41,226	50.15	23,069	28.06
2. Mae Charim	6	102	16,272	8,335	51.22	9,505	58.41
3. Ban Luang	4	54	11,747	5,945	50.61	9,020	76.79
4. Na Noi	10	125	32,891	16,446	50.00	15,548	47.27
5. Pua	7	83	64,679	32,186	49.76	21,756	33.64
6. Tha Wang Pha	3	233	50,924	25,438	49.95	24,174	47.47
7. Wiang Sa	14	112	70,855	35,533	50.15	29,815	42.08
8. Thung Chang	13	120	18,861	9,542	50.59	10,138	53.75
9. Chiang Klang	11	93	27,655	13,782	49.84	12,379	44.76
10. Na Muen	5	45	14,549	7,413	50.79	9,487	65.21
11. Santi Suk	8	119	15,793	8,069	51.09	11,601	73.46
12. Bo Kluea	4	44	15,111	7,732	51.17	13,112	86.77
13. Song Khwae	7	93	12,281	6,379	51.94	8,394	68.35
14. Phu Phiang	11	109	36,154	18,092	50.04	14,925	41.28
15. Chaloem Phra Kiat	11	120	9,853	5,031	51.06	7,837	79.54
Total	130	1,530	479,838	241,149	50.26	220,760	46.01

*percent of all adults

Table 3-2 Population in Tha Wang Pha, Nan province aged between 40 and 65 in 2018

Age	Male	Female	Total	Age	Male	Female	Total
40	299	295	594	41	329	339	668
42	304	307	611	43	349	331	680
44	299	351	650	45	288	339	627
46	271	334	605	47	317	307	624
48	362	355	717	49	339	385	724
50	389	417	806	51	423	409	832
52	439	480	919	53	460	500	960
54	416	377	793	55	467	417	884
56	430	382	812	57	353	393	746
58	375	404	779	59	338	357	695
60	345	361	706	61	346	355	701
62	314	343	657	63	341	339	680
64	272	301	573	65	263	291	554

a)* Nan province, Thailand

b) Tha Wang Pha district, Nan province

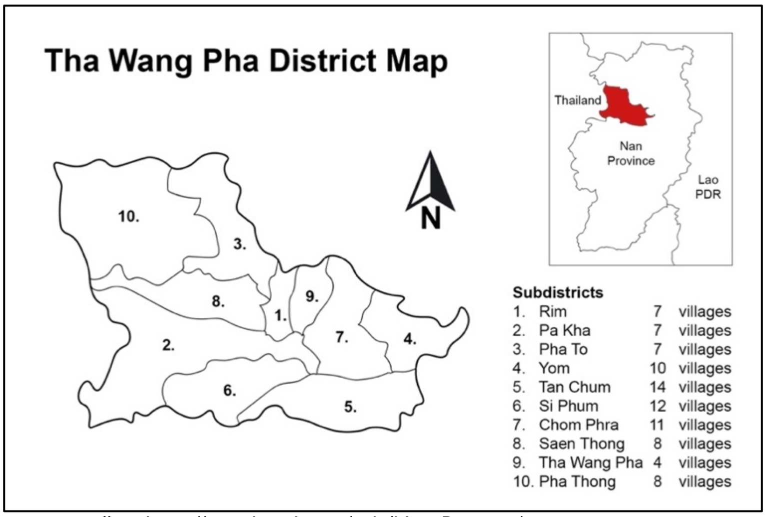


*Figure a) was adapted from "Thailand Nan locator map.svg" on https://en.wikipedia.org/wiki/Nan_Province/.

Figure 3-1 Tha Wang Pha district and Nan province, Thailand maps

Cochran's sample size formula was used to calculate the minimum sample size. (261) Pothirat *et al.* previously surveyed a comparative COPD study in adult populations in Chiangmai, a province in the Northern region in Thailand and found that 34% of rural villagers aged over 40 were farmers. (262) At the 95% confidence interval (CI), standard normal deviation number (Z-score) with a desired precision level of 5%, the calculated minimum sample size was 345.

$$\text{Sample size } (n_0) = \frac{Z^2pq}{e^2} = \frac{(1.96)^2(0.34)(0.66)}{(0.05)^2} = 344.8$$

Z^2 = the abscissa of the normal curve that cuts off an area α at the tails using at 95% confidence interval

p = the estimated proportion of an attribute in the population (farming population)

q = $1-p$

e = the level of precision

Using a cluster random sampling method, all villagers in villages number 3, 11 and 13 of the Tan Chum subdistricts aged 40 to 65 were selected. I obtained relevant health data and statistics from the local health authorities. The use of health data was approved by Dr Pongthep Wongwatcharapaiboon, the acting director of Nan provincial hospital and Ms Sriwan Nosri, the chief of Tan Chum primary care unit. All study visits took place in village/community halls in Tan Chum subdistrict, Nan province. Within the three villages, 345 local villagers aged 40 to 65 were resident according to the Tan Chum primary care unit records. Between 22 April and 15 May 2019, all eligible villagers and government employees were informed of the fieldwork study by local public health officers and volunteers.

Having surveyed the first two villages (3 and 11, Tan Chum subdistrict), I made a preliminary check of the data collected and found that the large majority of villagers (185 of 218 who participated in the study; 84.9%) reported 'farming' as their longest held jobs. To increase exposure contrast (i.e. to avoid having only farmers) for the association analysis, I additionally recruited all (n=82) local government employees (including school teachers, municipality officers, police officers, nurses, public health officers and Buddhist monks) aged 40 to 65 who worked full-time in the same subdistrict and did not have their name registered as local farming villagers. Therefore, a total 427 participants were invited to participate in the study.

3.3.4 Study questionnaires

I used four questionnaires from the BOLD study due to their suitability to my study aim and objectives, to collect information on several subjects' characteristics.

1) Spirometry questionnaire: to assess whether the subject had any contraindications to perform spirometry, and to record body measurements including weight and height (appendix B-5)
2) Core questionnaire: to obtain a range of information, including general demographics, socioeconomic status (household asset score; education level) respiratory symptoms, diagnoses and medication, tobacco smoking (appendix B-6)
3) Occupational questionnaire: to obtain information about the longest held occupation and high-risk jobs (other than farming) to respiratory health. Part of this occupational questionnaire is an adaptation of the Occupational Self-Coding and Automatic Recording (OSCAR) tool. (263) (appendix B-7)
4) Environmental questionnaire: to obtain information mainly about biomass fuel use for cooking, lighting and heating (appendix B-8)

To assess farming and pesticide activities, practice and exposure I reviewed existing questionnaires, which have been used in this setting to evaluate both exposures and outcomes (see below). Guided by these, I developed a new questionnaire to assess exposure(s) to potentially harmful substances in a manner appropriate to low- and middle-income countries such as Thailand. In addition, common pesticide use in the local area was reviewed and incorporated into the questionnaire. (252)

All questionnaires were translated into the Thai language using standard methods for forward and backward translation. Later, I transferred the questionnaires in both English and Thai to Open Data Kit (ODK) electronic forms. (259)

Before using the questionnaires on study participants, I conducted a 'dummy' run, on 15 to 16 May 2019, with 19 people from village number 14 of Tan Chum subdistrict, Tha Wang Pha district, Nan province. These people had similar characteristics to participants in the planned cross-sectional study. Following this small pilot, I amended some details of the questionnaires and improved the methods of approaching the participants.

3.3.5 Agricultural questionnaire development

Before developing a new instrument, I reviewed previous survey instruments. AGRICOH, a consortium of agricultural cohort studies, includes various agricultural health surveys examining a wide array of pesticide exposures and health outcomes including cancer, neurological, immunological and respiratory effects. (142) Brouwer *et al.* also gave examples of the assessment of exposure to pesticides and summarised agricultural study techniques with a focus on lymph-haematological malignancy outcomes in the US Agricultural Health Study (AHS), the French Agriculture and Cancer Study (AGRICAN) and the Cancer in the Norwegian Agricultural Population (CNAP) study. The authors emphasise the importance of a precise estimation of pesticide exposure. (264) In the United Kingdom, the Health and Safety Executive (HSE) established the Prospective Investigation of Pesticide Applicators' Health (PIPAH) study in 2013 with the aim of studying the long-term health effects of pesticide users in that country; the project has developed questionnaires and validated these in 2016. (265)

According to previous reviews by a group of American Thoracic Society researchers and Kirkhorn *et al.*, farming exposures affecting respiratory health can be classified as organic dusts (such as animal confinement operations, working in silos), inorganic dusts (such as tilling and ploughing), gases (such as applying fertilizer in the field) and chemicals (such as applying pesticides, working in the storage containers). (104, 116) Farming activities can lead to exposure to silica in soils which may affect the lung. (266) In the AHS cohort study, use of diesel farm machinery was associated with an increased risk of lung cancer. (267) The AHS and PIPAH questionnaires were thoroughly studied and adapted to low- and middle-income country settings. Agricultural variables cover contexts in northern Thailand such as crop types and domestic livestock (268) and agricultural behaviours. (111, 269)

The newly developed questionnaire components are composed of 1) farming environment and activities; 2) crops grown and animals raised; 3) pesticide use and use of personal protection equipment (PPE); and 4) crop burning and exposure to diesel. Full details of the agricultural questionnaire can be seen in appendix B-10.

Farming environment and activities

The first part of the questionnaire enquires about agricultural background, including the duration of living on a farm, the participant's own farm size, participant's characteristics and related farming activities. (table 3-3)

Agricultural crops and animals

I grouped types of agricultural products including crops and animals according to the Indicative Crop Classification Version 1.0 (ICC) of the Food and Agriculture Organization of the United Nations (FAO). (270) Crop statistics in Nan province, Thailand 2014/15 collected by Nan Provincial Agricultural Extension Office were used for the lists of crops grown in the questionnaire. (271) (table 3-4)

Pesticide use, exposure and personal protection equipment

Pesticides are mainly classified into herbicides, insecticides and fungicides. All pesticide types available in the questionnaire can be seen in tables 3-7 to 3-9. During fieldwork, I showed the photographs with tradenames of all available pesticide packages, taken from all three local stores in the subdistrict (figure 3-2), to each participant to help them identify those they were using/had ever used (see below). Pesticide risk behaviours are also included in the questionnaire. Table 3-5 shows groups of variables in the pesticide use and exposure section. Questions on personal protection equipment (PPE) use were also asked.

Farming environment and other variables

I included questions on the use of farm machines as classified by the Thai Office of Industrial Economics (OIE) report in 2011. (272) I also added a question on the type of fuel used in each machine. Burning forest or crops for converting to farmland is asked in detail in the questionnaire. (table 3-6)

a) A pesticide store in Nan province, Thailand

b) Pesticide marketplace survey

Figure 3-2 Pesticides survey in Tha Wang Pha district, Nan province

Table 3-3 Overview of general agricultural background variables in the questionnaire

Group	Variable	Details
Living on a farm	Living duration	Years of living on a farm
	Farm size; • Rai (0.16 hectares, 0.3954 acres); • Ngan (a quarter of rai); • Squared Wa; Wa^2 (0.0004 hectares, 0.0009884 acres)	Local units used in the area (in Thailand)
Farming activities	Ploughing the soil (for planting)	Duration and frequency
	Fertiliser use	Natural and chemical fertilisers
	Working in a barn/silo storing grain or fodder	Duration and frequency
	Threshing	Only those who plant cereals.
	Harvesting	

Table 3-4 Agricultural crops and animal variables in the questionnaire

Group	Variable	Details
Crops	Cereals (including harvesting and threshing activities)	Rice; maize; sweet corn; wheat
	Vegetables and melons	Cauliflower; cabbage; Chinese kale; pak choi; coriander; Chinese convolvulus; water convolvulus; Chinese cabbage; mustard green; lettuce; broccoli; courgette; cucumber; suhyo; watermelon; wax gourd; pumpkin; tomato; Thai eggplant; aubergine; eggplant; bitter melon; garlic; onion; shallot; Indian oyster
	Fruit and nuts	Pineapple; santol; banana; rambutan; durian; guava; monkey apple; tamarind; lime; mango; papaya; langsat; longan; lychee; strawberry; mulberry; tangerine; pomelo; passion fruit; avocado; tung oil; cashew tree
	Oilseed crops	Sesame; peanut; soybean; oil palm
	Root and tuber crops	Sweet potato; potato; cassava
	Beverage and spice crops	Coffee bean; tea; ginger; bird eye chili; chilli pepper; sweet pepper; bell pepper; Sichuan pepper (makhwaen)
	Leguminous crops	Mung bean; black gram; cow pea; common bean; asparagus bean; pea
	Other crops	• Sugar crops • Grasses and other fodder crops • Fibre crops • Cotton • Medicinal, aromatic, pesticidal, or similar crops • Flower crops • Others: teak; calameae; bamboo; agarwood/eagle wood
Animals	Insects	Bees; silkworms; other worms or insects
	Large ruminants	Cattle; buffaloes; yaks
	Small ruminants	Sheep; goats
	Poultry	Hens; ducks; geese
	Equines	
	Pigs or swine	
	Dogs and cats	
	Rabbits and hares	

Table 3-5 Pesticide use, exposure and personal protection equipment variables in the questionnaire

Group	Variable	Details
Herbicides	14 types of herbicides available in Nan province (see table 3-7)	• Years of spraying each pesticide • Frequency (average in each year): months; days; hours • Also include other types not included in the lists
Insecticides	21 types of insecticides available in Nan province (see table 3-8)	• Years of spraying each pesticide • Frequency (average in each year): months; days; hours • Also include other types not included in the lists
Fungicides	13 types of herbicides available in Nan province (see table 3-9)	• Years of spraying each pesticide • Frequency (average in each year): months; days; hours • Also include other types not included in the lists
Chemicals used for crop storage	Rodenticides	
	Fumigants	
Pesticide risk behaviours	Part of body in contact with pesticides	Face; hands; arms; trunk; legs; none
	Practice	Pesticide mixing; clothing; washing after pesticide use
PPE	Boots; gloves; respirator; goggles/Safety glasses; mask; hat; full face shield; apron; balaclavas and none of them	Both standard PPEs and some non-standard tools such as balaclavas (cloths wrapped around the face) are included in the multiple choice.

Table 3-6 Farming environmental factors and other variables in the questionnaire

Group	Variable	Details
Farm machines	Types of farm machines driven	• Tractors; tillage equipment; planting equipment; crop protection equipment; harvesting equipment and other equipment • Duration and frequency
	Fuels	Diesel; petrol; biodiesel and gasohol
Burning forest/previous crops	Duration and frequency	

Pesticide variables

On 24 April 2019, I visited the area and surveyed all three local pesticide marketplaces and stores. The available pesticides can be classified by site of action and substance group (273, 274) on tables 3-7 to 3-9.

There were 14 types of herbicides available in the local area. I classified them by the Herbicide Resistance Action Committee (HRAC) classification system and the Weed Science Society of America (WSSA) Classification. (275, 276) (table 3-7) There were 21 types of insecticides available in the local area. I classified them by the Insecticide Resistance Action Committee (IRAC) classification (277) (table 3-8) There were 13 types of fungicides available in the local area. I classified them by the Fungicide Resistance Action Committee (FRAC) classification (278) (table 3-9)

Table 3-7 Herbicides classified by classification groups and substance groups

Herbicide common name	Substance group	HRAC** Classification group	WSAA Classification group
Quizalofop-P-tefuryl	Aryloxyphenoxypropionate	A	1
Metsulfuron-methyl	Sulfonylurea	B	2
Atrazine	Triazine	C1	5
Paraquat	Bipyridylium	D	22
Fomesafen	Organochlorine	E	14
Isoxaflutole	Oxyacetamide	F2	27
Cyprosulfamide* + isoxaflutole			
Glyphosate	Phosphonoglycine	G	9
Glufosinate-ammonium	Phosphinic acid	H	10
Pendimethalin	Dinitroaniline	K1	3
Acetochlor	Chloroacetamide	K3	15
Alachlor			

*Cyprosulfamide: herbicide safener; other substance

**HRAC classification site of action:

- A Inhibition of acetyl CoA carboxylase (ACCase)
- B Inhibition of acetolactate synthase (ALS)
- C1 Inhibition of photosynthesis at PS II
- D Photosystem I-electron diversion
- E Inhibition of protoporphyrinogen oxidase (PPO)
- F2 Inhibition of 4-hydroxyphenyl-pyruvate-dioxygenase (4-HPPD)
- G Inhibition of 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase
- H Inhibition of glutamine synthetase
- K1 Inhibition of microtubule assembly
- K3 Inhibition of VLCFAs (inhibition of cell division)

Table 3-8 Insecticides classified by classification groups and substance groups

Insecticide common name	Substance group	IRAC** Classification group	Target site
Carbaryl	Carbamate (1A)	1	Nerve action
Chlorpyrifos	Organophosphate (1B)		Nerve action
Fipronil	Phenylpyrazole (2B)	2	Nerve action
Cypermethrin	Pyrethroid (3A)	3	Nerve action
Lambda-cyhalothrin			Nerve action
Acetamiprid	Neonicotinoid (4A)	4	Nerve action
Imidacloprid			Nerve action
Dinotefuran			Nerve action
Thiamethoxam			Nerve action
Emamectin benzoate	Avermectins; Micro-organism derived	6	Nerve and muscle action
Abamectin			Nerve and muscle action
B Thuringiensis	*B Thuringiensis*; Micro-organism derived	11	Midgut
Propargite	Sulphite ester (12C)	12	Energy metabolism
Chlorfenapyr	Pyrrole	13	Energy metabolism
Cartap hydrochloride	Thiocarbamate	14	Nerve action
Buprofezin	Buprofezin	16	Growth regulation
Pyridaben	Pyridazinone (21A)	21	Energy metabolism
Indoxacarb	Oxadiazine (22A)	22	Nerve action
Sulphur	Inorganic compound	Not known***	
Chlorpyrifos + cypermethrin*			

*Chlorpyrifos + cypermethrin is a mixed type of insecticide.
**IRAC classification site of action:

1	Acetylcholinesterase (AChE) inhibitors
2	GABA-gated chloride channel antagonists
3	Sodium channel modulators
4	Nicotinic acetylcholine receptor (nAChR) agonists
6	Chloride channel activators
11	Microbial disruptors of insect midgut membranes
12	Inhibitors of mitochondrial ATP synthase
13	Uncouplers of oxidative phosphorylation via disruption of the proton gradient
14	Nicotinic acetylcholine receptor (nAChR) channel blockers
16	Inhibitors of chitin biosynthesis, type 1
21	Mitochondrial complex I electron transport inhibitors
22	Voltage-dependent sodium channel blockers

***classified as FRAC M2 fungicide

Table 3-9 Fungicides classified by classification groups and substance groups

Fungicide common name	Substance group	FRAC Classification group	Target site
Carbendazim	Benzimidazole	1	ß-tubulin assembly in mitosis
Tetraconazole	Triazole	3	C14- demethylase in sterol biosynthesis (erg11/cyp51)
Hexaconazole			
Triforine	Piperazine		
Prochloraz	Imidazole		
Pyraclostrobin	Strobilurin	11	complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site (cyt b gene)
Etridiazole	1,2,4-thiadiazoles	14	cell peroxidation (proposed)
Quintozene*+ etridiazole**	*Chlorophenyl and **1,2,4-thiadiazoles		
Dimethomorph	Cinnamic acid amides	40	cellulose synthase
Cuprous oxide	Inorganic compound	M01	multi-site contact activity
Copper II hydroxide			
Mancozeb	Dithio-carbamates and relatives	M03	multi-site contact activity
Thiram			

*Quintozene is a chlorophenyl.; **Etridiazole is an 1,2,4-thiadiazoles.

3.3.6 Spirometry

Only participants with no contraindication performed pre- and post-bronchodilator spirometry. I conducted spirometry on all participants using the ndd EasyOne™ spirometer, (ndd Medizintechnik; Zurich, Switzerland). Participants were tested before and at least 20 minutes after 2 puffs (200µg) of salbutamol administered via a spacer. I calibrated the spirometer daily with a 3-litre syringe. Each week, spirometry data were uploaded via a secure internet connection to Imperial College London database. Each spirogram was reviewed and scored by one of my supervisors (Professor Burney) using the American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and reproducibility criteria. (279) This study includes only spirometry results which meet the ATS/ERS criteria, including at least three trials with two acceptable curves. Specifically, the largest difference allowed between the largest and the second values was <200 mL. Only spirometry results which passed these criteria were accepted.

3.3.7 Data analysis

Demographic data

Age, gender, socioeconomic status (e.g. household asset, education), body mass index (BMI) using a classification for Asian populations (280), smoking status, main occupational, farming and pesticide exposure data of all participants were described.

Respiratory symptoms and spirometric outcomes

All spirometric values were assessed using the Global Lung Initiative (GLI) 2012 equations for South East Asia, which were based on data from the region, including Thailand. (18) Lower limit of normal (LLN) and predicted values of FEV_1/FVC, FVC and FEV_1 using GLI 2012 equations were calculated. An FEV_1/FVC lower than the LLN and FVC lower than the LLN were defined as chronic airflow obstruction and spirometric restriction, accordingly. Respiratory symptoms, spirometry data, both raw and percent predicted values, were analysed.

Farming and pesticide exposure risk factors

Farming variables including years of living on a farm, farm size, types of crops and reared animals, and household biomass fuel use were included in the analyses. Farming activities such as ploughing, harvesting, chemical protecting of crops use, fertilizer use and crop burning exposure were analysed as potential risk factors associated with farming practice.

Pesticide exposure variables included pesticide practice risk factors consisted of mixing pesticide and personal protective equipment use, and time of the last exposure to pesticides. Pesticide exposures were also classified by specific types of pesticide used. An assessment of amount of pesticide exposure was estimated by 1) duration: years of exposure, 2) intensity: estimated hours of exposure per year and 3) cumulative hours of exposure in a lifetime.

Statistical analysis

I analysed differences between farming villagers and government employees by Student's t-test and chi-squared test or Fisher's exact test (for n<5), as appropriate. All identified risk factors were examined by univariable and multivariable models. Those unexposed to identified risk factor groups were used as referents. In all multivariable models, age, gender, smoking status and subject group (farming villagers or government employees), and additionally height for models with FVC or FEV_1 as outcomes, were considered as potential covariates. I evaluated potential exposure-responses by testing for trend using both categorical and continuous exposure variables. Statistical significance was set at p-value<0.05. I performed all analyses using Stata 15 (Stata Corp., College Station, TX, USA).

3.4 Results

3.4.1 Demographic characteristics

Overall, the response rates in farming villagers and government employees were similar, 93.3% and 95.1%, respectively (table 3-10). 400 participants participated in the study and completed all questionnaires; 358 (90%) of them had acceptable spirometric results.

Table 3-10 Participants' response rates

	Number of participants in the sampling frame	Number of respondents	Response rates
Villagers (from villages 3, 11 and 13)	345	322	93.3%
Government employees	82	78	95.1%
Total	427	400	93.7%

Table 3-11 summarises characteristics of the study populations. Compared with the control group of government employees, farming villagers who responded were 3.4 years older ($p < 0.001$), 3.3 centimetres shorter in males ($p<0.001$) and 2.3 centimetres shorter in females ($p=0.03$). Most farming villagers had their highest educational level at primary school (68.5%) while the government employees had mostly had a university education. Household asset scores show that farming villagers were significantly poorer than government employees ($p<0.001$). Most of both groups were lifelong non-smokers. The BMI of both groups were identical. 86.6% of farming villagers reported farming as their longest held job while 91% of government employees had held semi-skilled or skilled jobs ($p<0.001$). Farming villagers had higher numbers who had worked in dusty jobs, had been engaged in farming jobs for more than three months in their lifetime and had ever applied pesticides.

Pesticide practice and personal protective equipment

Tables 3-12 describes the comparison of pesticide use by gender. Male participants were significantly more likely to spray pesticides (82%) than were females (70%) ($p=0.005$). Specific activities i.e., mixing pesticides and most recent exposure to pesticides were also different between men and women. Table 3-13 shows that most survey participants used boots (93%), non-standard face-protecting balaclavas (92%), gloves (85%) and hats (79%) while spraying pesticides. A small number of sprayers used goggles and mask but none of them used a full face shield and apron. Table 3-14 reports parts of body exposed to pesticides while spraying among pesticide applicators. More than half of them reported that their hands and faces were usually exposed to pesticides while spraying. Figure 3-3 illustrates a typical farmer in Nan province spraying and mixing pesticide and how personal protective equipment is used. Figure 3-4 illustrates converted farmland after burning, and the burning of crop residues in the area of study in Tan Chum subdistrict, Nan.

Table 3-11 Demographic characteristics of the study subjects

Study variables†	Farming villagers (n=322)		Government employees (n=78)		p-value
	Mean	SD	Mean	SD	
Age (year)	53.8	0.4	50.4	0.7	**<0.001****
Height (cm) Male Farming villagers (n=156) Government employee (n=41)	163.4	0.4	166.7	0.9	**<0.001****
Height (cm) Female Farming villagers (n=166) Government employee (n=37)	154.7	0.4	157.0	0.9	**0.03***
Working hours (hour/week)	43.4	0.9	39.9	1.2	0.09
Study variables††	*n*	Percent	*n*	Percent	p-value
Sex					1.00
Male	156	48.5%	41	52.6%	
Female	166	51.5%	37	47.4%	
Education					**<0.001****
None	13	4.1%	0	0.0%	
Primary school	220	68.5%	4	5.1%	
Secondary/high/vocational school	78	24.3%	18	23.1%	
University	10	3.1%	56	71.8%	
Household asset score					**<0.001****
<12	147	45.6%	9	11.5%	
≥12	175	54.4%	69	88.5%	
Smoking status					0.15
Never	200	62.1%	49	62.3%	
Ex	90	28.0%	16	26.5%	
Current	32	9.9%	13	11.2%	
Body Mass Index (Asian)[280]					0.15
Normal (18.5 to <23.0 kg/m^2)	128	39.8%	30	38.5%	
Underweight (<18.5 kg/m^2)	39	12.1%	3	3.8%	
Overweight (23.0 to <25.0 kg/m^2)	69	21.4%	17	21.8%	
Obese level 1 (25.0 to <30.0 kg/m^2)	73	22.7%	23	29.5%	
Obese level 2 (≥30.0 kg/m^2)	13	4.0%	5	6.4%	

Table 3-11 *continued from previous page*

Study variables††	Farming villagers (n=322)		Government employees (n=78)		p-value
	n	Percent	*n*	Percent	
History of tuberculosis					0.60
No	316	98.1%	78	100.0%	
Yes	6	1.9%	0	0.0%	
Longest held job in lifetime					**<0.001****
Farming	278	86.6%	2	2.6%	
Manual labour	18	5.6%	5	6.4%	
Semi-skilled and skilled jobs	25	7.8%	71	91.0%	
Ever worked in dusty jobs					**<0.001****
No	209	64.9%	69	88.5%	
Yes	113	35.1%	9	11.5%	
Ever engaged in farming					**<0.001****
No	19	5.9%	38	48.7%	
Yes	303	94.1%	40	51.3%	
Ever applied pesticides					**<0.001****
No	36	11.2%	60	76.9%	
Yes	286	88.8%	18	23.1%	

†Analysing differences between subject groups by Student's t-test
††Analysing differences between subject groups by chi-squared test or Fisher's exact test (for n<5)
***p<0.05, **p<0.001**

Table 3-12 Pesticide practice classified by gender

Study variables	Male (n=197)		Female (n=203)		p-value
	n	Percent	*n*	Percent	
Apply pesticide					**0.005****
No	35	17.8%	61	30.0%	
Yes	162	82.2%	142	70.0%	
Mix pesticide					**0.005****
Never use pesticide	35	17.8%	61	30.1%	
Not involved with	43	21.8%	49	24.1%	
Involved with	119	60.4%	93	45.8%	
Last pesticide exposure					**0.02***
Unexposed	35	17.8%	61	30.1%	
More than 12 months	21	10.6%	27	13.3%	
Within 12 months	65	33.0%	55	27.1%	
Recent (within 1 week)	76	38.6%	60	29.5%	

Analysing differences between subject groups by chi-squared test or Fisher's exact test (for n<5)
***p<0.05, **p<0.01**

Table 3-13 Personal protective equipment used while spraying pesticides (only pesticide applicators)

Equipment variable (n=304)	*n*	Percent
Boots	283	93%
Gloves	259	85%
Respirator	23	8%
Goggles/safety glasses	21	7%
Mask	33	11%
Balaclavas	280	92%
Hat	239	79%
Full face shield	0	0%
Apron	0	0%

Table 3-14 Parts of sprayers' body usually coming into contact with pesticides (only pesticide applicators)

Body part (n=304)	*n*	Percent
Face	180	59%
Hands	197	65%
Arms	107	35%
Trunk	17	6%
Legs	21	7%
None of them	89	29%

a) A farmer spraying pesticide in Nan province b) A truck containing mixed pesticides

Figure 3-3 Pesticide use in Tha Wang Pha district, Nan province

a) A converted land for new season plant after burning b) Crop residues being burnt in a farming area

Figure 3-4 Burnt farmland and burning crop residues

3.4.2 Respiratory outcomes

Post-bronchodilator spirometry

In all, 358 of 400 participants completed all questionnaires and had adequate post-bronchodilator spirometry results. To examine the validity of the spirometric outcomes, I regressed lung function parameters against age, gender, height and smoking status, which are well known to influence lung function. Table 3-15 shows that all spirometric parameters are negatively associated with age ($p<0.001$). FVC and FEV_1 are both significantly lower in women ($p<0.001$), positively associated with height ($p<0.001$) and smoking ($p<0.001$ for FVC, and $p<0.01$ for FEV_1). Smoking status was not statistically associated with FEV_1/FVC ratio. Table 3-16 describes absolute values of FEV_1/FVC, FVC and FEV_1 and comparisons between study subject groups and by pesticide use.

Among all participants, the prevalence of airflow obstruction (FEV_1/FVC<LLN) was 4.5% and of spirometric restriction (FVC<LLN) was 10.8%. Compared with government employees, farming villagers had significantly lowered percent predicted FEV_1/FVC ($p=0.04$). FVC and FEV_1 were not statistically different between farming villagers and government employees. Comparisons between pesticide applicators and non-applicators found no statistically significant differences in any of the percent predicted values for spirometric parameters (table 3-17).

Respiratory symptoms

The prevalence of chronic cough was 11%, of chronic phlegm 7%, of shortness of breath 2%, of wheezing 6% and of self-reported chronic bronchitis 1%. Table 3-17 shows that respiratory symptoms were not statistically different between farming villagers and government employees or between pesticide applicators and non-applicators.

Table 3-15 Spirometric parameters by age, height, gender and smoking

Study variables (n=358)	FEV_1/FVC (%)		FVC (L)		FEV_1 (L)	
	β	95% CI	β	95% CI	β	95% CI
Age (year)	**-0.29**	**-0.38 to -0.20*** **	**-0.02**	**-0.03 to -0.02*** **	**-0.03**	**-0.31 to -0.21*** **
Gender						
Male (n=171)	ref		ref		ref	
Female (n=187)	1.14	-0.61 to 2.90	**-0.32**	**-0.47 to -0.17*** **	**-0.26**	**-0.39 to -0.13*** **
Height (cm)	-0.11	-0.22 to 0.01	**0.04**	**0.03 to 0.05*** **	**0.03**	**0.02 to 0.04*** **
Smoking						
Never (n=227)	ref		ref		ref	
Ever (n=131)	0.27	-1.56 to 2.09	**0.18**	**0.05 to 0.31*** **	**0.16**	**0.05 to 0.27** **

The coefficients (β) were all adjusted for all other variables.
****p<0.01, ***p<0.001**

Table 3-16 Post-bronchodilator spirometric parameters of the study subjects by sex, group and by pesticide use

Study variables	Male (n=171)					Female (n=187)					All (n=358)				
	Farming villagers (n=135)		Government employees (n=36)			Farming villagers (n=155)		Government employees (n=32)			Farming villagers (n=290)		Government employees (n=68)		
Spirometric parameters	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
FEV_1/FVC (%)	80.47	6.89	81.60	3.88	0.35	81.60	5.98	84.42	3.15	**0.01***	81.07	6.42	82.93	3.80	**0.02***
FVC (L)	3.21	0.55	3.43	0.54	**0.04***	2.46	0.46	2.51	0.40	0.50	2.81	0.63	2.99	0.66	**0.03***
FEV_1 (L)	2.59	0.50	2.80	0.48	**0.02***	2.00	0.39	2.09	0.29	0.22	2.28	0.53	2.47	0.54	**<0.01****
Study variables	Pesticide applicators (n=141)		Non-applicators (n=30)			Pesticide applicators (n=133)		Non-applicators (n=54)			Pesticide applicators (n=274)		Non-applicators (n=84)		
Spirometric parameters	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
FEV_1/FVC (%)	80.66	6.78	80.96	4.06	0.81	81.62	6.28	83.21	3.70	0.08	81.12	6.55	82.41	3.96	0.09
FVC (L)	3.24	0.56	3.36	0.51	0.28	2.44	0.43	2.53	0.50	0.20	2.85	0.64	2.82	0.64	0.74
FEV_1 (L)	2.62	0.52	2.72	0.43	0.33	1.99	0.37	2.08	0.37	0.11	2.32	0.55	2.31	0.50	0.93

Analysing differences between subject groups by Student's t-test.
***p<0.05, **p<0.01**

Table 3-17 Comparison of percent predicted values of post-bronchodilator spirometric parameters (GLI 2012 equation), prevalence of respiratory symptoms and abnormal spirometric patterns between the study groups

Study variables	Farming villagers (n=322)		Government employees (n=78)			Pesticide applicators (n=304)		Non-applicators (n=96)		
Respiratory symptoms†	*n*	Percent	*n*	Percent	p-value	*n*	Percent	*n*	Percent	p-value
Chronic cough	37	11.5%	6	7.7%	0.41	35	11.5%	8	8.3%	0.45
Chronic phlegm	25	7.8%	3	3.9%	0.32	23	7.6%	5	5.2%	0.50
Shortness of breath	9	2.8%	0	0.0%	0.22	9	3.0%	0	0.0%	0.12
Wheezing	20	6.2%	4	5.3%	1.00	20	6.6%	4	4.2%	0.47
Self-reported chronic bronchitis	3	0.9%	1	1.3%	0.58	4	1.3%	0	0.0%	0.58
Study variables	Farming villagers (n=290)		Government employees (n=68)			Pesticide applicators (n=274)		Non-applicators (n=84)		
Spirometric patterns†	*n*	Percent	*n*	Percent	p-value	*n*	Percent	*n*	Percent	p-value
Airflow obstruction	16	5.5%	0	0.0%	0.05	15	5.5%	1	1.2%	0.13
Spirometric restriction	30	10.3%	9	13.0%	0.51	27	9.8%	12	14.1%	0.32
Spirometric parameter††	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
FEV_1/FVC (%predicted)	**98.34**	**7.51**	**100.32**	**3.99**	**0.04***	98.43	7.63	99.68	4.35	0.15
FVC (%predicted)	92.88	13.28	90.93	11.83	0.26	92.50	12.79	92.55	13.82	0.98
FEV_1 (%predicted)	91.41	14.04	90.93	11.91	0.80	91.13	13.88	91.95	12.96	0.63

Spirometric patterns are classified by LLN (GLI)– airflow obstruction: FEV_1/FVC<LLN and spirometric restriction: FVC<LLN.
†Analysing differences between subject groups by chi-squared test or Fisher's exact test (for n<5).
††Analysing differences between subject groups by Student's t-test.
***p<0.05**

Categorical educational levels were not associated with any spirometric parameters. Similarly, household asset score using (≥12 of 14 score) as a cut-point for a binary variable, showed no statistically significant associations with any spirometric parameters.

3.4.3 Lung function and farming variables

Multivariable analyses summarised in Table 3-18 report that most farming variables were not significantly associated with spirometric parameters except rearing poultry which was associated with a small increase of FEV_1/FVC and household charcoal use which was associated with an increase in FEV_1/FVC and a small decline in FVC. As shown in table 3-19, pesticide practices were not statistically associated with spirometric parameters.

3.4.4 Lung function and pesticide exposures

Pesticides were classified into three main types: herbicides, insecticides and fungicides. Specifically, 304 pesticide sprayers used: glyphosate (91%); paraquat (69%); atrazine (13%); organophosphates (chlorpyrifos and other combined chlorpyrifos formulae) - 34%; pyrethroid (lambda-cyhalothrin, cypermethrin and other combined cypermethrin formulae) - 69%; mancozeb (17%) and pyraclostrobin (23%).

Pesticide exposure-response relationships were examined using medians of the distributions of duration, intensity and cumulative hours of exposure. Table 3-20 is a summary of the associations between duration (year) of each pesticide exposure and spirometric parameters. Duration of atrazine exposure was positively associated with FEV_1/FVC (p-trend<0.01). There was a significant negative association of <10 years of atrazine exposure with FVC but not for longer durations.

There were also similar trends in the relationships between all spirometric parameters and intensity (hours/year) and lifetime cumulative hours of pesticide exposure as shown in tables 3-21 and 3-22.

Table 3-18 Post-bronchodilator spirometric parameters and farming variables

Farming variables (n=358)	*n*	FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
		β	95% CI			β	95% CI			β	95% CI		
Years of living on a farm		ref				ref				ref			
<33 years	162	-0.48	-2.88	to	1.93	0.05	-0.12	to	0.22	0.03	-0.12	to	0.18
≥33 years	164	-0.21	-2.75	to	2.33	0.04	-0.14	to	0.22	0.02	-0.13	to	0.18
Years of farm work		ref				ref				ref			
<31 years	155	-0.65	-2.68	to	1.39	0.06	-0.09	to	0.20	0.03	-0.09	to	0.16
≥31 years	155	0.50	-1.76	to	2.75	0.08	-0.08	to	0.24	0.08	-0.06	to	0.22
Farmland size		ref				ref				ref			
≥18.5 rai (7.3 acre)	159	0.57	-0.79	to	1.93	0.02	-0.07	to	0.12	0.04	-0.05	to	0.12
Engage in farming jobs		ref				ref				ref			
Yes	310	-0.33	-2.33	to	1.67	0.07	-0.08	to	0.21	0.05	-0.08	to	0.17
Plant rice		ref				ref				ref			
Yes	210	0.64	-0.62	to	1.91	0.02	-0.07	to	0.11	0.04	-0.03	to	0.12
Plant maize/corn		ref				ref				ref			
Yes	183	0.00	-1.30	to	1.30	-0.05	-0.15	to	0.04	-0.05	-0.13	to	0.03
Plant longan		ref				ref				ref			
Yes	268	1.07	-0.46	to	2.59	0.03	-0.08	to	0.14	0.06	-0.03	to	0.15
Plant rubber tree		ref				ref				ref			
Yes	252	1.14	-0.36	to	2.65	0.01	-0.10	to	0.11	0.03	-0.06	to	0.13
Keep poultry		ref				ref				ref			
Yes	142	**1.38***	**0.17**	to	**2.59**	-0.02	-0.11	to	0.06	0.01	-0.06	to	0.09
Keep cat/dog		ref				ref				ref			
Yes	118	0.87	-0.40	to	2.14	0.04	-0.05	to	0.13	0.06	-0.015	to	0.14
Plough		ref				ref				ref			
Yes	169	0.36	-0.96	to	1.67	-0.05	-0.14	to	0.05	-0.02	-0.10	to	0.06
Harvest cereal		ref				ref				ref			
Yes	191	1.15	-0.43	to	2.73	0.00	-0.12	to	0.11	0.03	-0.06	to	0.13
Thresh cereal		ref				ref				ref			
Yes	74	1.77	-0.16	to	3.69	-0.02	-0.15	to	0.12	0.03	-0.08	to	0.15
Work in a silo storing grain/fodder		ref				ref				ref			
Yes	9	-1.06	-4.86	to	2.74	0.16	-0.10	to	0.42	0.12	-0.11	to	0.36
Apply fumigant		ref				ref				ref			
Yes	4	-0.04	-5.72	to	5.64	0.04	-0.32	to	0.41	0.05	-0.26	to	0.37
Apply rodenticide		ref				ref				ref			
Yes	51	0.24	-1.47	to	1.95	0.00	-0.12	to	0.12	0.00	-0.10	to	0.11
Apply natural fertilizer		ref				ref				ref			
Yes	228	0.40	-0.89	to	1.68	0.06	-0.03	to	0.15	0.07	-0.01	to	0.14
Apply chemical fertilizer		ref				ref				ref			
Yes	264	0.11	-1.41	to	1.63	0.03	-0.07	to	0.14	0.05	-0.04	to	0.14
Expose to burning crop-residue smoke		ref				ref				ref			
Yes	76	0.73	-0.78	to	2.23	0.02	-0.09	to	0.13	0.03	-0.06	to	0.12
Convert an arable land by burning		ref				ref		to		ref		to	
Yes	130	1.20	-0.05	to	2.44	0.00	-0.09	to	0.09	0.03	-0.04	to	0.11
Household firewood use		ref				ref				ref			
Yes	254	0.10	-1.32	to	-1.32	0.06	-0.04	to	0.16	0.04	-0.05	to	0.13
Household charcoal use		ref				ref				ref			
Yes	91	**2.65****	**1.30**	to	**3.99**	**-0.12***	**-0.21**	to	**-0.02**	-0.02	-0.10	to	0.06

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01**

Table 3-19 Post-bronchodilator spirometric parameters and pesticide practice

Pesticide practice (n=358)	*n*	FEV1/FVC (%)				FVC (L)				FEV1 (L)			
		β	95% CI			β	95% CI			β	95% CI		
Spray pesticide													
Never	84	ref				ref				ref			
Ever	274	-0.25	-2.02	to	1.52	-0.02	-0.15	to	0.10	-0.02	-0.13	to	0.77
Mix pesticide													
Never use pesticide	84	ref				ref				ref			
Not involved with	85	-0.68	-2.68	to	1.33	0.00	-0.14	to	0.14	0.00	-0.12	to	0.13
Involved with	189	0.00	-1.85	to	1.85	-0.04	-0.17	to	0.09	-0.03	-0.14	to	0.09
Part of body usually contact pesticide													
Never use pesticide	84	ref				ref				ref			
No contact	83	-0.98	-2.96	to	1.00	-0.06	-0.21	to	0.08	-0.06	-0.19	to	0.06
At least one part	191	0.25	-1.62	to	2.12	0.00	-0.13	to	0.14	0.02	-0.10	to	0.13
Last pesticide exposure													
Unexposed	84	ref				ref				ref			
More than 12 months	39	-0.90	-3.30	to	1.50	-0.02	-0.19	to	0.16	-0.04	-0.18	to	0.11
Within 12 months	109	-1.15	-3.09	to	0.79	-0.02	-0.16	to	0.11	-0.04	-0.16	to	0.08
Recent (within 1 week)	126	0.79	-1.12	to	2.71	-0.03	-0.16	to	0.11	0.01	-0.11	to	0.13

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01**

Table 3-20 Post-bronchodilator spirometric parameters and duration (years) of pesticide exposure classified by pesticide types

Years of exposure (years) (n=358)	*n*	FEV1/FVC (%) β	95% CI			FVC (L) β	95% CI			FEV1 (L) β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<11 years	123	0.23	-1.42	to	1.89	0.03	-0.11	to	0.17	0.04	-0.07	to	0.14
≥11 years	127	0.13	-1.54	to	1.80	0.00	-0.11	to	0.11	0.01	-0.09	to	0.11
Paraquat		ref				ref				ref			
<11 years	89	-0.13	-1.69	to	1.42	0.02	-0.09	to	0.13	0.02	-0.08	to	0.11
≥11 years	97	-0.37	-1.89	to	1.16	-0.01	-0.12	to	0.10	-0.01	-0.10	to	0.09
Atrazine		**ref††**				ref				ref			
<10 years	21	**2.90***	**0.35**	to	**5.45**	**-0.27****	**-0.45**	to	**-0.09**	-0.13	-0.29	to	0.03
≥10 years	18	**3.16***	**0.43**	to	**5.89**	-0.01	-0.21	to	0.18	0.07	-0.10	to	0.24
Other herbicides		ref				ref				ref			
<5 years	9	1.52	-2.31	to	5.35	1.65	-2.16	to	5.46	0.14	-0.09	to	0.38
≥5 years	19	0.04	-2.64	to	2.71	0.39	-2.30	to	3.07	-0.07	-0.24	to	0.09
Insecticide													
Organophosphate		ref				ref				ref			
<10 years	39	-0.07	-2.03	to	1.89	0.03	-0.11	to	0.17	0.06	-0.06	to	0.17
≥10 years	54	-0.17	-1.87	to	1.53	-0.05	-0.17	to	0.07	-0.03	-0.14	to	0.07
Pyrethroid		ref				ref				ref			
<10 years	91	0.59	-1.02	to	2.21	-0.01	-0.13	to	0.10	-0.01	-0.11	to	0.08
≥10 years	102	0.51	-1.04	to	2.06	-0.06	-0.17	to	0.05	-0.04	-0.14	to	0.05
Other insecticides		ref				ref				ref			
<10 years	23	-0.97	-3.45	to	1.51	0.06	-0.11	to	0.24	0.03	-0.12	to	0.19
≥10 years	23	-0.49	-2.93	to	1.95	0.04	-0.12	to	0.21	0.03	-0.12	to	0.18
Fungicide													
Mancozeb		ref				ref				ref			
<6 years	23	-0.76	-3.22	to	1.71	-0.77	-3.22	to	1.69	0.04	-0.10	to	0.19
≥6 years	22	-0.67	-3.17	to	1.83	-0.75	-3.23	to	1.74	0.07	-0.08	to	0.23
Pyraclostrobin		ref				ref				ref			
<4 years	31	-0.36	-2.51	to	1.77	-0.23	-2.37	to	1.90	0.05	-0.08	to	0.18
≥4 years	28	0.30	-1.93	to	2.54	0.36	-1.87	to	2.58	0.07	-0.07	to	0.20
Other fungicides		ref				ref				ref			
<6 years	35	1.47	-0.56	to	3.50	1.62	-0.41	to	3.64	0.08	-0.05	to	0.20
≥6 years	32	0.73	-1.39	to	2.85	0.77	-1.34	to	2.88	0.00	-0.13	to	0.13

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

Table 3-21 Post-bronchodilator spirometric parameters and intensity (hours/year) of pesticide exposure classified by pesticide types

Intensity		FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
(hours/year) (n=358)	*n*	β	95% CI			β	95% CI			β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<20 hours/year	120	0.44	-1.20	to	2.08	0.02	-0.10	to	0.14	0.04	-0.06	to	0.14
≥20 hours/year	130	-0.13	-1.82	to	1.56	-0.01	-0.13	to	0.11	0.01	-0.10	to	0.11
Paraquat		ref				ref				ref			
<17 hours/year	93	0.24	-1.28	to	1.76	0.00	-0.11	to	0.11	0.00	-0.10	to	0.09
≥17 hours/year	93	-0.81	-2.38	to	0.76	0.01	-0.10	to	0.12	0.01	-0.08	to	0.11
Atrazine		**ref††**				ref				ref			
<16 hours/year	17	**2.90***	**0.11**	to	**5.69**	**-0.27****	**-0.46**	to	**-0.08**	-0.14	-0.32	to	0.03
≥16 hours/year	22	**3.12***	**0.60**	to	**5.63**	-0.05	-0.23	to	0.13	0.05	-0.11	to	0.21
Other herbicides		ref				ref				ref			
<8 hours/year	12	-0.70	-4.04	to	2.64	-0.46	-3.79	to	2.86	0.08	-0.12	to	0.29
≥8 hours/year	16	1.40	-1.49	to	4.30	1.73	-1.17	to	4.62	-0.07	-0.25	to	0.11
Insecticide													
Organophosphate		ref				ref				ref			
<18 hours/year	43	-0.45	-2.33	to	1.43	-0.01	-0.14	to	0.12	0.01	-0.10	to	0.13
≥18 hours/year	50	0.14	-1.62	to	1.90	-0.02	-0.14	to	0.11	0.00	-0.11	to	0.10
Pyrethroid		ref				ref				ref			
<16 hours/year	89	-0.05	-1.64	to	1.55	-0.02	-0.14	to	0.09	-0.04	-0.13	to	0.06
≥16 hours/year	104	1.09	-0.46	to	2.65	-0.06	-0.17	to	0.06	-0.02	-0.12	to	0.07
Other insecticides		ref				ref				ref			
<17 hours/year	21	-0.49	-3.04	to	2.06	-0.05	-0.22	to	0.13	-0.06	-0.21	to	0.10
≥17 hours/year	25	-0.93	-3.31	to	1.45	0.15	-0.02	to	0.32	0.11	-0.04	to	0.26
Fungicide													
Mancozeb		ref				ref				ref			
<18 hours/year	20	0.25	-2.36	to	2.86	0.22	-2.38	to	2.82	0.06	-0.09	to	0.21
≥18 hours/year	25	-1.49	-3.86	to	0.87	-1.54	-3.90	to	0.81	0.06	-0.09	to	0.20
Pyraclostrobin		ref				ref				ref			
<8 hours/year	26	-0.08	-2.41	to	2.26	0.01	-2.31	to	2.34	0.02	-0.12	to	0.17
≥8 hours/year	33	-0.03	-2.10	to	2.04	0.07	-1.99	to	2.14	0.08	-0.04	to	0.21
Other fungicides		ref				ref				ref			
<15 hours/year	33	1.66	-0.41	to	3.74	1.76	-0.31	to	3.82	0.03	-0.10	to	0.16
≥15 hours/year	34	0.58	-1.49	to	2.65	0.68	-1.38	to	2.73	0.05	-0.08	to	0.18

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

Table 3-22 Post-bronchodilator spirometric parameters and lifetime cumulative hours of pesticide exposure classified by pesticide types

Cumulative exposure (total hours in lifetime) (n=358)	*n*	FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
		β	95% CI			β	95% CI			β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<240 hours	117	-0.06	-1.71	to	1.59	0.06	-0.06	to	0.17	0.05	-0.05	to	0.15
≥240 hours	133	0.44	-1.23	to	2.12	-0.05	-0.17	to	0.07	-0.01	-0.11	to	0.09
Paraquat		ref				ref				ref			
<240 hours	83	0.30	-1.27	to	1.86	0.01	-0.10	to	0.12	0.01	-0.08	to	0.11
≥240 hours	103	-0.75	-2.27	to	0.77	0.00	-0.11	to	0.10	0.00	-0.10	to	0.09
Atrazine		**ref†**				ref				ref			
<240 hours	19	**2.91***	**0.26**	to	**5.56**	**-0.28****	**-0.46**	to	**-0.09**	-0.15	-0.32	to	0.01
≥240 hours	20	**3.13***	**0.49**	to	**5.78**	-0.02	-0.21	to	0.17	0.08	-0.09	to	0.24
Other herbicides		ref				ref				ref			
<54 hours	13	0.77	-2.45	to	3.98	0.87	-2.33	to	4.07	0.16	-0.03	to	0.36
≥54 hours	15	0.29	-2.70	to	3.28	0.72	-2.28	to	3.72	-0.15	-0.33	to	0.04
Insecticide													
Organophosphate		ref				ref				ref			
<144 hours	44	0.70	-1.15	to	2.56	0.01	-0.12	to	0.14	0.06	-0.06	to	0.17
≥144 hours	49	-0.87	-2.64	to	0.90	-0.04	-0.16	to	0.09	-0.04	-0.15	to	0.07
Pyrethroid		ref				ref				ref			
<128 hours	98	-0.04	-1.60	to	1.53	-0.02	-0.13	to	0.09	-0.03	-0.12	to	0.07
≥128 hours	95	1.17	-0.42	to	2.76	-0.07	-0.18	to	0.05	-0.03	-0.13	to	0.07
Other insecticides		ref				ref				ref			
<120 hours	21	-0.50	-3.05	to	2.05	-0.02	-0.20	to	0.16	-0.03	-0.18	to	0.13
≥120 hours	25	-0.92	-3.28	to	1.44	0.12	-0.05	to	0.28	0.08	-0.06	to	0.23
Fungicide													
Mancozeb		ref				ref				ref			
<120 hours	18	-0.06	-2.83	to	2.70	-0.03	-2.78	to	2.72	0.06	-0.10	to	0.23
≥120 hours	27	-1.14	-3.41	to	1.14	-1.23	-3.50	to	1.03	0.06	-0.08	to	0.19
Pyraclostrobin		ref				ref				ref			
<24 hours	27	-0.09	-2.37	to	2.20	0.01	-2.27	to	2.28	0.04	-0.10	to	0.18
≥24 hours	32	-0.02	-2.12	to	2.08	0.08	-2.01	to	2.17	0.07	-0.06	to	0.20
Other fungicides		ref				ref				ref			
<87 hours	33	0.47	-1.61	to	2.54	0.52	-1.54	to	2.59	0.03	-0.10	to	0.16
≥87 hours	34	1.77	-0.30	to	3.84	1.91	-0.15	to	3.97	0.05	-0.08	to	0.18

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

3.4.5 Pre-bronchodilator spirometry

To examine the effect of bronchodilator reversibility (281) I reran all analyses using pre-bronchodilator spirometric parameters as outcomes. Farming villagers had significantly lower percent predicted pre-bronchodilator FEV_1/FVC than government employees. There were higher prevalences of both airflow obstruction and spirometric restriction compared to the results from post-bronchodilator spirometry. (table 3-23) However, with adjustment for confounding factors (age, sex, smoking status, farming villagers vs government employees and, additionally for FVC and FEV_1, height), multivariable analyses showed that most of the relationships between farming and pesticide variables and pre-bronchodilator spirometry were similar to post-bronchodilator spirometry results. (tables 3-24 to 3-28)

Table 3-23 Comparison of percent predicted values of pre-bronchodilator spirometric parameters (GLI 2012 equation) and prevalence of abnormal spirometric patterns between the study groups

Study variables	Farming villagers (n=290)		Government employees (n=68)			Pesticide applicators (n=274)		Non-applicators (n=84)		
Spirometric patterns†	*n*	Percent	*n*	Percent	p-value	*n*	Percent	*n*	Percent	p-value
Airflow obstruction	29	10.7%	0	0.0%	**0.004****	28	10.9%	1	1.3%	**0.009****
Spirometric restriction	25	9.2%	8	13.3%	0.33	21	8.1%	12	16.0%	**0.04***
Spirometric parameter††	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
FEV_1/FVC (%predicted)	95.73	0.46	98.03	0.51	**0.02***	95.82	0.49	97.26	0.47	0.13
FVC (%predicted)	94.34	0.91	90.98	1.47	0.10	94.07	0.92	92.57	1.62	0.43
FEV_1 (%predicted)	90.13	0.81	89.20	1.44	0.63	89.87	0.82	90.33	1.45	0.79

Spirometric patterns are classified by LLN (GLI)– airflow obstruction: FEV_1/FVC<LLN and spirometric restriction: FVC<LLN.
†Analysing differences between subject groups by chi-squared test or Fisher's exact test (for n<5).
††Analysing differences between subject groups by Student's t-test.
***p<0.05; **p<0.01**

Table 3-24 Pre-bronchodilator spirometric parameters and farming variables

Farming variables (n=332)	*n*	FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
		β	95% CI			β	95% CI			β	95% CI		
Years of living on a farm		ref				ref				ref			
<33 years	150	0.12	-2.59	to	2.84	0.02	-0.19	to	0.23	0.01	-0.14	to	0.17
≥33 years	155	0.83	-1.99	to	3.65	-0.02	-0.24	to	0.20	0.02	-0.13	to	0.18
Years of farm work		ref				ref				ref			
<31 years	145	-0.58	-2.76	to	1.60	0.14	-0.05	to	0.34	0.07	-0.07	to	0.21
≥31 years	143	1.07	-1.35	to	3.49	0.09	-0.13	to	0.31	0.09	-0.07	to	0.24
Farmland size		ref				ref				ref			
≥18.5 rai (7.3 acre)	143	0.21	-1.27	to	1.69	-0.01	-0.12	to	0.11	0.01	-0.08	to	0.09
Engage in farming jobs		ref				ref				ref			
Yes	288	-0.14	-2.29	to	2.01	0.08	-0.09	to	0.24	0.06	-0.07	to	0.18
Plant rice		ref				ref				ref			
Yes	202	0.29	-1.07	to	1.65	0.04	-0.07	to	0.14	0.06	-0.02	to	0.13
Plant maize/corn		ref				ref				ref			
Yes	172	-0.93	-2.29	to	0.44	-0.04	-0.14	to	0.07	-0.06	-0.14	to	0.01
Plant longan		ref				ref				ref			
Yes	248	1.15	-0.49	to	2.78	-0.02	-0.15	to	0.10	0.02	-0.07	to	0.11
Plant rubber tree		ref				ref				ref			
Yes	233	1.52	-0.10	to	3.14	-0.02	-0.15	to	0.10	0.01	-0.08	to	0.11
Keep poultry		ref				ref				ref			
Yes	132	0.46	-0.83	to	1.75	0.01	-0.09	to	0.11	0.00	-0.07	to	0.07
Keep cat/dog		ref				ref				ref			
Yes	112	0.26	-1.10	to	1.61	0.07	-0.03	to	0.17	0.05	-0.03	to	0.13
Plough		ref				ref				ref			
Yes	160	-0.01	-1.42	to	1.41	-0.04	-0.15	to	0.07	-0.02	-0.10	to	0.06
Harvest cereal		ref				ref				ref			
Yes	177	0.33	-1.37	to	2.03	0.04	-0.09	to	0.17	0.03	-0.06	to	0.13
Thresh cereal		ref				ref				ref			
Yes	69	1.32	-0.72	to	3.36	0.01	-0.15	to	0.17	0.05	-0.07	to	0.16
Work in a silo storing grain/fodder		ref				ref				ref			
Yes	8	0.73	-3.38	to	4.84	0.23	-0.08	to	0.55	0.18	-0.04	to	0.39
Apply fumigant		ref				ref				ref			
Yes	6	1.64	-3.13	to	6.40	-0.01	-0.38	to	0.36	0.09	-0.18	to	0.37
Apply rodenticide		ref				ref				ref			
Yes	48	0.06	-1.75	to	1.87	-0.03	-0.17	to	0.11	-0.01	-0.11	to	0.09
Apply natural fertilizer		ref				ref				ref			
Yes	210	0.53	-0.83	to	1.90	0.03	-0.08	to	0.14	0.03	-0.05	to	0.11
Apply chemical fertilizer		ref				ref				ref			
Yes	245	0.19	-1.45	to	1.82	0.07	-0.05	to	0.20	0.05	-0.04	to	0.14
Expose to burning crop-residue smoke		ref				ref				ref			
Yes	74	-0.41	-1.99	to	1.17	0.07	-0.05	to	0.20	0.02	-0.07	to	0.11
Convert an arable land by burning		ref				ref				ref			
Yes	117	1.04	-0.29	to	2.37	0.00	-0.11	to	0.10	0.03	-0.05	to	0.10
Household firewood use		ref				ref				ref			
Yes	237	0.54	-0.96	to	2.03	0.04	-0.08	to	0.16	0.05	-0.03	to	0.14
Household charcoal use		ref				ref				ref			
Yes	83	**2.34****	**0.90**	to	**3.79**	**-0.12***	**-0.23**	to	**-0.01**	-0.02	-0.10	to	0.07

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01**

Table 3-25 Pre-bronchodilator spirometric parameters and pesticide practice

Pesticide practice (n=332)	*n*	FEV$_1$/FVC (%)				FVC (L)				FEV$_1$ (L)			
		β	95% CI			β	95% CI			β	95% CI		
Spray pesticide													
Never	75	ref				ref				ref			
Ever	257	-0.14	-2.05	to	1.78	0.00	-0.14	to	0.15	-0.02	-0.15	to	0.10
Mix pesticide													
Never use pesticide	75	ref				ref				ref			
Not involve with	75	-0.47	-2.66	to	1.72	0.06	-0.11	to	0.23	0.00	-0.14	to	0.14
Involve with	182	0.03	-1.96	to	2.02	-0.02	-0.18	to	0.13	-0.04	-0.17	to	0.09
Part of body usually contact pesticide													
Never use pesticide	75	ref				ref				ref			
None	72	-0.51	-2.70	to	1.67	-0.08	-0.25	to	0.09	-0.06	-0.21	to	0.08
At least one part	185	0.08	-1.93	to	2.09	0.05	-0.10	to	0.21	0.00	-0.13	to	0.14
Last pesticide exposure													
Unexposed	75	ref				ref				ref			
More than 12 months	41	-0.71	-3.20	to	1.78	0.00	-0.19	to	0.20	-0.02	-0.19	to	0.16
Within 12 months	99	-0.30	-2.44	to	1.84	-0.02	-0.19	to	0.14	-0.02	-0.16	to	0.11
Recent within 1 week	117	0.24	-1.84	to	2.32	0.03	-0.13	to	0.19	-0.03	-0.16	to	0.11

FEV$_1$/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV$_1$ values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01**

Table 3-26 Pre-bronchodilator spirometric parameters and duration (years) of pesticide exposure classified by pesticide types

Years of exposure		FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
(years) (n=332)	*n*	β	95% CI			β	95% CI			β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<11 years	114	-0.33	-2.13	to	1.46	0.08	-0.05	to	0.22	0.04	-0.06	to	0.14
≥11 years	121	0.12	-1.67	to	1.91	0.04	-0.10	to	0.18	0.03	-0.07	to	0.13
Paraquat		ref				ref				ref			
<11 years	85	-0.49	-2.14	to	1.17	0.07	-0.06	to	0.20	0.02	-0.07	to	0.12
≥11 years	95	-0.21	-1.82	to	1.39	0.01	-0.12	to	0.13	0.01	-0.08	to	0.10
Atrazine		**ref††**				ref				ref			
<10 years	20	**3.78****	**1.13**	to	**6.43**	**-0.27***	**-0.48**	to	**-0.06**	-0.09	-0.24	to	0.07
≥10 years	17	**3.05***	**0.19**	to	**5.91**	-0.01	-0.24	to	0.21	0.10	-0.07	to	0.26
Other herbicides		ref				ref				ref			
<5 years	7	1.51	-2.90	to	5.92	0.05	-0.29	to	0.39	0.03	-0.21	to	0.28
≥5 years	18	0.23	-2.57	to	3.04	-0.08	-0.29	to	0.14	-0.04	-0.19	to	0.12
Insecticide													
Organophosphate		ref				ref				ref			
<10 years	37	-1.21	-3.26	to	0.83	0.12	-0.04	to	0.28	0.05	-0.06	to	0.17
≥10 years	51	0.06	-1.73	to	1.84	-0.02	-0.16	to	0.12	-0.01	-0.11	to	0.09
Pyrethroid		ref				ref				ref			
<10 years	83	0.93	-0.79	to	2.66	-0.05	-0.18	to	0.08	-0.01	-0.10	to	0.09
≥10 years	99	0.39	-1.25	to	2.02	-0.09	-0.22	to	0.04	-0.03	-0.12	to	0.06
Other insecticides		ref				ref				ref			
<10 years	22	-0.19	-2.77	to	2.38	0.02	-0.18	to	0.22	0.03	-0.12	to	0.18
≥10 years	23	1.19	-1.29	to	3.68	-0.02	-0.21	to	0.17	0.01	-0.13	to	0.15
Fungicide													
Mancozeb		ref				ref				ref			
<6 years	24	-0.54	-3.01	to	1.94	0.09	-0.10	to	0.28	0.08	-0.06	to	0.22
≥6 years	23	0.47	-2.04	to	2.98	0.10	-0.09	to	0.29	0.09	-0.06	to	0.23
Pyraclostrobin		ref				ref				ref			
<4 years	25	-1.90	-4.29	to	0.49	0.10	-0.09	to	0.29	0.04	-0.10	to	0.17
≥4 years	26	1.47	-0.88	to	3.82	0.07	-0.11	to	0.25	0.08	-0.05	to	0.21
Other fungicides		ref				ref				ref			
<6 years	33	1.64	-0.50	to	3.78	-0.04	-0.20	to	0.13	0.06	-0.06	to	0.18
≥6 years	30	0.76	-1.48	to	3.01	0.00	-0.17	to	0.18	0.02	-0.11	to	0.14

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

Table 3-27 Pre-bronchodilator spirometric parameters and intensity (hours/year) of pesticide exposure classified by pesticide types

Intensity		FEV_1/FVC (%)				FVC (L)				FEV_1 (L)			
(hours/year) (n=332)	*n*	β	95% CI			β	95% CI			β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<20 hours/year	111	0.55	-1.21	to	2.31	0.09	-0.05	to	0.22	0.06	-0.03	to	0.16
≥20 hours/year	124	-0.88	-2.69	to	0.94	0.03	-0.11	to	0.17	-0.01	-0.11	to	0.10
Paraquat		ref				ref				ref			
<17 hours/year	87	0.11	-1.51	to	1.73	0.05	-0.07	to	0.18	0.02	-0.07	to	0.11
≥17 hours/year	93	-0.82	-2.46	to	0.82	0.02	-0.10	to	0.15	0.01	-0.08	to	0.11
Atrazine		**ref††**				ref				ref			
<16 hours/year	16	**3.54***	**0.62**	to	**6.46**	**-0.20****	**-0.43**	to	**0.03**	-0.08	-0.25	to	0.09
≥16 hours/year	21	**3.37***	**0.75**	to	**5.99**	-0.11	-0.31	to	0.10	0.06	-0.09	to	0.21
Other herbicides		ref				ref				ref			
<8 hours/year	11	-0.86	-4.41	to	2.68	0.02	-0.25	to	0.30	0.03	-0.17	to	0.23
≥8 hours/year	14	1.73	-1.43	to	4.88	-0.09	-0.33	to	0.16	-0.05	-0.22	to	0.12
Insecticide													
Organophosphate		ref				ref				ref			
<18 hours/year	41	-1.23	-3.19	to	0.74	0.09	-0.06	to	0.24	0.04	-0.07	to	0.15
≥18 hours/year	47	0.17	-1.67	to	2.02	-0.01	-0.15	to	0.13	0.00	-0.11	to	0.10
Pyrethroid		ref				ref				ref			
<16 hours/year	83	0.26	-1.43	to	1.96	-0.07	-0.20	to	0.06	-0.03	-0.13	to	0.06
≥16 hours/year	99	0.97	-0.68	to	2.62	-0.07	-0.20	to	0.05	-0.01	-0.10	to	0.08
Other insecticides		ref				ref				ref			
<17 hours/year	21	0.30	-2.30	to	2.90	-0.08	-0.28	to	0.12	-0.05	-0.20	to	0.09
≥17 hours/year	24	0.73	-1.74	to	3.19	0.07	-0.11	to	0.26	0.09	-0.05	to	0.23
Fungicide													
Mancozeb		ref				ref				ref			
<18 hours/year	21	0.55	-2.06	to	3.17	0.10	-0.10	to	0.30	0.12	-0.02	to	0.27
≥18 hours/year	26	-0.52	-2.90	to	1.86	0.09	-0.09	to	0.27	0.05	-0.09	to	0.19
Pyraclostrobin		ref				ref				ref			
<8 hours/year	21	0.00	-2.64	to	2.64	0.01	-0.19	to	0.22	0.03	-0.11	to	0.17
≥8 hours/year	30	-0.31	-2.52	to	1.90	0.13	-0.04	to	0.30	0.08	-0.04	to	0.21
Other fungicides		ref				ref				ref			
<15 hours/year	28	1.60	-0.68	to	3.89	-0.09	-0.27	to	0.09	0.02	0.06	to	0.15
≥15 hours/year	35	0.91	-1.19	to	3.02	0.04	-0.12	to	0.20	0.05	0.06	to	0.17

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

Table 3-28 Pre-bronchodilator spirometric parameters and lifetime cumulative hours of pesticide exposure classified by pesticide types

Cumulative exposure (total hours in lifetime) (n=332)	*n*	FEV1/FVC (%) β	95% CI			FVC (L) β	95% CI			FEV1 (L) β	95% CI		
Herbicide													
Glyphosate		ref				ref				ref			
<240 hours	107	1.04	-1.68	to	1.89	0.12	-0.02	to	0.25	0.07	-0.03	to	0.17
≥240 hours	128	-0.32	-2.12	to	1.48	0.00	-0.13	to	0.14	-0.01	-0.11	to	0.09
Paraquat		ref				ref				ref			
<240 hours	75	0.16	-1.53	to	1.85	0.06	-0.07	to	0.19	0.02	-0.07	to	0.12
≥240 hours	105	-0.74	-2.32	to	0.84	0.02	-0.10	to	0.14	0.01	-0.08	to	0.10
Atrazine		**ref†**				ref				ref			
<240 hours	18	**3.72****	**0.95**	to	**6.49**	**-0.23****	**-0.45**	to	**-0.02**	-0.10	-0.25	to	0.06
≥240 hours	19	**3.17***	**0.41**	to	**5.94**	-0.07	-0.28	to	0.15	0.09	-0.07	to	0.25
Other herbicides		ref				ref				ref			
<54 hours	11	0.30	-3.24	to	3.84	0.16	-0.11	to	0.44	0.11	-0.08	to	0.30
≥54 hours	14	0.82	-2.34	to	3.98	-0.20	-0.44	to	0.04	-0.13	-0.30	to	0.05
Insecticide													
Organophosphate		ref				ref				ref			
<144 hours	42	-0.60	-2.55	to	1.34	0.09	-0.06	to	0.24	0.05	-0.06	to	0.16
≥144 hours	46	-0.36	-2.23	to	1.51	-0.01	-0.16	to	0.13	-0.01	-0.12	to	0.09
Pyrethroid		ref				ref				ref			
<128 hours	90	0.23	-1.44	to	1.90	-0.07	-0.20	to	0.06	-0.03	-0.12	to	0.06
≥128 hours	92	1.04	-0.64	to	2.71	-0.07	-0.20	to	0.06	-0.01	-0.11	to	0.08
Other insecticides		ref				ref				ref			
<120 hours	21	0.29	-2.32	to	2.89	-0.04	-0.24	to	0.16	-0.03	-0.18	to	0.12
≥120 hours	24	0.73	-1.72	to	3.19	0.03	-0.15	to	0.22	0.06	-0.08	to	0.20
Fungicide													
Mancozeb		ref				ref				ref			
<120 hours	18	0.16	-2.68	to	2.99	0.11	-0.11	to	0.33	0.12	-0.03	to	0.28
≥120 hours	29	-0.16	-2.42	to	2.10	0.09	-0.09	to	0.26	0.06	-0.07	to	0.19
Pyraclostrobin		ref				ref				ref			
<24 hours	20	-1.60	-4.28	to	1.08	0.08	-0.13	to	0.28	0.03	-0.12	to	0.17
≥24 hours	31	0.71	-1.46	to	2.88	0.09	-0.08	to	0.26	0.09	-0.04	to	0.21
Other fungicides		**ref†**				ref				ref			
<87 hours	29	0.17	-2.08	to	2.41	-0.04	-0.21	to	0.14	0.02	-0.07	to	0.15
≥87 hours	34	**2.16***	**0.03**	to	**4.29**	0.00	-0.17	to	0.16	0.05	-0.07	to	0.17

FEV_1/FVC ratio values (β) were adjusted for age, sex, smoking status and study subject (farming villagers vs government employees).
FVC and FEV_1 values (β) were adjusted for age, height, sex, smoking status and study subject (farming villagers vs government employees).
ref. means a reference representing an unexposed group of each variable.; ***p<0.05, **p<0.01, †p-trend<0.05, ††p-trend<0.01**

3.5 Discussion

The published literature on farming and adverse respiratory health effects in Thailand is very limited (167, 262, 282); this survey is the first community-based study in the northern region of Thailand to examine the relationship between post-bronchodilator spirometry and a comprehensive set of farming factors, particularly details of specific pesticides used. Overall, I found that chronic airflow obstruction was uncommon in Nan; farming and pesticide use are unlikely to be a major cause of respiratory problems there.

Generally, as in other developing South East Asian countries (33), there was a low prevalence of smokers among farming villagers, and, on the basis of asset scores and educational levels, farming villagers tended to have lower socioeconomic status than government employees. The farming villagers reported a low prevalence of chronic respiratory symptoms; similarly, the prevalence of airflow obstruction was no higher than would be expected in a healthy population (4.5% overall, 5.5% among farmers). This figure is at the lower end of those reported from previous studies of the association between farming and COPD, where the prevalence of airflow obstruction varied between 3% and 68% (134). One explanation is that those with poor lung health were disproportionately represented in the group who could not produce reliable measures of lung function. Of the 400 participants, 393 undertook spirometry, of whom 358 (91.1%) had acceptable and repeatable post-bronchodilator results. I found that the remainder, not included in analyses (n=35), had higher prevalences of self-reported chronic respiratory symptoms[2] than those with acceptable post-bronchodilator spirometry results although the differences were not statistically significant. (appendix B-11) Another explanation may be selective survival whereby those exposed to farming may have left this occupation (or died) before the lower end of the study's age range. A similar study in the central region of Thailand, undertaken in early 2020 but using the FEV_1/FVC ratio<0.70 criterion to define COPD, reported a similar prevalence of COPD (5.5%) among farmers aged over 18. (282) However, the prevalence of COPD is generally low (4.5% to 9.4%) in South East Asian populations, perhaps reflecting low smoking prevalence in these populations (14, 35). Another explanation might be regarding the type of farming in the Nan province, which is mainly crop farming conducted in open fields. Most previous studies were undertaken in the context of high-density livestock farming with typically higher concentrations of hazardous respiratory exposures. (148, 283, 284) A similar cross-sectional study by Guillien *et al.* in France, classified by type of farm, also found that only 2.9% of crop farmers had airflow obstruction, (150) a figure much lower than those from other studies in European farming populations mainly working in livestock farms where the reported COPD prevalence ranged between 10.7% and 30.2%. (51)

It is also interesting that my findings suggest a relatively high prevalence of a restrictive spirometric pattern (10.3%) among farming villagers. Currently, few studies report a relationship between farming exposures and restrictive spirometry pattern (RSP). Indeed, the determinants of a RSP itself remain poorly understood; explanations in developing country settings might include genetic factors or some adverse early life exposures impacting on childhood development. (16)

In this study, I observed a statistically significant lower percent predicted FEV_1/FVC in farming villagers compared to government employees, although there was no significant difference using a dichotomous variable for spirometric airflow obstruction. A systematic review published in 2017 reported that although the majority of published studies found that farming

[2] Chronic respiratory symptoms: chronic cough; chronic phlegm; shortness of breath; wheezing and self-reported chronic bronchitis

was significantly associated with a higher prevalence of COPD (mainly diagnosed by pre-bronchodilator spirometry), the association varied by type of farm with higher prevalence of COPD in livestock farmers than in crop farmers. (134) A more recent meta-analysis by Guillien *et al.* published in 2019 (135), shows that four (67, 139, 140, 150) of five studies specific to crop farmers, as in Nan province, showed no significant associations with an increased risk of airflow obstruction. In addition, I found no significant associations between living on a farm ≥33 years (46% of all participants) and working on a farm ≥31 years (43% of all participants) with a decline in lung function; this is in contrast to a previous study in the Philippines, which reported that working on a farm for ≥40 years (18%; 131 of 722 participants) increased the risk of COPD, based on GOLD stage. (57)

I assessed a variety of relationships between organic dust exposure variables and lung function (table 3-18) but found no association of these, including harvesting, threshing cereals and working in a silo, with significant changes in spirometry. These findings are in agreement with a recent nationwide study in Denmark on occupational organic dust exposure which indicated no association of cumulative organic dust exposure and an increased risk of COPD. (285) However, I did find an association between rearing poultry and a small increase in FEV_1/FVC with no significant change of FVC; studies in North America reported the associations of activities related to poultry farming in confinement with the decline in lung function especially FEV_1/FVC (286, 287), whereas another recent AHS study concluded that that there was no association between raising animals, including poultry, and a doctor's diagnosis of COPD, without direct measurement of lung function. (288) The apparently contradictory finding from my study might have occurred by chance or in reflection of a 'healthy worker' effect. (289)

In addition, I examined diverse farming roles related to high levels of dust and fume including ploughing, burning crops and household charcoal use. (table 3-18) While ploughing has generated high levels of exposure to inorganic soil dust with potential health effects (266), I found no association between ploughing and lung function. One explanation might be due to open air farmland, which is typical in the study region and presents better ventilation and lower exposure intensity. (52) Burning forests and crops is common in several developing countries including in Nan province. Ambient air pollution in agricultural areas, as a result of crop-residue burning, has given rise to widespread concern over its health consequences; however, there are only a few studies that show such association. Studies in India found a decline in local subjects' lung function parameters during the period of intense agricultural burning (290, 291); in contrast, I found no such association among farming villagers in Nan. These differences might be explained by different study designs; my study focused on a long-term exposure effect using self-reported history of burning exposures while the others focused on short-term changes of agricultural residue burning throughout the period of study. Importantly, in this population villagers tend to use modern fuels (bottled gas, rather than biomass) for cooking indoors. My study findings suggest that household charcoal use (mainly used for cooking outdoors) was associated with an increase in FEV_1/FVC and a small decrease in FVC. While the former may have arisen by chance or a healthy worker effect, a 0.12L decline in FVC among household charcoal users might be considered as indicative of spirometric restriction. Previous studies on the effect of biomass fuel on lung remain controversial. A number of studies in LMICs found an association of household wood smoke exposure with impaired lung function (292-294) but a recent analysis of the multinational BOLD study found no association with either airflow obstruction or spirometric restriction. (295)

I found no significant associations between the use of natural or chemical fertilizers, fumigants or rodenticides and a decline in lung function. In multivariable analysis after adjusting for several confounding factors, the findings concerning the relationships between several metrics of pesticide exposure - duration (years), intensity (hours/year), and cumulative lifetime hours - and lung function parameters were consistent. There were three main herbicides used in the study area: glyphosate, paraquat and atrazine. My study reported that high exposure to paraquat (duration ≥11 years; intensity ≥17 hours/year and cumulative hours ≥240 hours) consistently decreased FEV_1/FVC; however, the association was not statistically significant. In my previous meta-analysis on the relationship between pesticide exposure and lung function I found no significant association of paraquat exposure with FEV_1/FVC. (296) An explanation is the low volatility of paraquat; although paraquat has high toxicity to lung tissues, the risk of damage due to occupational exposure, mainly via an inhalation route, is low. (163) I found no association between glyphosate exposure and reduction in lung function. There were significant associations of atrazine exposure (duration, intensity and cumulative lifetime hours) and a higher FEV_1/FVC consistent with a lower FVC; these associations could reflect early lung restriction. There is very limited information on glyphosate and atrazine and respiratory outcomes, particularly lung function. In the US, a study of male sprayers reported significant relationships between self-reported wheeze symptoms (no measurement of lung function) and the use of glyphosate and atrazine. (170)

Organophosphate and pyrethroid were common insecticides used by villagers in Nan. I found no association of spraying organophosphate with significant changes in lung function. Longer duration (≥10 years) and cumulative hours (≥144 hours) of organophosphate use were associated with all spirometric parameters (FEV_1/FVC, FVC and FEV_1) but none of the associations was statistically significant. This is in contrast to my previous systematic review indicating a significant decline in FEV_1/FVC among those exposed to ChE-inhibiting insecticides, mainly organophosphates (296) I found weak dose-response associations of pyrethroid exposure (intensity ≥16 hours/year and cumulative hours ≥128 hours) with an increase in FEV_1/FVC but a decrease in FVC, although these were not statistically significant. This is consistent with a Canadian general population-based study suggesting an association between pyrethroid exposure and higher FEV_1/FVC and lower FVC. (193)

Nan sprayers mainly used mancozeb and pyraclostrobin as fungicides of choice. My study showed that higher mancozeb exposures (duration ≥6 years; intensity ≥18 hours/year and cumulative hours ≥120 hours) was associated with a decline in FEV_1/FVC and FVC, although these were not statistically significant. A meta-analysis by Pourhassan *et al.* (241) included two articles reporting an association of unspecified fungicide exposures with obstructive lung disease defined both by spirometry (242) and self-reported questionnaires (246); my study did not replicate these findings.

3.5.1 Strengths and limitations

This study has several strengths. First, the response rate was high (93.7%) compared with a range between 42% and 92% in previous similar cross-sectional studies included in recent systematic reviews. (134, 135) (table 1-3) This was achieved in part because in the study villages, the public health volunteer system organised by local villagers helped my research team to communicate with eligible participants before and during the fieldwork. Second, Nan farmers typically use pesticides to remove weeds and pests between March and April before sowing both rice and corn/maize in the summer from May. (168) Since this survey was performed during the crop season, the data on farming and pesticide exposures collected would be contemporary but were not validated by biomarker measurement. Third, the study questionnaire was developed by adaptation from previous large studies, such as the AHS (US) and PIPAH (UK) studies, with additions relevant to the local context so that the farming exposure data truly reflected local participants' exposures. This study has filled a gap in that most previous studies did not examine associations with specific farming activities and specific types of pesticides. (134) Moreover, it is likely to have provided complete and detailed indices of pesticide exposures as we used photos of all available pesticides taken from local district marketplaces to prompt recall. Further, the study had very few missing data due to the use of an electronic data collection system. As a result, the study complied closely to the standards of a well-designed research tool. (24) Fourth, I undertook high quality pre- and post-spirometry using the BOLD study's standards (32); the majority of previous studies identified abnormalities of respiratory outcomes only from either self-reported questionnaires or pre-bronchodilator spirometry. (134, 135) In addition, as there are diverse spirometric measurement standards across different studies especially in epidemiological settings (51, 135) and the fixed GOLD cut-point has been found potentially to misclassify airflow obstruction in older populations. (297) I used the 5% LLN GLI criterion which corrects for age, height, sex and ethnicity. (10)

My study has some limitations. As there was no previous study regarding farming exposure and respiratory health effect in the study area, I selected a cross-sectional design as an initial exploration. A limitation of a cross-sectional study is its inability to assess the direction of any potentially causal relationship. Furthermore, the self-reported information on respiratory symptoms and farming and pesticide exposure might be open to recall bias. (298) Exposure misclassification might occur (e.g., accurate duration of pesticide exposure) and, if at random, would bias the study findings towards the 'null' (false negative findings). In addition, my study only calculated dose-response relationships based on job titles and lengths and frequencies of exposures; these may not accurately reflect true 'doses' of each farming and pesticide variable. Few of the multivariable models showed statistically significant associations between farming practices or pesticide exposures and spirometric parameters. This might be due to a healthy worker effect whereby healthier farmers might have 'survived' and tend to work longer and accept riskier farming tasks. (289) In this present study, having around a hundred tests run in regression analyses will have, through multiple hypothesis testing, increased the probability of a false positive, Type I, error (299); for example, this study found a positive relationship between rearing poultry and FEV_1/FVC. Another difficulty arose from inconsistent national and provincial census data. Previously, national data indicated that farmers in Tha Wang Pha, Nan province represented about a half of the overall adult population. However, when I collected the data from the (cluster) randomly sampled villagers, I found that about 85% of the population aged between 40 and 65 actively worked on a farm. Following the additional recruitment of government employees, I computed the estimated post-hoc power of this study. Given the predicted percent of the FEV_1/FVC ratio was 100.3% (SD=4.0%) in government employees with acceptable post-bronchodilator spirometry (n=68) and 98.3% (SD=7.5%) in farming villagers (n=290), with the difference as significant at $p<0.05$, (300) the power to detect the difference in the FEV_1/FVC ratio between these two groups of participants was 0.86.

3.5.2 Suggestions

As there were some potential significant relationships between lung function and farming variables (i.e., working in a silo and household charcoal use) and pesticide exposures (i.e., paraquat, atrazine, organophosphate, pyrethroid and mancozeb) which might be limited by this study design (cross-sectional) and statistical power, I suggest future studies on short and long-term exposure to some of these farming and pesticide variables and pesticides. These might include a longitudinal study of a lung function parameters or of differences in respiratory outcomes between the farming season and off-season. To prevent exposure misclassification or recall bias, more precise or valid exposure monitoring methods such as a job-exposure matrix (JEM), personal monitoring and biomarkers and environmental monitoring are also recommended. (134, 298) Furthermore, although these study findings show no increased risk of abnormal respiratory outcomes with farming, particularly pesticide exposures, it does not necessarily mean that such exposures have no serious effects on other aspects of health. There is growing evidence examining the associations of pesticide exposures and health effects such as cancer, endocrine, immunology and nervous system abnormalities. (142, 156)

Most exposures in the farming context are preventable (51) and effective preventive measures remain crucial. During my fieldwork, I found that few farmers use complete PPE. In the crop season when I undertook the survey (May to August 2019), the temperature was in the range of 35°C to 40°C; many farmers mentioned that it was uncomfortable and too hot to wear full PPE while spraying in the open field. They tended to wear balaclavas that they thought were sufficient protection and were readily available in the local marketplace. More than a half of pesticide applicators reported that at least one part of their body was usually contaminated by pesticides while spraying. In addition, in informal interviews, some villagers mentioned that they tend to mix multiple pesticides together on the basis of their own experience or on advice from chemical company advertisements or local agrochemical retailers. Local healthcare providers should play a major role in providing proper training and education to the farming communities in terms of agricultural health and safety, alternative pest controls, reducing pesticide use and the wearing of proper PPE. (301) A good agricultural practice (113) campaign should also be implemented by the local authorities.

3.6 Conclusion

In conclusion, to the best of my knowledge, this is the first community-based study the Northern region of Thailand examining the relationship between farming factors and full, pre- and post-bronchodilator, spirometry. Chronic airflow obstruction was uncommon in the studied villages; as with other studies in developing countries, farming villagers had a low prevalence of smoking. Nan farmers had a high percentage of pesticide applicators but farming and pesticide use seem unlikely to be a major cause of respiratory problems there. However, I suggest further longitudinal studies on lung function changes with more reliable farming and pesticide exposure monitoring methods. Occupational health education for farming villagers and effective preventive measures of reducing pesticides and PPE use are also recommended.

CHAPTER 4

Occupational exposures and respiratory health effects: results from the Burden of Obstructive Lung Disease (BOLD) study

CHAPTER 4 Occupational exposures and respiratory health effects: results from the Burden of Obstructive Lung Disease (BOLD) study

4.2 Introduction

Chronic respiratory disease is a leading cause of morbidity and mortality worldwide. Globally, chronic obstructive pulmonary disease (COPD) causes at least three million deaths each year. (2) Smoking has been considered the main risk factor of chronic respiratory disease, particularly in high-income countries (HICs). However, in low- and middle-income countries (LMICs) where smoking is relatively uncommon, the prevalence of chronic respiratory disease may also be high. (14, 33)

There is a wide body of literature indicating that occupational exposures may also play an important role in respiratory disease. (27, 49) It has been estimated that about 14% of COPD cases in the population are attributable to workplace exposures. (48) Noticeably, most of the supporting evidence comes from studies performed in HICs, (47) so there is a lack of knowledge in LMICs where high-risk manufacturing remains common. (46) The Burden of Obstructive Lung Disease (BOLD) study, a large multinational population-based epidemiological survey of chronic respiratory disease, collected data on a variety of potential risk factors, including occupational exposures, for respiratory diseases across several regions of the world, including Africa and Asia. (32).

4.2 Aim and objectives

The aim of this analysis was to explore the relationship between occupational exposures and respiratory health, particularly in LMICs.

The specific objectives were to assess, from an international cross-sectional survey of a general population, the association between employment in high-risk occupations and both lung function and respiratory symptoms.

4.3 Methods

4.3.1 Study population and design

I used data from the BOLD study, which was undertaken in 41 sites in 34 countries, between 2003 and 2016 (20, 32) Fourteen sites are in HICs and 27 sites in LMICs (table 4-1), classified by their Gross National Income per capita, as estimated by the World Bank (103).

The BOLD study recruited a minimum of 600 adults, aged 40 years or older, from each site. The study protocol was approved by local ethics committees in each site and all participants provided informed consent. (32) The sampling design used by each BOLD site and response rates are shown in table 4-1.

4.3.2 Study base

The study base includes the 34,279 BOLD study participants who completed face-to-face interviews on general demographic information, respiratory symptoms and illnesses and occupational exposures, and undertook pre- and post-bronchodilator lung function testing. This analysis is based on the 28,823 participants who completed the core and occupational questionnaires and had acceptable and repeatable post-bronchodilator spirometry measurements. The interviews and lung function testing were conducted by trained and certified staff using a standardised protocol and a set of questionnaires formally translated into local languages.

Occupational exposure

Exposure to pre-defined high-risk occupations was established if participants had ever worked for at least three months in any one of them. In addition, data from a question on the longest-held job up to the time of survey were coded using the International Standard Classification of Occupations (ISCO-88) (302) and grouped into 11 high-risk occupations[3]. (303) I subsequently grouped high-risk occupations into three categories of exposure: organic dust; inorganic dust and fumes. (Table 4-2) Finally, I calculated the total number of cumulative years of exposure in each high-risk occupation or category.

Respiratory symptoms and lung function

Respiratory symptoms comprised chronic cough, chronic phlegm, wheeze and dyspnoea. Chronic cough was defined by cough on most days for at least three months per year. Similarly, chronic phlegm was defined by the production of sputum on most days for at least three months per year. Wheeze was defined by having had any whistling in the chest at any time in last 12 months; and dyspnoea through the modified Medical Research Council (MRC) dyspnoea scale as breathlessness at least when walking more slowly than people of the same age or having to stop walking due to shortness of breath. (304)

Certified technicians undertook lung function testing using an EasyOne™ (ndd Medizintechnik AG) spirometer. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured before and after the delivery of 200µg of salbutamol through a metered-dose inhaler, via a spacer. All lung function curves were centrally evaluated and scored by a certified spirometry expert based on the American Thoracic Society and European Respiratory Society (ATS/ERS) acceptability and reproducibility criteria. (279) In this analysis, I considered a decline in the post-bronchodilator ratio of FEV_1 to FVC (FEV_1/FVC) as a proxy for chronic airflow obstruction and a decline in the post-bronchodilator FVC as a proxy for restriction.

[3] 11 high-risk occupations: farming; flour, feed or grain milling; cotton or jute processing; hard-rock mining; coal mining; sandblasting; working with asbestos; chemical or plastics manufacturing; foundry or steel milling; welding; and firefighting.

Table 4-1 BOLD study sampling strategy and response rate for each site

Region	BOLD site	Year of study (middle date)	Sampling design	*N*‡	Response rate (%)†	Cooperation rate (%)††
High-income countries (14 sites)						
East Asia and Pacific (1 site)	Australia (Sydney)	2006	Stratified random sampling	585	25	33
Europe and Central Asia (9 sites)	Austria (Salzburg)	2005	Stratified random sampling	1,349	65	67
	Estonia (Tartu)	2009	Stratified random sampling	658	49	70
	Germany (Hannover)	2005	Stratified random sampling	713	59	61
	Iceland (Reykjavik)	2005	Simple random sampling	758	81	84
	The Netherlands (Maastricht)	2008	Stratified random sampling	634	48	55
	Norway (Bergen)	2005	Stratified random sampling	707	68	71
	Portugal (Lisbon)	2008	Stratified cluster sampling	745	10	27
	Sweden (Uppsala)	2007	Stratified random sampling	588	61	63
	UK (London)	2007	Stratified random sampling	697	17	37
Latin America and the Caribbean (1 site)	Trinidad and Tobago (Port of Spain)	2015	Stratified random sampling	1,387	100	100
Middle East and North Africa (1 site)	Saudi Arabia (Riyadh)	2012	Stratified random sampling	784	98	98
North America (2 sites)	Canada (Vancouver)	2005	Random digit dialling	856	26	51
	USA (Lexington, Kentucky (KY))	2006	Random digit dialling	563	14	27
Low- and middle-income countries (27 sites)						
East Asia and Pacific (4 sites)	China (Guangzhou)	2002	Stratified random sampling	602	87	87
	Malaysia (Penang)	2013	Stratified random sampling	713	59	88
	The Philippines (Manila)	2005	Stratified cluster sampling	918	58	58
	The Philippines (Nampicuan and Talugtug)	2007	Stratified cluster sampling	991	86	86
Europe and Central Asia (5 sites)	Albania (Tirana)	2013	Cluster sampling	997	82	84
	Kyrgyzstan (Chui)	2013	Cluster sampling	1,070	98	100
	Kyrgyzstan (Naryn)	2013	Cluster sampling	1,105	98	100
	Poland (Krakow)*	2005	Stratified random sampling	603	78	79
	Turkey (Adana)	2003	Stratified cluster sampling	875	82	85
Latin America and the Caribbean (1 site)	Jamaica**	2015	Cluster sampling	796	89	90

Table 4-1 *continued from previous page*

Region	BOLD site	Year of study (middle date)	Sampling design	*N*‡	Response rate (%)†	Cooperation rate (%)††
Low- and middle-income countries (27 sites)						
Middle East and North Africa (3 sites)	Algeria (Annaba)	2012	Stratified random sampling	917	95	95
	Morocco (Fes)	2010	Cluster sampling	966	98	98
	Tunisia (Sousse)	2010	Stratified cluster sampling	717	90	92
South Asia (6 sites)	India (Mumbai)	2007	Stratified cluster sampling	515	55	66
	India (Mysore)	2012	Cluster sampling	725	98	99
	India (Pune)	2009	Simple random sampling	1,388	97	97
	India (Srinagar)	2011	Stratified cluster sampling	953	87	88
	Pakistan (Karachi)	2015	Cluster sampling	1,052	63	100
	Sri Lanka**	2013	Stratified cluster sampling	1,184	85	85
Sub-Saharan Africa (8 sites)	Benin (Sèmè-Kpodji)	2014	Stratified cluster sampling	848	97	97
	Cameroon (Limbe)	2015	Stratified random sampling	433	71	71
	Malawi (Blantyre)	2013	Stratified random sampling	586	85	85
	Malawi (Chikwawa)	2015	Stratified random sampling	828	100	100
	Nigeria (Ife)	2011	Stratified cluster sampling	1,148	76	98
	South Africa (Cape Town)	2005	Cluster sampling	896	63	68
	Sudan (Gezira)	2016	Cluster sampling	834	79	79
	Sudan (Khartoum)	2013	Simple random sampling	595	93	93

‡ Participants with core questionnaire and any post-bronchodilator spirometry.
† Denominator includes people of unknown eligibility status who could not be contacted. Only known ineligible participants were excluded.
†† Denominator includes only participants who were contacted and eligible.
* Poland was classified by World Bank Gross National Income (GNI) per capita in the study year 2005 as an upper middle-income country.
** Jamaica and Sri Lanka sites were studied in multiple cities.

Table 4-2 Groups of dusty jobs and occupational data collected by the BOLD Study

High-risk occupations*	Longest held occupations (ISCO-88)**	
Organic dust		
Farming	6111	Field crop & vegetable growers
	6112	Gardeners, horticultural & nursery growers
	6121	Dairy & livestock producers
	6122	Poultry producers
	6129	Animal producers & related workers
	6130	Crop & animal producers
	6141	Forestry workers & logger
	6142	Charcoal burners & related workers
	8331	Motorised farm & forestry plant operators
	9211	Farm hands & labourers
	9212	Forestry labourers
Flour, feed or grain milling	8273	Grain & spice milling machine operators
	8274	Baked goods & cereal products machine operators
Cotton or jute processing	8261	Fibre preparing, spinning & winding machine operators
	8262	Weaving and knitting machine operators
	8263	Sewing machine operators
	8264	Bleaching, dyeing & cleaning machine operators
	8265	Fur & leather preparing machine operators†
	8269	Textile, fur & leather products machine operators†
Inorganic dust		
Hardrock mining	7111	Miners & quarry workers
	7113	Stone splitters, cutters & carvers
	9311	Mining & quarrying labourers
Coal mining	8111	Mining plant operators
	8112	Mineral ore & stone processing plant operators
	9311	Mining & quarrying labourers
Sandblasting	7143	Building structure cleaners
Working with asbestos	7124	Carpenters & joiners
	7131	Roofers
	7136	Plumbers & pipe fitters
	7137	Building & related electricians

Table 4-2 *continued from previous page*

High-risk occupations*	Longest held occupations (ISCO-88)**	
Fumes		
Chemical or plastics manufacturing	8151	Crushing, grinding & chemical mixing machinery operators
	8152	Chemical heat-treating plant operators
	8153	Chemical filtering & separating equipment operators
	8154	Chemical still & reactor operators
	8155	Petroleum & natural gas refining plant operators
	8159	Chemical processing plant operators
	8221	Pharmaceutical & toiletry products machine operators
	8223	Metal finishing, plating & coating machine operators
	8224	Photographic products machine operators
	8229	Chemical products machine operators
	8231	Rubber products machine operators
	8232	Plastic products machine operators
	8284	Metal, rubber & plastic products assemblers
Foundry or steel milling	7211	Metal moulders & coremakers
	7221	Blacksmiths, hammer smiths & forging press workers
	8121	Ore & metal furnace operators
	8122	Metal melters, casters & rolling mill operators
	8123	Metal heat-treating plant operators
	8124	Metal drawers & extruders
Welding	7211	Metal moulders & coremakers
	7212	Welders & flame cutters
	7213	Sheetmetal workers
	7214	Structural metal preparers & erectors
	7215	Riggers & cable splicers
	7231	Motor vehicle mechanics & fitters
	7232	Aircraft engine mechanics & fitters
	7233	Agricultural or industrial machinery mechanics & fitters
Firefighting	5161	Firefighters

*High-risk occupations classified by US Department of Labour Dictionary of Occupational Titles (4th Ed., Rev. 1991)[303]
**Longest held jobs classified by the International Standard Classification of Occupations (ISCO-88)[302]
†This study included only participants responding to these codes and specifying work in cotton or jute processing industries.

4.3.3 Data analysis

Participants with no occupational exposure to any high-risk jobs were used as the reference group for all analyses. To compare the main characteristics of the relationships between occupational exposure and respiratory outcomes, I used Student's t-test for continuous outcomes (FEV_1/FVC and FVC) and Pearson's chi-squared test for dichotomous outcomes respiratory symptoms. To assess these associations while adjusting for potential confounders, I used linear regression when the outcome was continuous and logistic regression when the outcome was dichotomous. All regression models were adjusted for sex, age (years) and smoking status (never smoker; <20 pack-years; and ≥20 pack-years). I used a cut-off value of 20 pack-years as a 'threshold' level of exposure sufficient to induce measurable airflow obstruction. (305) Models with FVC as the outcome were further adjusted for height (cm). Models with wheeze or dyspnoea as outcomes were also adjusted for body mass index (BMI) using the World Health Organization BMI classification (306) (underweight <18.5 kg/m^2; overweight ≥25 and <30 kg/m^2; obese class I ≥30 and <35 kg/m^2; obese class II ≥35 and <40 kg/m^2; and obese class III ≥40 kg/m^2). Exposure-response trends were evaluated using both continuous and categorical exposure variables. In order to have equivalent statistical power in each stratum, the median year of each duration of occupational exposure duration was used as a cut off value for analysing exposure-response trends.[4] In sensitivity analyses, I examined the associations of lung function measures with each of the three occupational categories by sex and by gross national income groups (HICs and LMICs). To further control for confounding by smoking, I conducted a sensitivity analysis examining associations among never-smoking participants only. All results were considered statistically significant at $p<0.05$.

Stata 15 (Stata Corp., College Station, TX, USA) was used to perform all data analyses. The association of respiratory outcomes with occupational variables was estimated for each of the 41 sites using the 'svy' command in Stata to account for sampling weights. (307) The effect size estimates for each association were then combined through random effects meta-analysis (184) using the Stata's command 'metan'. The level of between-site heterogeneity was summarised by the I^2 statistic. (185)

[4] Median year cut-off values

- Organic dusts category (20 years):
  Farming (20 years); flour, feed or grain milling (5 years); and cotton or jute processing (7 years);
- Inorganic dusts category (6 years)
  hard-rock mining (3 years); coal mining (13 years); sandblasting (3 years); and
  working with asbestos (7 years)
- Fumes category (11 years):
  chemical or plastics manufacturing (9 years); foundry or steel milling (10 years); welding (10 years); and firefighting (13 years)

4.4 Results

4.4.1 Demographic characteristics

Table 4-4 presents the sociodemographic characteristics of the participants in each of the 41 sites (n=28,823). The mean age across sites ranged from 46.7 to 63.3 years; 47.4% were male. The prevalence of never-smokers was higher in LMIC sites (67.2%) than in HIC sites (47.2%). (Table 4-3)

Occupational characteristics varied across the 41 sites. In HICs 1,742 (17.2%) participants and in LMICs 5,870 (31.4%) participants reported working in jobs with exposure to organic dust. Working in jobs with exposure to inorganic dust was reported by 636 (6.3%) HIC participants and 651 (3.5%) LMIC participants. Working in jobs with exposure to fumes was reported by 1,309 (12.9%) HIC participants and 1,043 (5.6%) LMIC participants. (table 4-3) The highest proportion of workers exposed to organic dust was in India (Pune) at 87.9%, while workers exposed to inorganic dust were most common in Poland (Krakow) at 26.4% and those exposed to fumes in the USA (Lexington, KY; 27.6%). The proportion of participants who were not exposed to any dusty or fume jobs varied across sites from 8.8% in India (Pune) to 98.2% in India (Mumbai). (table 4-5)

Table 4-7 reports the unadjusted associations of all respiratory outcomes with occupational variables. Overall, most of the occupationally exposed groups show a higher prevalence of respiratory symptoms than the unexposed group. In addition, the unexposed group had significantly higher mean values of FEV_1/FVC but lower FVC values than those exposed.

The prevalence of respiratory symptoms varied: chronic cough from 0.5% in Nigeria (Ife) to 19.5% in USA (Lexington, KY); chronic phlegm from 0.3% in both Malawi (Blantyre) and Nigeria (Ife) to 16.3% in USA (Lexington, KY); wheeze from 0.8% in India (Mysore) to 44.1% in USA (Lexington, KY); and dyspnoea from 0.0% in India (Mysore) to 30.7% in Pakistan (Karachi). The mean values of lung function also varied: FEV_1/FVC from 74.3% to 82.6%; and FVC from 2.3 L to 4.0 L as shown in table 4-6.

Table 4-3 Smoking and occupational variables classified by sex and sites' country economy

	Male				Female				All			
	HICs		LMICs		HICs		LMICs		HICs		LMICs	
Variables	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Smoking variables	(n=4,927)		(n=8,708)		(n=5,230)		(n=9,921)		(n=10,157)		(n=18,629)	
Never-smokers	1,716	34.8%	3,849	44.2%	3,082	58.9%	8,677	87.5%	4,798	47.2%	12,526	67.2%
< 20 pack-years	1,589	32.3%	2,369	27.2%	1,274	24.4%	873	8.8%	2,863	28.2%	3,242	17.4%
≥ 20 pack-years	1,622	32.9%	2,490	28.6%	874	16.7%	371	3.7%	2,496	24.6%	2,861	15.4%
Occupational variables	(n=4,927)		(n=8,728)		(n=5,230)		(n=9,938)		(n=10,157)		(n=18,666)	
Unexposed to any dusty job	3,023	61.4%	4,420	50.6%	4,280	81.8%	6,761	68.0%	7,303	71.9%	11,181	59.9%
Organic dust	1,005	20.4%	3,282	37.6%	737	14.1%	2,588	26.0%	1,742	17.2%	5,870	31.4%
Farming	921	18.7%	3,131	35.9%	647	12.4%	2,379	23.9%	1,568	15.4%	5,510	29.5%
Flour, feed or grain milling	161	3.3%	132	1.5%	66	1.3%	52	0.5%	227	2.2%	184	1.0%
Cotton or jute processing	38	0.8%	166	1.9%	93	1.8%	219	2.2%	131	1.3%	385	2.1%
Inorganic dust	579	11.8%	577	6.6%	57	1.1%	74	0.7%	636	6.3%	651	3.5%
Hard-rock mining	108	2.2%	187	2.1%	7	0.1%	33	0.3%	115	1.1%	220	1.2%
Coal mining	114	2.3%	177	2.0%	3	0.1%	19	0.2%	117	1.2%	196	1.1%
Sandblasting	107	2.2%	76	0.9%	15	0.3%	12	0.1%	122	1.2%	88	0.5%
Working with asbestos	357	7.2%	211	2.4%	36	0.7%	19	0.2%	393	3.9%	230	1.2%
Fumes	1,074	21.8%	879	10.1%	235	4.5%	164	1.7%	1,309	12.9%	1,043	5.6%
Chemical or plastics manufacturing	404	8.2%	191	2.2%	185	3.5%	112	1.1%	589	5.8%	303	1.6%
Foundry or steel milling	315	6.4%	311	3.6%	37	0.7%	37	0.4%	352	3.5%	348	1.9%
Welding	575	11.7%	441	5.1%	41	0.8%	11	0.1%	615	6.1%	452	2.4%
Firefighting	142	2.9%	52	0.6%	2	0.0%	6	0.1%	144	1.4%	58	0.3%

Table 4-4 Sociodemographic characteristics of 28,823 participants from 41 sites of the BOLD Study

BOLD sites (14 HIC sites) n=10,157	Australia (Sydney)	Austria (Salzburg)	Canada (Vancouver)	Estonia (Tartu)	Germany (Hannover)	Iceland (Reykjavik)	The Netherlands (Maastricht)	Norway (Bergen)	Portugal (Lisbon)	Sweden (Uppsala)	Saudi Arabia (Riyadh)	Trinidad & Tobago (Port of Spain)	UK (London)	USA (Lexington, KY)
n	541	1,253	827	613	680	757	590	658	711	547	700	1,097	675	508
Age (year), mean (SD)	58.9 (12.4)	57.7 (11.4)	56.0 (11.8)	60.9 (12.0)	58.1 (11.0)	56.4 (11.7)	57.5 (10.7)	59.8 (12.6)	63.3 (11.3)	58.4 (10.9)	50.3 (7.7)	54.1 (10.8)	58.2 (11.5)	56.6 (9.9)
Height (cm), mean (SD)	165.3 (9.6)	170.1 (8.9)	167.2 (10.1)	169.2 (9.8)	169.1 (9.6)	173.1 (9.4)	169.9 (9.6)	170.9 (9.5)	160.7 (9.4)	171.0 (9.7)	162.5 (8.9)	165.1 (11.3)	168.1 (9.7)	167.1 (9.9)
BMI (kg/m^2), mean (SD)	28.0 (5.2)	26.4 (4.2)	26.7 (5.2)	28.5 (5.3)	27.3 (4.6)	27.9 (4.9)	27.4 (4.5)	26.5 (4.3)	28.2 (4.6)	27.0 (4.4)	31.2 (6.0)	29.1 (10.0)	27.1 (5.0)	30.8 (6.8)
Sex (male), %	49.0	54.5	41.6	50.2	51.0	53.2	50.9	49.2	46.6	51.7	53.6	39.8	47.6	40.6
Smoking, %														
Never-smokers	46.0	44.8	43.2	52.4	38.1	33.7	32.9	35.7	59.5	39.1	73.1	72.4	35.9	35.8
< 20 pack-years	31.1	28.6	33.9	30.2	30.2	41.0	34.8	38.6	16.6	38.8	11.7	14.2	32.9	21.3
≥ 20 pack-years	22.9	26.7	23.0	31.8	31.8	25.4	32.4	25.7	23.9	22.1	15.1	13.4	31.3	42.9
Highest level of education, %														
none	0.2	0.1	0.2	0.3	0.9	0.4	0.5	0.0	6.6	0.2	12.4	1.6	0.6	0.2
primary school	3.3	10.8	1.9	2.5	0.6	8.2	12.5	7.5	40.1	12.8	21.8	37.0	4.6	2.4
middle school	23.8	6.5	5.1	9.7	9.4	16.3	26.1	11.6	21.4	11.3	16.4	8.8	2.4	15.0
high school	11.8	58.0	16.6	34.7	58.9	12.0	5.8	44.1	11.0	26.1	23.0	31.8	37.2	34.5
college	34.8	9.7	26.6	16.4	6.3	34.5	23.6	17.8	7.2	22.1	3.9	15.2	24.3	26.6
university	26.1	14.9	49.5	36.5	23.9	28.6	31.5	19.2	13.2	27.4	22.5	5.8	31.0	21.3
History of tuberculosis, %	0.7	2.7	3.1	7.5	3.7	4.8	1.4	0.3	4.6	1.1	2.0	0.0	2.5	1.8

Table 4-4 *continued from previous page*

BOLD sites (27 LMIC sites) n=18,666	Albania (Tirana)	Algeria (Annaba)	Benin (Sèmè-Kpodji)	Cameroon (Limbe)	China (Guangzhou)	India (Mumbai)	India (Mysore)	India (Pune)	India (Srinagar)	Jamaica*	Kyrgyzstan (Chui)	Kyrgyzstan (Naryn)	Malawi (Blantyre)	Malawi (Chikwawa)
n	939	890	698	331	461	439	604	845	760	578	891	859	403	448
Age (year), mean (SD)	54.6 (10.8)	52.5 (9.9)	51.5 (9.8)	51.3 (9.9)	54.0 (10.6)	51.1 (8.9)	46.7 (7.3)	52.4 (9.9)	51.4 (10.4)	55.9 (11.6)	52.4 (9.1)	52.7 (10.2)	52.2 (10.0)	53.7 (10.5)
Height (cm), mean (SD)	164.2 (8.8)	164.6 (9.7)	164.9 (8.0)	165.8 (8.0)	160.0 (8.4)	160.8 (8.4)	158.6 (6.6)	158.8 (8.9)	160.5 (8.8)	165.7 (8.8)	161.1 (8.8)	160.1 (8.7)	161.2 (8.2)	161.6 (9.1)
BMI (kg/m^2), mean (SD)	28.0 (4.7)	28.3 (5.7)	26.4 (5.6)	26.6 (5.4)	23.3 (3.3)	23.8 (4.0)	24.7 (3.8)	22.1 (3.8)	22.4 (3.6)	27.5 (6.6)	28.4 (5.7)	27.0 (5.0)	25.0 (5.4)	21.8 (3.9)
Sex (male), %	49.7	49.7	43.3	59.5	49.7	62.6	42.7	59.4	54.7	42.0	31.4	38.2	40.0	51.3
Smoking, %														
Never-smokers	62.9	61.7	98.0	77.6	56.4	90.2	89.7	87.5	45.1	62.3	70.4	75.4	86.3	69.7
< 20 pack-years	10.2	15.7	1.9	16.6	18.7	7.7	8.4	11.7	7.4	19.4	14.5	14.9	12.7	27.8
≥ 20 pack-years	26.8	22.6	0.1	5.7	25.0	2.1	1.8	0.8	47.5	18.3	15.2	9.7	1.0	2.6
Highest level of education, %														
none	2.9	17.1	48.0	6.1	6.5	11.4	6.3	37.9	74.8	1.2	0.1	3.0	7.2	36.1
primary school	9.7	24.0	27.4	50.9	22.6	9.8	12.9	19.3	6.9	21.0	2.7	2.0	51.6	54.9
middle school	27.6	24.9	14.9	18.0	26.3	12.8	16.2	18.5	5.3	31.5	16.6	27.5	28.4	7.9
high school	20.1	12.8	5.2	14.6	32.8	36.9	31.7	17.5	10.3	32.9	40.0	11.2	8.5	0.9
college	17.5	13.6	0.3	7.6	5.9	13.0	25.9	4.0	0.7	9.1	31.0	41.7	4.0	0.2
university	22.3	7.5	4.2	2.7	6.0	16.2	7.0	2.8	2.1	4.4	9.7	14.6	0.3	0.0
History of tuberculosis, %	0.8	2.3	0.4	0.9	3.5	0.9	0.0	0.8	0.4	0.7	1.2	0.7	5.5	3.9

Table 4-4 *continued from previous page*

BOLD sites (27 LMIC sites, continued) n=18,666	Malaysia (Penang)	Morocco (Fes)	Nigeria (Ife)	Pakistan (Karachi)	The Philippines (Manila)	The Philippines (Nampicuan & Talugtug)	Poland (Krakow)**	South Africa (Cape Town)	Sri Lanka*	Sudan (Gezira)	Sudan (Khartoum)	Tunisia (Sousse)	Turkey (Adana)
n	663	768	884	610	892	722	526	846	1,035	590	517	661	806
Sociodemographic variables													
Age (year), mean (SD)	54.5 (9.5)	55.1 (10.3)	55.3 (12.0)	51.6 (9.6)	52.4 (10.2)	54.1 (10.5)	55.7 (11.5)	54.2 (10.5)	53.7 (9.5)	53.7 (10.2)	54.0 (10.4)	53.0 (9.1)	53.6 (10.4)
Height (cm), mean (SD)	158.8 (8.2)	161.7 (9.1)	162.7 (7.7)	159.5 (9.6)	156.4 (8.6)	158.7 (8.6)	167.0 (8.5)	161.6 (8.9)	156.4 (8.8)	163.0 (10.8)	165.5 (9.5)	163.2 (9.4)	160.7 (9.3)
BMI (kg/m^2), mean (SD)	26.1 (4.5)	27.9 (5.3)	25.3 (5.4)	26.5 (5.5)	24.9 (4.7)	21.5 (3.9)	27.7 (4.7)	27.9 (7.5)	24.2 (4.6)	27.3 (17.1)	26.5 (6.4)	29.2 (5.6)	29.6 (5.3)
Sex (male), %	51.3	46.1	39.1	44.1	42.4	49.3	50.6	37.2	44.9	51.5	59.4	46.8	48.3
Smoking, %													
Never-smokers	74.5	72.1	88.6	74.1	46.6	46.8	38.2	32.3	78.1	74.3	76.0	57.8	45.2
< 20 pack-years	12.4	13.4	10.4	13.3	35.4	26.2	28.5	48.1	17.5	19.9	17.0	12.3	23.3
≥ 20 pack-years	13.1	14.5	1.0	12.5	17.9	27.0	33.3	19.6	4.4	5.8	7.0	30.0	31.5
Highest level of education, %													
none	0.3	56.5	19.1	42.8	4.9	3.7	2.3	3.8	2.3	36.0	20.6	15.2	37.1
primary school	34.7	19.0	28.9	14.5	5.3	12.1	35.7	40.7	24.6	28.7	35.5	36.1	41.7
middle school	53.3	9.2	11.6	12.5	31.9	39.3	3.4	31.6	52.3	10.9	11.7	8.8	7.2
high school	4.6	8.2	20.4	15.5	35.1	31.2	44.9	16.9	18.1	17.1	18.6	29.1	10.6
college	4.1	0.5	10.4	6.1	8.4	5.4	6.3	4.0	1.1	1.6	5.1	2.4	1.2
university	3.0	6.5	9.6	8.6	14.4	8.3	7.4	3.1	1.7	5.8	8.5	8.4	2.2
History of tuberculosis, %	0.0	1.7	0.5	0.5	7.5	3.6	2.7	15.1	0.8	0.5	1.0	0.0	2.5

HICs: high-income countries; LMICs low- and middle-income countries classified by the World Bank

*Jamaica and Sri Lanka sites were studied in multiple cities.; **Poland was classified by World Bank Gross National Income (GNI) per capita in the study year 2005 as an upper middle-income country.

Table 4-5 Occupational characteristics of 28,823 participants from 41 sites of the BOLD Study

BOLD sites (14 HIC sites) n=10,157	Australia (Sydney)	Austria (Salzburg)	Canada (Vancouver)	Estonia (Tartu)	Germany (Hannover)	Iceland (Reykjavik)	The Netherlands (Maastricht)	Norway (Bergen)	Portugal (Lisbon)	Sweden (Uppsala)	Saudi Arabia (Riyadh)	Trinidad & Tobago (Port of Spain)	UK (London)	USA (Lexington, KY)
n	541	1,253	827	613	680	757	590	658	711	547	700	1,097	675	508
Unexposed to any dusty job, n (%)	442 (81.7)	831 (66.3)	678 (82.0)	439 (71.6)	491 (72.2)	306 (40.4)	444 (75.3)	419 (63.7)	544 (76.5)	381 (69.7)	617 (88.1)	909 (82.9)	596 (88.3)	206 (40.6)
Organic dusts, n (%)	40 (7.4)	307 (24.5)	80 (9.7)	99 (16.2)	71 (10.4)	369 (48.8)	55 (9.3)	95 (14.4)	132 (18.6)	91 (16.6)	60 (8.6)	96 (8.8)	36 (5.3)	211 (41.5)
Farming, n (%)	31 (5.7)	288 (23.0)	66 (8.0)	91 (14.9)	51 (7.5)	350 (46.2)	38 (6.4)	64 (9.7)	120 (16.9)	86 (15.7)	60 (8.6)	92 (8.4)	27 (4.0)	204 (40.2)
Flour, feed or grain milling, n (%)	7 (1.3)	37 (3.0)	21 (2.5)	13 (2.1)	16 (2.4)	43 (5.7)	14 (2.4)	21 (3.2)	2 (0.3)	25 (4.6)	0 (0.0)	4 (0.4)	5 (0.7)	19 (3.7)
Cotton or jute processing, n (%)	6 (1.1)	19 (1.5)	4 (0.5)	4 (0.7)	13 (1.9)	18 (2.4)	7 (1.2)	24 (3.7)	12 (1.7)	5 (1.0)	0 (0.0)	1 (0.1)	7 (1.0)	11 (2.2)
Inorganic dusts, n (%)	30 (5.6)	59 (4.7)	44 (5.3)	24 (3.9)	58 (8.5)	62 (8.2)	49 (8.3)	87 (13.2)	10 (1.4)	49 (9.0)	3 (0.4)	27 (2.5)	18 (2.7)	116 (22.8)
Hard-rock mining, n (%)	4 (0.7)	16 (1.3)	14 (1.7)	5 (0.8)	6 (0.9)	27 (3.6)	4 (0.7)	9 (1.4)	2 (0.3)	8 (1.5)	0 (0.0)	2 (0.2)	3 (0.4)	15 (3.0)
Coal mining, n (%)	3 (0.6)	6 (0.5)	2 (0.2)	1 (0.2)	11 (1.6)	1 (0.1)	7 (1.2)	4 (0.6)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	78 (15.4)
Sandblasting, n (%)	1 (0.2)	15 (1.2)	8 (1.0)	4 (0.7)	14 (2.1)	13 (1.7)	2 (0.3)	20 (3.0)	1 (0.1)	11 (2.0)	3 (0.4)	6 (0.6)	5 (0.7)	19 (3.7)
Working with asbestos, n (%)	26 (4.8)	30 (2.4)	26 (3.1)	19 (3.1)	36 (5.3)	29 (3.8)	39 (6.6)	73 (11.1)	5 (0.7)	36 (6.6)	0 (0.0)	21 (1.9)	12 (1.8)	41 (8.1)
Fumes, n (%)	64 (11.8)	162 (12.9)	59 (7.3)	88 (14.4)	115 (16.9)	177 (23.4)	84 (14.2)	156 (23.7)	38 (5.3)	87 (15.9)	24 (3.4)	74 (6.8)	41 (6.1)	140 (27.6)
Chemical/plastics manufacturing, n (%)	28 (5.2)	44 (3.5)	25 (3.0)	45 (7.3)	50 (7.4)	78 (10.3)	43 (7.3)	102 (15.5)	35 (3.5)	37 (6.8)	8 (1.1)	20 (1.8)	24 (3.6)	60 (11.8)
Foundry or steel milling, n (%)	11 (2.1)	22 (4.1)	20 (2.4)	17 (1.4)	16 (2.6)	30 (4.4)	92 (12.2)	26 (4.4)	59 (9.0)	21 (3.8)	0 (0.0)	5 (0.5)	8 (1.2)	33 (6.5)
Welding, n (%)	28 (5.2)	77 (6.2)	19 (2.3)	34 (5.6)	62 (9.1)	95 (12.6)	35 (5.9)	64 (9.7)	9 (1.3)	42 (7.7)	14 (2.0)	52 (4.7)	14 (2.1)	71 (14.0)
Firefighting, n (%)	6 (1.2)	52 (4.2)	6 (0.7)	10 (1.6)	8 (1.2)	11 (1.5)	4 (0.7)	6 (0.9)	2 0.3)	9 (1.7)	2 (0.3)	2 (0.2)	2 (0.3)	24 (4.7)

Table 4-5 *continued from previous page*

BOLD sites (27 LMIC sites) n=18,666	Albania (Tirana)	Algeria (Annaba)	Benin (Sèmè-Kpodji)	Cameroon (Limbe)	China (Guangzhou)	India (Mumbai)	India (Mysore)	India (Pune)	India (Srinagar)	Jamaica*	Kyrgyzstan (Chui)	Kyrgyzstan (Naryn)	Malawi (Blantyre)	Malawi (Chikwawa)
n	939	890	698	331	461	439	604	845	760	578	891	859	403	448
Unexposed to any dusty job, n (%)	486 (51.8)	356 (40.0)	650 (93.1)	108 (32.6)	396 (85.9)	431 (98.2)	506 (83.8)	74 (8.8)	495 (65.1)	353 (61.1)	535 (60.0)	240 (27.9)	204 (50.6)	396 (88.4)
Organic dusts, n (%)	352 (37.5)	33 (3.7)	9 (1.3)	194 (58.6)	20 (4.3)	7 (1.6)	91 (15.1)	743 (87.9)	259 (34.1)	172 (29.8)	317 (35.6)	617 (71.8)	189 (46.9)	28 (6.3)
Farming, n (%)	334 (35.6)	24 (2.7)	8 (1.2)	194 (58.6)	1 (0.2)	0 (0.0)	91 (15.1)	739 (87.5)	259 (34.1)	163 (28.2)	307 (34.5)	617 (71.8)	182 (45.2)	21 (4.7)
Flour, feed or grain milling, n (%)	7 (0.8)	9 (1.0)	1 (0.1)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	12 (1.4)	0 (0.0)	1 (0.2)	8 (0.9)	1 (0.1)	4 (1.0)	0 (0.0)
Cotton or jute processing, n (%)	15 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	16 (3.5)	7 (1.6)	98 (16.2)	5 (0.6)	0 (0.0)	8 (1.4)	17 (1.9)	0 (0.0)	9 (2.2)	8 (1.8)
Inorganic dusts, n (%)	68 (7.2)	24 (2.7)	17 (2.4)	8 (2.4)	8 (1.7)	0 (0.0)	1 (0.2)	60 (7.1)	4 (0.5)	26 (4.5)	24 (2.7)	0 (0.0)	13 (3.2)	14 (3.1)
Hard-rock mining, n (%)	20 (2.1)	3 (0.3)	3 (0.4)	2 (0.6)	3 (0.7)	0 (0.0)	0 (0.0)	48 (5.7)	0 (0.0)	0 (0.0)	6 (0.7)	0 (0.0)	7 (1.7)	7 (1.6)
Coal mining, n (%)	16 (1.7)	1 (0.1)	3 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	14 (1.6)	0 (0.0)	2 (0.5)	1 (0.2)
Sandblasting, n (%)	10 (1.1)	7 (0.8)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.8)	4 (0.5)	1 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Working with asbestos, n (%)	34 (3.6)	15 (1.7)	14 (2.0)	5 (1.5)	3 (0.7)	0 (0.0)	1 (0.2)	5 (0.6)	0 (0.0)	25 (4.3)	2 (0.2)	0 (0.0)	6 (1.5)	6 (1.3)
Fumes, n (%)	57 (6.1)	194 (21.8)	10 (1.4)	4 (1.2)	42 (9.1)	1 (0.2)	3 (0.5)	61 (7.2)	3 (0.4)	44 (7.6)	42 (4.7)	3 (0.4)	10 (2.5)	5 (1.1)
Chemical/plastics manufacturing, n (%)	22 (2.3)	14 (1.6)	0 (0.0)	0 (0.0)	11 (2.4)	0 (0.0)	0 (0.0)	18 (2.1)	1 (0.1)	13 (2.3)	18 (2.0)	0 (0.0)	2 (0.5)	1 (0.2)
Foundry or steel milling, n (%)	11 (1.2)	156 (17.5)	0 (0.0)	0 (0.0)	18 (3.9)	0 (0.0)	2 (0.3)	43 (5.1)	1 (0.1)	0 (0.0)	13 (1.5)	0 (0.0)	1 (0.3)	1 (0.2)
Welding, n (%)	24 (2.6)	50 (5.6)	10 (1.4)	4 (1.2)	16 (3.5)	1 (0.2)	1 (0.2)	4 (0.5)	0 (0.0)	29 (5.0)	12 (1.4)	3 (0.4)	3 (0.7)	3 (0.7)
Firefighting, n (%)	3 (0.3)	7 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.5)	0 (0.0)	0 (0.0)	4 (1.0)	0 (0.0)

Table 4-5 *continued from previous page*

BOLD sites (27 LMIC sites, continued) n=18,666	Malaysia (Penang)	Morocco (Fes)	Nigeria (Ife)	Pakistan (Karachi)	The Philippines (Manila)	The Philippines (Nampicuan & Talugtug)	Poland (Krakow)**	South Africa (Cape Town)	Sri Lanka*	Sudan (Gezira)	Sudan (Khartoum)	Tunisia (Sousse)	Turkey (Adana)
n	663	768	884	610	892	722	526	846	1,035	590	517	661	806
Unexposed to any dusty job, n (%)	557 (84.0)	514 (66.9)	417 (47.2)	556 (91.2)	674 (75.6)	145 (20.1)	193 (36.7)	641 (75.8)	715 (69.1)	265 (44.9)	322 (62.3)	613 (92.7)	339 (42.1)
Organic dusts, n (%)	69 (10.4)	209 (27.2)	424 (49.1)	24 (3.9)	159 (17.8)	574 (79.5)	176 (33.5)	92 (10.9)	228 (22.0)	291 (49.3)	124 (24.0)	23 (3.5)	436 (54.1)
Farming, n (%)	52 (7.8)	184 (24.0)	416 (47.1)	21 (3.44)	128 (14.4)	559 (77.4)	164 (31.2)	21 (2.5)	218 (21.1)	284 (48.1)	116 (22.4)	13 (2.0)	394 (48.9)
Flour, feed or grain milling, n (%)	3 (0.5)	17 (2.2)	24 (2.7)	0 (0.0)	11 (1.2)	8 (1.1)	18 (3.4)	16 (1.9)	3 (0.3)	13 (2.2)	8 (1.2)	2 (0.3)	15 (1.9)
Cotton or jute processing, n (%)	16 (2.4)	18 (2.3)	16 (1.8)	3 (0.5)	29 (3.3)	34 (4.7)	3 (0.6)	62 (7.3)	10 (1.0)	14 (2.4)	14 (2.7)	8 (1.2)	73 (9.1)
Inorganic dusts, n (%)	9 (1.4)	19 (2.5)	46 (5.2)	10 (1.6)	13 (1.5)	17 (2.4)	139 (26.4)	44 (5.2)	21 (2.0)	31 (5.3)	11 (2.1)	6 (0.9)	18 (2.2)
Hard-rock mining, n (%)	4 (0.6)	8 (1.0)	15 (1.7)	0 (0.0)	4 (0.5)	4 (0.6)	27 (5.1)	8 (1.0)	9 (0.9)	26 (4.4)	4 (0.8)	5 (0.8)	7 (0.9)
Coal mining, n (%)	3 (0.5)	2 (0.3)	3 (0.3)	0 (0.0)	0 (0.0)	14 (1.9)	117 (22.2)	3 (0.4)	3 (0.3)	5 (0.9)	0 (0.0)	1 (0.2)	4 (0.5)
Sandblasting, n (%)	4 (0.6)	3 (0.4)	12 (1.4)	0 (0.0)	5 (0.6)	0 (0.0)	6 (1.1)	14 (1.7)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	9 (1.1)
Working with asbestos, n (%)	1 (0.2)	10 (1.3)	24 (2.7)	10 (1.6)	6 (0.7)	1 (0.1)	13 (2.5)	30 (3.6)	10 (1.0)	2 (0.3)	7 (1.4)	0 (0.0)	0 (0.0)
Fumes, n (%)	33 (5.0)	48 (6.3)	36 (4.1)	13 (2.1)	59 (6.6)	23 (3.2)	103 (19.6)	102 (12.0)	17 (1.6)	35 (5.9)	26 (5.0)	19 (2.9)	50 (6.2)
Chemical/plastics manufacturing, n (%)	20 (3.0)	15 (2.0)	8 (0.9)	4 (0.7)	19 (2.1)	7 (1.0)	29 (5.5)	54 (6.4)	5 (0.5)	12 (2.0)	11 (2.1)	4 (0.6)	15 (1.9)
Foundry or steel milling, n (%)	8 (1.2)	12 (1.6)	13 (1.5)	2 (0.3)	6 (0.7)	4 (0.6)	19 (3.6)	16 (1.9)	0 (0.0)	2 (0.3)	2 (0.4)	2 (0.3)	16 (2.0)
Welding, n (%)	7 (1.1)	25 (3.3)	22 (2.5)	8 (1.3)	33 (3.7)	13 (1.8)	46 (8.8)	47 (5.6)	12 (1.2)	23 (3.9)	14 (2.7)	14 (2.1)	28 (3.5)
Firefighting, n (%)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	6 (0.7)	0 (0.0)	20 (3.8)	1 (0.1)	0 (0.0)	2 (0.3)	3 (0.6)	1 (0.2)	4 (0.5)

HICs: high-income countries; LMICs low- and middle-income countries classified by the World Bank

*Jamaica and Sri Lanka sites were studied in multiple cities.; **Poland was classified by World Bank Gross National Income (GNI) per capita in the study year 2005 as an upper middle-income country.

Table 4-6 Respiratory outcome characteristics of 28,823 participants from 41 sites of the BOLD Study

BOLD sites (14 HIC sites) n=10,157	Australia (Sydney)	Austria (Salzburg)	Canada (Vancouver)	Estonia (Tartu)	Germany (Hannover)	Iceland (Reykjavik)	The Netherlands (Maastricht)	Norway (Bergen)	Portugal (Lisbon)	Sweden (Uppsala)	Saudi Arabia (Riyadh)	Trinidad & Tobago (Port of Spain)	UK (London)	USA (Lexington, KY)
n	541	1,253	827	613	680	757	590	658	711	547	700	1,097	675	508
Chronic cough, %	7.0	5.3	11.3	7.0	8.4	11.5	5.3	7.9	10.6	7.9	12.1	7.5	12.2	19.5
Chronic phlegm, %	5.7	7.9	10.6	9.4	8.2	9.3	3.2	10.0	13.1	11.5	12.9	3.7	11.7	16.3
Wheeze, %	25.4	13.2	26.0	22.8	18.7	24.2	16.7	23.7	27.9	25.4	40.7	11.8	34.2	44.1
Dyspnoea, %	7.0	6.6	6.9	14.0	4.0	8.4	9.5	5.4	14.6	5.1	22.0	8.7	12.1	20.0
Spirometry (post-bronchodilation)														
FEV$_1$/FVC (%), mean (SD)	76.4 (8.9)	74.3 (8.6)	76.0 (8.8)	77.2 (7.8)	76.2 (7.9)	76.1 (8.5)	74.6 (10.0)	74.9 (8.8)	75.8 (9.0)	76.3 (8.0)	82.6 (6.0)	79.6 (7.6)	75.0 (9.2)	76.2 (9.4)
FVC (L), mean (SD)	3.6 (1.0)	4.0 (1.0)	3.9 (1.1)	3.8 (1.1)	3.9 (1.0)	4.0 (1.0)	4.0 (1.1)	3.9 (1.1)	3.2 (0.9)	4.0 (1.1)	3.0 (0.8)	2.7 (0.8)	3.7 (1.0)	3.4 (1.0)
FEV$_1$ (L), mean (SD)	2.8 (0.9)	3.0 (0.8)	3.0 (0.9)	3.0 (0.9)	3.0 (0.9)	3.1 (0.9)	2.9 (0.9)	2.9 (0.9)	2.4 (0.8)	3.0 (0.9)	2.5 (0.7)	2.2 (0.7)	2.7 (0.8)	2.6 (0.9)
BOLD sites (27 LMIC sites) n=18,666	Albania (Tirana)	Algeria (Annaba)	Benin (Sèmè-Kpodji)	Cameroon (Limbe)	China (Guangzhou)	India (Mumbai)	India (Mysore)	India (Pune)	India (Srinagar)	Jamaica*	Kyrgyzstan (Chui)	Kyrgyzstan (Naryn)	Malawi (Blantyre)	Malawi (Chikwawa)
n	939	890	698	331	461	439	604	845	760	578	891	859	403	448
Chronic cough, %	8.8	3.2	2.4	0.9	5.6	2.1	1.7	1.9	5.7	4.2	10.2	10.7	2.2	1.4
Chronic phlegm, %	1.8	2.6	2.2	1.2	6.9	2.3	1.7	1.4	5.7	4.3	7.0	7.8	0.3	0.5
Wheeze, %	3.7	14.5	2.8	4.5	1.5	3.2	0.8	4.7	3.0	16.4	14.5	13.4	8.0	3.0
Dyspnoea, %	8.0	11.8	1.4	5.8	3.8	9.9	0.0	6.6	4.9	12.9	14.2	21.1	2.0	1.3
Spirometry (post-bronchodilation)														
FEV$_1$/FVC (%), mean (SD)	78.4 (9.0)	78.6 (7.3)	79.3 (7.1)	80.4 (6.9)	78.1 (7.3)	79.1 (7.5)	79.5 (7.4)	79.7 (8.1)	76.4 (10.6)	78.4 (9.2)	77.4 (8.1)	78.0 (7.2)	78.2 (7.8)	76.3 (9.2)
FVC (L), mean (SD)	3.6 (0.9)	3.4 (0.9)	2.8 (0.7)	3.0 (0.8)	3.1 (0.8)	2.8 (0.7)	2.6 (0.7)	2.7 (0.7)	3.3 (0.9)	2.9 (0.8)	3.4 (0.9)	3.5 (0.9)	3.0 (0.7)	3.1 (0.7)
FEV$_1$ (L), mean (SD)	2.8 (0.8)	2.7 (0.8)	2.2 (0.6)	2.4 (0.7)	2.4 (0.7)	2.3 (0.6)	2.1 (0.6)	2.2 (0.6)	2.5 (0.8)	2.3 (0.7)	2.6 (0.7)	2.7 (0.7)	2.3 (0.6)	2.4 (0.6)

Table 4-6 *continued from previous page*

BOLD sites (27 LMIC sites, continued) n=18,666	Malaysia (Penang)	Morocco (Fes)	Nigeria (Ife)	Pakistan (Karachi)	The Philippines (Manila)	The Philippines (Nampicuan & Talugtug)	Poland (Krakow)**	South Africa (Cape Town)	Sri Lanka*	Sudan (Gezira)	Sudan (Khartoum)	Tunisia (Sousse)	Turkey (Adana)
n	663	768	884	610	892	722	526	846	1,035	590	517	661	806
Chronic cough, %	4.5	9.8	0.5	11.4	4.5	7.1	8.2	11.5	6.6	2.6	4.1	11.4	7.8
Chronic phlegm, %	4.2	7.9	0.3	10.1	11.4	9.6	7.8	13.7	10.9	3.8	4.6	15.4	8.7
Wheeze, %	6.6	12.1	2.2	11.5	15.5	28.0	26.3	27.7	30.2	19.9	8.5	25.0	35.0
Dyspnoea, %	9.2	14.5	3.5	30.7	21.8	25.5	23.7	29.2	26.8	8.0	6.7	16.4	23.3
Spirometry (post-bronchodilation)													
FEV_1/FVC (%), mean (SD)	81.0 (6.8)	78.1 (8.3)	78.5 (8.4)	80.1 (9.7)	79.0 (8.9)	77.0 (10.6)	75.1 (9.2)	75.6 (11.1)	79.7 (8.7)	80.1 (7.2)	77.9 (8.4)	80.0 (7.5)	75.8 (8.7)
FVC (L), mean (SD)	2.7 (0.7)	3.3 (0.9)	2.7 (0.7)	2.5 (0.8)	2.6 (0.7)	2.7 (0.8)	3.8 (1.0)	2.9 (0.8)	2.3 (0.6)	3.0 (0.8)	2.9 (0.8)	3.4 (0.9)	3.4 (0.9)
FEV_1 (L), mean (SD)	2.2 (0.6)	2.6 (0.7)	2.1 (0.6)	2.0 (0.6)	2.1 (0.6)	2.1 (0.7)	2.9 (0.9)	2.2 (0.7)	1.9 (0.5)	2.4 (0.7)	2.3 (0.6)	2.7 (0.8)	2.6 (0.7)

HICs: high-income countries; LMICs low- and middle-income countries classified by the World Bank

*Jamaica and Sri Lanka sites were studied in multiple cities.; **Poland was classified by World Bank Gross National Income (GNI) per capita in the study year 2005 as an upper middle-income country.

Table 4-7 Respiratory symptoms and post-bronchodilator spirometric parameters classified by occupational variables; unadjusted associations

Occupational variables	Respiratory symptoms									Spirometry				
		Cough		Phlegm		Wheeze		Dyspnoea			FEV_1/FVC (%)		FVC (L)	
	n	Percent	p-value*	Percent	p-value*	Percent	p-value*	Percent	p-value*	*n*	Mean (SE)	p-value**	Mean (SE)	p-value**
Unexposed to any dusty job	18,455	6.72%	ref	7.07%	ref	16.21%	ref	11.19%	ref	18,484	79.28 (0.19)	ref	3.09 (0.02)	ref
Organic dusts	7,606	7.77%	**0.003**	7.35%	0.43	18.28%	**< 0.001**	14.39%	**< 0.001**	7,612	77.32 (0.32)	**< 0.001**	3.37 (0.03)	**< 0.001**
Farming	7,072	7.85%	**0.002**	7.36%	0.43	17.96%	**0.001**	14.30%	**< 0.001**	7,078	77.23 (0.32)	**< 0.001**	3.38 (0.03)	**< 0.001**
Flour, feed or grain milling	411	10.71%	**0.002**	11.68%	**< 0.001**	31.14%	**< 0.001**	12.60%	0.39	411	75.68 (1.01)	**< 0.001**	3.79 (0.08)	**< 0.001**
Cotton or jute processing	516	6.80%	0.95	6.98%	0.93	23.45%	**< 0.001**	17.46%	**< 0.001**	516	78.03 (0.98)	**< 0.001**	3.19 (0.14)	**0.02**
Inorganic dusts	1,285	10.19%	**< 0.001**	10.11%	**< 0.001**	26.85%	**< 0.001**	12.22%	0.29	1,287	76.58 (0.79)	**< 0.001**	3.92 (0.08)	**< 0.001**
Hard-rock mining	335	7.76%	0.45	10.75%	**0.01**	23.28%	**0.001**	10.14%	0.57	335	72.89 (2.62)	**< 0.001**	3.71 (0.13)	**< 0.001**
Coal mining	312	12.78%	**< 0.001**	12.78%	**< 0.001**	33.01%	**< 0.001**	19.92%	**< 0.001**	313	74.44 (0.76)	**< 0.001**	3.86 (0.06)	**< 0.001**
Sandblasting	210	10.48%	**0.03**	9.05%	0.27	29.05%	**< 0.001**	11.24%	0.99	210	71.79 (3.01)	**< 0.001**	3.70 (0.20)	**< 0.001**
Working with asbestos	622	11.92%	**< 0.001**	10.45%	**0.001**	27.49%	**< 0.001**	10.82%	0.78	623	77.53 (0.88)	**< 0.001**	4.01 (0.08)	**< 0.001**
Fumes	2,351	9.78%	**< 0.001**	9.99%	**< 0.001**	25.18%	**< 0.001**	11.63%	0.55	2,352	76.42 (0.61)	**< 0.001**	3.78 (0.05)	**< 0.001**
Chemical or plastics manufacturing	891	11.88%	**< 0.001**	11.32%	**< 0.001**	27.61%	**< 0.001**	13.03%	0.11	892	76.28 (0.79)	**< 0.001**	3.63 (0.06)	**< 0.001**
Foundry or steel milling	700	9.73%	**0.002**	10.14%	**0.002**	26.57%	**< 0.001**	11.45%	0.83	700	76.51 (1.29)	**< 0.001**	3.87 (0.18)	**< 0.001**
Welding	1,068	9.64%	**< 0.001**	10.39%	**< 0.001**	25.56%	**< 0.001**	11.40%	0.84	1,068	76.17 (1.16)	**< 0.001**	3.90 (0.05)	**< 0.001**
Firefighting	202	7.92%	0.50	11.88%	**0.008**	29.21%	**< 0.001**	8.94%	0.34	202	76.87 (1.04)	**< 0.001**	4.03 (0.08)	**< 0.001**

*Analysing differences between each occupational group and unexposed group by Pearson's chi-squared test

**Analysing differences between each occupational group and unexposed group by Student's t-test

4.4.2 Respiratory symptoms and occupational factors

Chronic cough

After adjustment for sex, age and smoking, chronic cough was positively associated with exposure to organic dust (OR=1.22, 95%CI 1.03 to 1.46), inorganic dust (OR=1.59, 95%CI 1.24 to 2.03), and fumes (OR=1.42, 95%CI 1.07 to 1.88). However, the relationship between exposure to fumes and chronic cough showed significant heterogeneity (I^2=53.6%, p<0.001). Analyses with cumulative years of exposure showed significantly positive exposure-response associations of chronic cough with working with asbestos ($OR_{<7\ years}$=2.19, 95%CI 1.47 to 3.27; $OR_{\geq 7\ years}$=4.15, 95%CI 2.29 to 7.53) and chemical or plastic manufacturing ($OR_{<9\ years}$=1.89, 95%CI 1.36 to 2.63; $OR_{\geq 9\ years}$=2.71, 95%CI 1.77 to 4.15). Being a farmer for 20 years or more was associated with chronic cough, as was work in flour, feed or grain milling, regardless of job duration. Chronic cough was positively associated with work below the median duration in coal mining; sandblasting; welding; and firefighting. There was no significant association between chronic cough and cotton or jute processing or hard-rock mining. (table 4-8)

Chronic phlegm

As shown in table 4-8, chronic phlegm was significantly associated with inorganic dusty jobs (OR=1.40, 95%CI 1.10 to 1.79). Chronic phlegm was associated with flour, feed or grain milling ($OR_{<5\ years}$=2.28, 95%CI 1.36 to 3.82; $OR_{\geq 5\ years}$=2.72, 95%CI 1.51 to 4.88), hard-rock mining ($OR_{<3\ years}$=2.05, 95%CI 1.16 to 3.62; $OR_{\geq 3\ years}$=3.91, 95%CI 1.79 to 8.58), chemical or plastic manufacturing ($OR_{<9\ years}$=1.73, 95%CI 1.23 to 2.44; $OR_{\geq 9\ years}$=2.31, 95%CI 1.62 to 3.29) and foundry or steel milling ($OR_{<10\ years}$=1.77, 95%CI 1.16 to 2.69; $OR_{\geq 10\ years}$=2.62, 95%CI 1.46 to 4.69). Working with asbestos was also associated with chronic phlegm ($OR_{\geq 7\ years}$=2.80, 95%CI 1.78 to 4.39), however, there was significant heterogeneity across sites when considering exposure duration under seven years (I^2=67.2%, p<0.001). Chronic phlegm was associated with the below-median year groups of: farming; cotton or jute procession and sandblasting. Chronic phlegm was associated with the above-median year groups of welding and firefighting. There was no significant association between chronic phlegm and coal mining.

Wheeze

Wheeze was significantly associated with exposures to organic dust (OR=1.37, 95%CI 1.21 to 1.55); inorganic dust (OR=1.92, 95%CI 1.47 to 2.52); and fumes (OR=1.42, 95%CI 1.22 to 1.66). There were exposure-response associations between wheeze and working with asbestos ($OR_{<7\ years}$=1.99, 95%CI 1.44 to 2.75; $OR_{\geq 7\ years}$=2.14, 95%CI 1.46 to 3.14), chemical and plastics manufacturing ($OR_{<9\ years}$=1.74, 95%CI 1.31 to 2.31; $OR_{\geq 9\ years}$=1.78, 95%CI 1.32 to2.41) and firefighting ($OR_{<13\ years}$=2.18, 95%CI 1.16 to 4.10; $OR_{\geq 13\ years}$=2.73, 95%CI 1.57 to 4.73). Regardless of job length, wheeze was associated with: farming; flour, feed or grain milling; hard-rock mining; coal mining and welding. Wheeze was also significantly associated with: ≥7 years of cotton or jute processing; <3 years of sandblasting and <10 years of foundry or steel milling. (table 4-8)

Dyspnoea

Dyspnoea was significantly associated with exposures to organic dust (OR=1.40, 95%CI 1.22 to 1.62); inorganic dust (OR=1.67, 95%CI 1.28 to 2.18) and fumes (OR=1.42, 95%CI 1.16 to 1.74). There were also exposure-response associations of dyspnoea with flour, feed or grain milling ($OR_{<5\ years}$=2.78, 95%CI 1.19 to 6.49; $OR_{\geq 5\ years}$=2.94, 95%CI 1.74 to 4.94), sandblasting ($OR_{<3\ years}$=4.87, 95%CI 2.02 to 11.76; $OR_{\geq 3\ years}$=6.87, 95%CI 2.63 to 17.95), work with asbestos ($OR_{<7\ years}$=2.33, 95%CI 1.22 to 4.44; $OR_{\geq 7\ years}$=2.90, 95%CI 1.73 to 4.88) and foundry or steel milling ($OR_{<10\ years}$=3.07, 95%CI 1.82 to 5.18; $OR_{\geq 10\ years}$=3.24, 95%CI 1.69 to 6.21). Regardless of job length, dyspnoea was associated with work in cotton or jute processing and in welding. Dyspnoea was significantly associated with: the above-median year of farming, hard-rock mining and chemical or plastics manufacturing; and the below-median year of coal mining. There was no significant association between dyspnoea and firefighting (table 4-8).

Table 4-8 Association of respiratory symptoms with occupational variables

Occupational variables	*n*	Cough†						Phlegm†					
		%	OR	95% CI			I^2 (%)	%	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	6.7%	ref					7.1%	ref				
Organic dusts													
ever exposed to	7,606	7.8%	**1.22***	**1.03**	to	**1.46**	**NS**	7.4%	1.16	0.99	to	1.37	NS
Farming													
< median 20 years	3,246	7.6%	1.2	0.96	to	1.50	NS	8.1%	**1.36*****	**1.15**	to	**1.61**	**NS**
≥ median 20 years	3,826	8.1%	**1.52****	**1.19**	to	**1.94**	**NS**	6.8%	1.22	0.93	to	1.60	NS
Flour, feed or grain milling													
< median 5 years	192	14.1%	**3.14*****	**1.78**	to	**5.52**	**NS**	12.5%	**2.28****	**1.36**	to	**3.82**	**NS**
≥ median 5 years	219	7.8%	**2.34****	**1.29**	to	**4.24**	**NS**	11.0%	**2.72****	**1.51**	to	**4.88**	**NS**
Cotton or jute processing													
< median 7 years	251	7.6%	1.70	0.86	to	3.37	NS	8.8%	**1.75***	**1.07**	to	**2.85**	**NS**
≥ median 7 years	265	6.0%	1.42	0.79	to	2.56	NS	5.3%	1.34	0.70	to	2.55	NS

Occupational variables	*n*	Wheeze††						Dyspnoea††					
		%	OR	95% CI			I^2 (%)	%	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	16.2%	ref					11.2%	ref				
Organic dusts													
ever exposed to	7,606	18.3%	**1.37*****	**1.21**	to	**1.55**	**NS**	14.4%	**1.40*****	**1.22**	to	**1.62**	**NS**
Farming													
< median 20 years	3,246	20.0%	**1.53*****	**1.29**	to	**1.83**	**NS**	11.2%	1.22	1.00	to	1.49	NS
≥ median 20 years	3,826	16.2%	**1.37*****	**1.16**	to	**1.63**	**NS**	16.9%	**1.83*****	**1.53**	to	**2.20**	**NS**
Flour, feed or grain milling													
< median 5 years	192	38.0%	**2.64*****	**1.78**	to	**3.92**	**NS**	12.2%	**2.78***	**1.19**	to	**6.49**	**NS**
≥ median 5 years	219	25.1%	**2.52*****	**1.72**	to	**3.70**	**NS**	12.9%	**2.94*****	**1.74**	to	**4.94**	**NS**
Cotton or jute processing													
< median 7 years	251	28.7%	2.58**	1.41	to	4.69	65.5%	17.4%	**2.43****	**1.28**	to	**4.64**	**NS**
≥ median 7 years	265	18.5%	**1.44***	**1.03**	to	**2.03**	**NS**	17.5%	**2.02***	**1.07**	to	**3.82**	**NS**

Table 4-8 *continued from previous page*

Occupational variables	*n*	Cough† %	OR	95% CI			I^2 (%)	Phlegm† %	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	6.7%	ref					7.1%	ref				
Inorganic dusts													
ever exposed to	1,285	10.2%	**1.59*** **	**1.24**	to	**2.03**	**NS**	10.1%	**1.40** **	**1.10**	to	**1.79**	**NS**
Hard-rock mining													
< median 3 years	164	7.3%	1.97	0.87	to	4.44	NS	12.2%	**2.05***	**1.16**	to	**3.62**	**NS**
≥ median 3 years	171	8.2%	1.73	0.71	to	4.21	NS	9.4%	**3.91** **	**1.79**	to	**8.58**	**NS**
Coal mining													
< median 13 years	156	12.1%	**2.82** **	**1.56**	to	**5.10**	**NS**	13.4%	1.59	0.84	to	3.04	NS
≥ median 13 years	156	13.5%	1.38	0.58	to	3.29	NS	12.2%	1.56	0.63	to	3.86	NS
Sandblasting													
< median 3 years	102	13.7%	**3.18** **	**1.49**	to	**6.82**	**NS**	12.8%	**3.49** **	**1.56**	to	**7.82**	**NS**
≥ median 3 years	108	7.4%	3.82	0.90	to	16.29	62.6%	5.6%	2.26	0.73	to	6.98	NS
Working with asbestos													
< median 7 years	312	12.5%	**2.19*** **	**1.47**	to	**3.27**	**NS**	10.9%	2.26*	1.19	to	4.30	67.2%
≥ median 7 years	310	11.3%	**4.15*** **	**2.29**	to	**7.53**	**NS**	10.0%	**2.80*** **	**1.78**	to	**4.39**	**NS**

Occupational variables	*n*	Wheeze†† %	OR	95% CI			I^2 (%)	Dyspnoea†† %	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	16.2%	ref					11.2%	ref				
Inorganic dusts													
ever exposed to	1,285	26.9%	1.92***	1.47	to	2.52	54.5%	12.2%	**1.67*** **	**1.28**	to	**2.18**	**NS**
Hard-rock mining													
< median 3 years	164	23.8%	**2.71*** **	**1.84**	to	**4.01**	**NS**	7.8%	2.02	0.81	to	5.05	NS
≥ median 3 years	171	22.8%	**2.28*** **	**1.60**	to	**3.24**	**NS**	12.3%	**2.64** **	**1.34**	to	**5.20**	**NS**
Coal mining													
< median 13 years	156	30.8%	**4.15*** **	**2.40**	to	**7.19**	**NS**	20.2%	**4.01*** **	**2.30**	to	**6.99**	**NS**
≥ median 13 years	156	35.3%	**2.52** **	**1.48**	to	**4.30**	**NS**	19.7%	1.77	0.85	to	3.69	NS
Sandblasting													
< median 3 years	102	41.2%	**2.55*** **	**1.60**	to	**4.31**	**NS**	12.6%	**4.87*** **	**2.02**	to	**11.76**	**NS**
≥ median 3 years	108	17.6%	2.00	0.84	to	4.76	NS	9.9%	**6.87*** **	**2.63**	to	**17.95**	**NS**
Working with asbestos													
< median 7 years	312	32.4%	**1.99*** **	**1.44**	to	**2.75**	**NS**	10.9%	**2.33***	**1.22**	to	**4.44**	**NS**
≥ median 7 years	310	22.6%	**2.14*** **	**1.46**	to	**3.14**	**NS**	10.7%	**2.90*** **	**1.73**	to	**4.88**	**NS**

Table 4-8 *continued from previous page*

Occupational variables		Cough†						Phlegm†					
	n	%	OR	95% CI			I^2 (%)	%	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	6.7%	ref					7.1%	ref				
Fumes													
ever exposed to	2,351	11.9%	1.42*	1.07	to	1.88	53.6%	11.3%	1.31	0.98	to	1.75	56.5%
Chemical or plastics-manufacturing													
< median 9 years	442	12.4%	**1.89*****	**1.36**	to	**2.63**	**NS**	11.3%	**1.73****	**1.23**	to	**2.44**	**NS**
≥ median 9 years	449	11.4%	**2.71*****	**1.77**	to	**4.15**	**NS**	11.4%	**2.31*****	**1.62**	to	**3.29**	**NS**
Foundry or steel milling													
< median 10 years	335	9.9%	**2.14****	**1.38**	to	**3.33**	**NS**	10.2%	**1.77****	**1.16**	to	**2.69**	**NS**
≥ median 10 years	365	9.6%	**2.09***	**1.19**	to	**3.65**	**NS**	10.1%	**2.62****	**1.46**	to	**4.69**	**NS**
Welding													
< median 10 years	506	9.9%	**1.56***	**1.08**	to	**2.25**	**NS**	11.1%	**1.41**	**0.98**	to	**2.02**	**NS**
≥ median 10 years	562	9.4%	1.42	0.95	to	2.12	NS	9.8%	**1.60****	**1.14**	to	**2.25**	**NS**
Firefighting													
< median 13 years	100	11.0%	**3.90***	**1.16**	to	**13.10**	**NS**	15.0%	2.03	0.98	to	4.22	**NS**
≥ median 13 years	102	4.9%	3.39	0.83	to	13.83	NS	8.8%	**3.46***	**1.19**	to	**10.06**	**NS**

Occupational variables		Wheeze††						Dyspnoea††					
	n	%	OR	95% CI			I^2 (%)	%	OR	95% CI			I^2 (%)
Unexposed to any dusty job	18,455	16.2%	ref					11.2%	ref				
Fumes													
ever exposed to	2,351	27.6%	**1.42*****	**1.22**	to	**1.66**	**NS**	13.0%	**1.42****	**1.16**	to	**1.74**	**NS**
Chemical or plastics-manufacturing													
< median 9 years	442	30.5%	**1.74*****	**1.31**	to	**2.31**	**NS**	14.9%	2.22*	1.182	to	4.18	56.5%
≥ median 9 years	449	24.7%	**1.78*****	**1.32**	to	**2.41**	**NS**	11.1%	**1.76***	**1.04**	to	**3.00**	**NS**
Foundry or steel milling													
< median 10 years	335	31.9%	**2.07*****	**1.54**	to	**2.78**	**NS**	11.0%	**3.07*****	**1.82**	to	**5.18**	**NS**
≥ median 10 years	365	21.6%	2.34***	1.49	to	3.67	50.4%	11.8%	**3.24*****	**1.69**	to	**6.21**	**NS**
Welding													
< median 10 years	506	28.9%	**1.65*****	**1.26**	to	**2.15**	**NS**	12.2%	**2.89*****	**1.69**	to	**4.95**	**NS**
≥ median 10 years	562	22.6%	**1.39***	**1.07**	to	**1.80**	**NS**	10.7%	**1.75****	**1.26**	to	**2.43**	**NS**
Firefighting													
< median 13 years	100	34.0%	**2.18***	**1.16**	to	**4.10**	**NS**	9.4%	2.50	0.71	to	8.83	NS
≥ median 13 years	102	24.5%	**2.73*****	**1.57**	to	**4.73**	**NS**	8.5%	1.97	0.71	to	5.43	NS

Table 4-8 *continued from previous page*

% Percents were from all 41-site participants together.

† The ORs were adjusted for sex, age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

†† The ORs were adjusted for sex, age (years) and smoking status (never, <20 pack-years, ≥20 pack-years) and the World Health Organization body mass index (BMI) classification.

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

4.4.3 Lung function and occupational factors

FEV_1/FVC

Overall, table 4-9 shows no association between FEV_1/FVC and high-risk jobs. In exposure-response analyses of 11 specific occupations using the median of cumulative exposure years, there was no evidence of exposure-response associations for FEV_1/FVC with any of the occupations. FEV_1/FVC was positively associated with fewer than 13 years of firefighting job (β=1.73, 95%CI 0.30 to 3.16), however, this association was significantly heterogeneous across sites (I^2=86.8%, p<0.001).

Table 4-10 presents sensitivity analyses of the relationship between FEV_1/FVC and categories of high-risk jobs. Among male subjects in HICs, FEV_1/FVC was negatively associated with a higher duration (≥20 years) of organic dust exposure (β=-0.34, 95%CI -0.42 to -0.27). Among men in LMICs working in organic dust jobs for ≥20 years, there was a negative association with FEV_1/FVC, however the association was not statistically significant (β=-1.01, 95%CI -2.77 to 0.75) and there was high heterogeneity across sites (I^2=92.2%, p<0.001). In men from LMICs exposed to fumes in the higher cumulative year category (≥11 years), FEV_1/FVC was significantly reduced (β=-0.29, 95%CI -0.41 to -0.16). Other occupational exposure stratifications had no significant association with FEV_1/FVC. Sensitivity analyses among never-smokers showed no significant associations between high-risk occupations and FEV_1/FVC. On stratification, there was no significant association between occupational exposure and FEV_1/FVC among women in either HICs or LMICs.

FVC

Table 4-9 shows no consistent associations between FVC and work in high-risk jobs. There were also no associations of FVC with any of the 11 occupations in exposure-response analyses. Work in foundry or steel milling above the median year of cumulative exposure (≥10 years) was negatively associated with FVC (β=-0.17, 95%CI -0.33 to -0.01); however, this association was significantly heterogeneous across sites (I^2=87.9%, p<0.001).

In sensitivity analyses, among male workers in HICs, FVC was negatively associated with a higher duration (≥20 years) of exposure to organic dust (β=-0.18, 95%CI -0.32 to -0.04; p for trend<0.05). Among women in LMICs, FVC was negatively associated with a higher duration (≥6 years) of inorganic dust exposure (β=-0.13, 95%CI -0.26 to 0.00), however, this association was significantly heterogeneous across sites (I^2=88.8%, p<0.001). Other occupational exposure stratifications showed no significant associations with FVC. In a never-smoker stratification analysis, male participants in HICs working with organic dusts for ≥20 years had significantly lower FVC (β=-0.24, 95%CI -0.47 to -0.02), but with marked heterogeneity (I^2=67.2%, p=0.001). Among never-smoking women, FVC was significantly associated with a higher duration (≥6 years) of exposure to inorganic dust in both HICs (β=0.60, 95%CI 0.53 to 0.66) and LMICs (β=-0.15, 95%CI -0.29 to 0.00), although in the latter there was significant heterogeneity across sites (I^2=87.4%, p<0.001). Never-smoking women exposed to fumes for ≥11 years in HICs had significantly higher values of FVC (β=0.13, 95%CI 0.01 to 0.26) with significant heterogeneity across sites (I^2=85.0%, p<0.001). Nevertheless, the number of never-smoking women occupationally exposed to each dusty job group was noticeably small: only five women in HICs were exposed to inorganic dust for ≥6 years; 28 women in LMICs were exposed to inorganic dust for ≥6 years and 41 women in HICs were exposed to fumes ≥11 years. (table 4-11)

All the results of the associations of ever exposed to each occupational variable (binary variables) with respiratory outcomes are shown in appendices C-1 to C-4.

Table 4-9 Association of post-bronchodilator spirometric parameters with occupational variables

Occupational variables	FEV$_1$/FVC (%)†							FVC (L)††						
	n	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Unexposed to any dusty job	18,484	79.28 (0.19)	ref					18,484	3.09 (0.02)	ref				
Organic dusts														
ever exposed to	7,612	77.32 (0.32)	-0.16	-0.44	to	0.13	NS	7,612	3.37 (0.03)	0.01	-0.01	to	0.03	NS
Farming			*p-trend=0.95*							*p-trend=0.80*				
< median 20 years	3,250	77.80 (0.51)	0.14	-0.24	to	0.52	NS	3,250	3.47 (0.03)	0.04	-0.01	to	0.09	77.9%
≥ median 20 years	3,828	76.37 (0.39)	0.04	-0.49	to	0.58	50.0%	3,828	3.25 (0.04)	0.02	-0.02	to	0.06	53.2%
Flour, feed or grain milling			*p-trend=0.84*							*p-trend=0.93*				
< median 5 years	192	77.27 (2.10)	-0.84	-3.96	to	2.29	97.0%	192	3.92 (0.22)	-0.01	-0.22	to	0.21	96.1%
≥ median 5 years	219	74.64 (1.99)	-0.27	-2.07	to	1.53	93.3%	219	3.70 (0.22)	0.02	-0.06	to	0.11	86.9%
Cotton or jute processing			*p-trend=0.82*							*p-trend=0.88*				
< median 7 years	251	80.19 (0.90)	1.02	-0.03	to	2.07	66.7%	251	3.44 (0.31)	-0.12	-0.24	to	0.00	88.7%
≥ median 7 years	265	76.57 (0.97)	0.32	-0.90	to	1.54	87.1%	265	3.02 (0.08)	0.02	-0.08	to	0.11	85.3%

Table 4-9 *continued from previous page*

Occupational variables	FEV_1/FVC (%)†					FVC (L)††				
	n	Mean (SE)	β	95% CI	I^2 (%)	*n*	Mean (SE)	β	95% CI	I^2 (%)
Unexposed to any dusty job	18,484	79.28 (0.19)	ref			18,484	3.09 (0.02)	ref		
Inorganic dusts										
ever exposed to	1,287	76.58 (0.79)	-0.19	-0.76 to 0.38	NS	1,287	3.92 (0.08)	0.02	-0.04 to 0.08	64.1%
Hard-rock mining			*p-trend=0.79*					*p-trend=0.95*		
< median 3 years	164	74.58 (4.18)	-0.68	-2.25 to 0.89	78.4%	164	3.79 (0.09)	0.03	-0.21 to 0.28	96.9%
≥ median 3 years	171	71.61 (3.30)	-0.39	-2.63 to 1.85	94.1%	171	3.64 (0.22)	0.01	-0.17 to 0.20	94.0%
Coal mining			*p-trend<0.05**					*p-trend=0.78*		
< median 13 years	157	74.63 (0.53)	0.13	-2.53 to 2.79	97.0%	157	3.79 (0.07)	-0.07	-0.21 to 0.08	90.7%
≥ median 13 years	156	74.05 (1.97)	-0.48	-3.36 to 2.41	94.3%	156	3.99 (0.12)	0.05	-0.22 to 0.32	97.1%
Sandblasting			*p-trend=0.27*					*p-trend=0.98*		
< median 3 years	102	73.20 (3.50)	0.15	-3.39 to 3.69	94.8%	102	3.86 (0.15)	-0.03	-0.22 to 0.15	92.7%
≥ median 3 years	108	70.83 (0.63)	-0.93	-6.09 to 4.22	99.4%	108	3.60 (0.05)	-0.03	-0.15 to 0.08	89.9%
Working with asbestos			*p-trend=0.72*					*p-trend=0.21*		
< median 7 years	313	75.71 (0.65)	-1.80	-4.60 to 1.01	93.6%	313	4.17 (0.07)	-0.07	-0.28 to 0.14	95.0%
≥ median 7 years	310	78.10 (1.13)	0.19	-1.25 to 1.63	74.6%	310	3.96 (0.10)	-0.05	-0.20 to 0.10	90.8%

Table 4-9 *continued from previous page*

Occupational variables	FEV$_1$/FVC (%)†							FVC (L)††						
	n	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Unexposed to any dusty job	18,484	79.28 (0.19)	ref					18,484	3.09 (0.02)	ref				
Fumes														
ever exposed to	2,352	76.42 (0.61)	0.13	-0.65	to	0.92	78.8%	2,352	3.78 (0.05)	0.00	-0.03	to	0.04	NS
Chemical or plastics manufacturing			*p-trend=0.28*							*p-trend=0.86*				
< median 9 years	443	76.29 (1.50)	0.13	-0.84	to	1.10	74.3%	443	3.68 (0.07)	0.01	-0.06	to	0.08	61.7%
≥ median 9 years	449	76.27 (1.31)	-0.65	-1.84	to	0.54	70.6%	449	3.59 (0.10)	-0.02	-0.15	to	0.11	89.7%
Foundry or steel milling			*p-trend=0.16*							*p-trend=0.06*				
< median 10 years	335	76.69 (0.96)	-0.68	-2.14	to	0.79	79.1%	335	3.90 (0.17)	0.04	-0.10	to	0.18	88.2%
≥ median 10 years	365	76.34 (2.68)	-1.70	-4.73	to	1.33	95.1%	365	3.84 (0.22)	-0.17*	-0.33	to	- 0.01	87.9%
Welding			*p-trend=0.07*							*p-trend=0.32*				
< median 10 years	506	77.45 (0.71)	-0.25	-1.79	to	1.28	87.3%	506	4.03 (0.06)	0.04	-0.27	to	0.35	98.3%
≥ median 10 years	562	75.61 (1.59)	0.93	-0.13	to	1.99	76.4%	562	3.85 (0.07)	-0.04	-0.12	to	0.04	79.2%
Firefighting			*p-trend=0.38*							*p-trend=0.39*				
< median 13 years	100	77.20 (1.24)	1.73*	0.30	to	3.16	86.8%	100	3.91 (0.10)	0.06	-0.11	to	0.23	94.0%
≥ median 13 years	102	76.38 (1.29)	-0.51	-2.89	to	1.87	96.9%	102	4.20 (0.11)	-0.05	-0.18	to	0.08	92.4%

Means (SE) were from all 41-site participants together.

† The coefficients (β) were adjusted for sex, age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

†† The coefficients (β) were adjusted for sex, age (years), height (cm) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

Table 4-10 Association of FEV_1/FVC (%) with groups of dusty jobs stratified by sex and sites' country economy

Groups of dusty jobs	Male FEV_1/FVC (%)					Female FEV_1/FVC (%)				
Organic dusts	*n*	Mean (SE)	β	95% CI	I^2 (%)	*n*	Mean (SE)	β	95% CI	I^2 (%)
All			*p-trend=0.65*					*p-trend=0.80*		
unexposed to any	7,443	78.48 (0.28)	ref			11,041	79.99 (0.17)	ref		
< median 20 years	2,005	77.48 (0.73)	0.13	-0.46 to 0.71	NS	1,626	78.90 (0.60)	0.07	-0.40 to 0.55	NS
≥ median 20 years	2,282	75.18 (0.45)	-0.95***	-1.48 to -0.42	88.9%	1,699	78.53 (0.59)	0.75	-0.26 to 1.77	86.6%
HICs			*p-trend=0.76*					*p-trend=0.83*		
unexposed to any	3,023	78.15 (0.26)	ref			4,280	78.98 (0.17)	ref		
< median 20 years	773	77.39 (0.77)	0.43	-0.38 to 1.23	NS	547	77.22 (0.44)	-0.29	-0.96 to 0.38	NS
≥ median 20 years	232	75.53 (0.87)	**-0.34*** **	**-0.42** to **-0.27**	**NS**	190	76.11 (1.19)	1.38	-1.67 to 4.42	90.1%
LMICs			*p-trend=0.56*					*p-trend=0.85*		
unexposed to any	4,420	78.56 (0.33)	ref			6,761	80.29 (0.21)	ref		
< median 20 years	1,232	77.50 (0.86)	-0.05	-0.83 to 0.74	50.5%	1,079	79.45 (0.80)	0.23	-0.40 to 0.85	NS
≥ median 20 years	2,050	75.14 (0.48)	-1.01	-2.77 to 0.75	92.2%	1,509	78.96 (0.63)	0.41	-0.57 to 1.39	83.4%

Table 4-10 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)							Female FEV_1/FVC (%)						
Organic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.53*							*p-trend=0.50*				
unexposed to any	3,144	79.78 (0.27)	ref					8,437	80.27 (0.18)	ref				
< median 20 years	819	76.81 (2.58)	0.16	-0.65	to	0.97	57.4%	1,227	79.34 (0.68)	0.07	-0.39	to	0.54	NS
≥ median 20 years	987	76.42 (0.60)	-0.36	-1.37	to	0.65	71.6%	1,471	79.20 (0.57)	0.44	-0.63	to	1.51	90.3%
HICs (never-smokers)			*p-trend=0.88*							*p-trend<0.05**				
unexposed to any	1,126	79.94 (0.33)	ref					2,551	80.20 (0.16)	ref				
< median 20 years	248	78.34 (0.65)	0.04	-1.02	to	1.09	NS	298	78.25 (0.50)	-0.35	-1.13	to	0.43	NS
≥ median 20 years	82	79.02 (1.48)	-0.69	-3.09	to	1.72	80.8%	136	76.65 (1.48)	0.17	-2.45	to	2.80	89.0%
LMICs (never-smokers)			*p-trend= 0.40*							*p-trend=0.85*				
unexposed to any	2,018	79.75 (0.32)	ref					5,886	80.29 (0.21)	ref				
< median 20 years	571	76.57 (2.95)	0.16	-0.98	to	1.30	65.3%	929	79.60 (0.85)	0.23	-0.39	to	0.85	NS
≥ median 20 years	905	76.24 (0.63)	-0.20	-1.23	to	0.84	62.6%	1,335	79.57 (0.59)	0.56	-0.61	to	1.73	90.7%

Table 4-10 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)								Female FEV_1/FVC (%)							
Inorganic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)		*n*	Mean (SE)	β	95% CI			I^2 (%)
All			*p-trend=0.73*								*p-trend=0.56*				
unexposed to any	7,443	78.48 (0.28)	ref						11,041	79.99 (0.17)	ref				
< median 6 years	550	76.48 (1.73)	0.19	-0.91	to	1.30	72.8%		77	75.10 (1.68)	0.09	-2.43	to	2.61	97.4%
≥ median 6 years	606	76.68 (1.26)	-0.04	-0.78	to	0.71	NS		54	77.50 (0.43)	0.73*	0.02	to	1.44	98.4%
HICs			*p-trend=0.13*								*p-trend=0.99*				
unexposed to any	3,023	78.15 (0.26)	ref						4,280	78.98 (0.17)	ref				
< median 6 years	344	75.47 (0.65)	0.54	-1.12	to	2.21	77.9%		43	74.85 (1.47)	-0.61	-6.56	to	5.34	97.3%
≥ median 6 years	235	75.75 (0.67)	0.91	-0.33	to	2.14	NS		14	77.59 (0.99)	-0.32	-3.29	to	2.66	96.1%
LMICs			*p-trend=0.08*								*p-trend=0.42*				
unexposed to any	4,420	78.56 (0.33)	ref						6,761	80.29 (0.21)	ref				
< median 6 years	206	77.66 (3.63)	-0.15	-1.72	to	1.42	69.8%		34	75.96 (5.56)	0.82	-0.92	to	2.57	90.1%
≥ median 6 years	371	76.97 (1.66)	-0.59	-1.31	to	0.13	NS		40	77.42 (0.07)	1.53	-1.13	to	4.20	98.9%

Table 4-10 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)							Female FEV_1/FVC (%)						
Inorganic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.11*							*p-trend<0.01***				
unexposed to any	3,144	79.78 (0.27)	ref					8,437	80.27 (0.18)	ref				
< median 6 years	154	79.96 (1.41)	1.12	-0.48	to	2.72	86.0%	43	76.82 (0.41)	-0.28	-4.27	to	3.70	99.4%
≥ median 6 years	191	82.11 (1.38)	0.97	-1.00	to	2.93	93.8%	33	77.16 (0.60)	0.62	-2.19	to	3.44	98.3%
HICs (never-smokers)			*p-trend=0.79*							*p-trend=0.25*				
unexposed to any	1,126	79.94 (0.33)	ref					2,551	80.20 (0.16)	ref				
< median 6 years	83	77.57 (1.06)	0.63	-1.92	to	3.18	85.7%	18	78.23 (0.56)	0.86	-4.94	to	6.66	99.1%
≥ median 6 years	52	78.88 (0.80)	0.21	-2.91	to	3.33	94.3%	5	81.71 (2.26)	0.04	-6.42	to	6.50	98.5%
LMICs (never-smokers)			*p-trend=0.14*							*p-trend<0.001****				
unexposed to any	2,018	79.75 (0.32)	ref					5,886	80.29 (0.21)	ref				
< median 6 years	71	81.39 (1.73)	1.47	-0.75	to	3.69	87.1%	25	72.98 (0.14)	-1.44	-6.94	to	4.05	99.5%
≥ median 6 years	139	82.69 (1.60)	1.42	-1.33	to	4.17	93.7%	28	75.61 (0.09)	0.84	-2.41	to	4.09	98.2%

Table 4-10 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)							Female FEV_1/FVC (%)						
Fumes	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All			*p-trend=0.45*							*p-trend<0.05**				
unexposed to any	7,443	78.48 (0.28)	ref					11,041	79.99 (0.17)	ref				
< median 11 years	951	77.62 (0.69)	0.22	-0.74	to	1.18	74.4%	229	77.57 (1.10)	-0.51	-1.63	to	0.60	82.4%
≥ median 11 years	1,002	75.23 (1.02)	**-0.28*****	**-0.39**	to	**-0.17**	**NS**	170	78.82 (1.87)	-0.79	-2.12	to	0.54	94.8%
HICs			*p-trend=0.73*							*p-trend=0.18*				
unexposed to any	3,023	78.15 (0.26)	ref					4,280	78.98 (0.17)	ref				
< median 11 years	595	75.44 (0.71)	-0.43	-1.13	to	0.28	NS	159	76.69 (1.03)	-0.21	-1.70	to	1.29	76.6%
≥ median 11 years	479	76.32 (0.65)	0.08	-0.70	to	0.86	NS	76	77.59 (1.49)	-0.78	-2.91	to	1.35	87.8%
LMICs			*p-trend=0.37*							*p-trend=0.10*				
unexposed to any	4,420	78.56 (0.33)	ref					6,761	80.29 (0.21)	ref				
< median 11 years	356	79.21 (1.09)	0.69	-0.63	to	2.01	75.4%	70	78.99 (2.52)	-0.82	-2.18	to	0.53	61.0%
≥ median 11 years	523	74.88 (1.31)	**-0.29*****	**-0.41**	to	**-0.16**	**NS**	94	79.43 (2.58)	-0.78	-2.75	to	1.20	96.3%

Table 4-10 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)							Female FEV_1/FVC (%)						
Fumes	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.55*							*p-trend=0.50*				
unexposed to any	3,144	79.78 (0.27)	ref					8,437	80.27 (0.18)	ref				
< median 11 years	266	79.80 (0.76)	0.48	-0.65	to	1.61	77.9%	104	78.62 (1.68)	-1.01	-2.76	to	0.74	95.8%
≥ median 11 years	311	79.66 (1.29)	0.16	-1.22	to	1.54	85.0%	114	79.48 (1.94)	0.09	-1.99	to	2.17	97.0%
HICs (never-smokers)			*p-trend=0.58*							*p-trend=0.95*				
unexposed to any	1,126	79.94 (0.33)	ref					2,551	80.20 (0.16)	ref				
< median 11 years	163	79.05 (0.68)	0.69	-0.52	to	1.89	NS	56	78.03 (1.06)	-1.47	-5.19	to	2.25	98.1%
≥ median 11 years	133	79.30 (0.87)	-0.54	-1.91	to	0.83	NS	41	80.21 (1.17)	0.43	-2.54	to	3.41	97.2%
LMICs (never-smokers)			*p-trend=0.32*							*p-trend=0.47*				
unexposed to any	2,018	79.75 (0.32)	ref					5,886	80.29 (0.21)	ref				
< median 11 years	103	80.25 (1.19)	0.34	-1.38	to	2.07	85.1%	48	79.00 (2.70)	-0.45	-1.79	to	0.89	72.3%
≥ median 11 years	178	79.78 (1.70)	0.76	-1.06	to	2.58	88.9%	73	79.24 (2.60)	-0.31	-3.69	to	3.07	97.0%

HIC: high-income countries; LMICs low- and middle-income countries classified by the World Bank; never-smokers stratification included only participants reporting 'never-smoking'.

All Means (SE) were from all 41-site participants; HIC Means (SE) were from 14 high-income site participants; LMIC Means (SE) were from 27 low- and middle-income site participants.

The coefficients (β) were adjusted for age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

Table 4-11 Association of FVC (L) with groups of dusty jobs stratified by sex and sites' country economy

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Organic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All			*p-trend=0.87*							*p-trend<0.05**				
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
< median 20 years	2,005	3.74 (0.07)	0.02	-0.02	to	0.07	NS	1,626	2.89 (0.05)	0.04	0.00	to	0.08	63.1%
≥ median 20 years	2,282	3.57 (0.05)	-0.02	-0.07	to	0.03	52.0%	1,699	2.63 (0.05)	0.03	-0.05	to	0.11	88.3%
HICs			*p-trend<0.05**							*p-trend=0.05*				
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
< median 20 years	773	4.06 (0.06)	0.01	-0.05	to	0.06	NS	547	2.89 (0.05)	0.01	-0.04	to	0.06	NS
≥ median 20 years	232	3.73 (0.07)	**-0.18***	**-0.32**	to	**-0.04**	**NS**	190	2.72 (0.08)	0.02	-0.17	to	0.21	90.7%
LMICs			*p-trend=0.14*							*p-trend=0.15*				
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
< median 20 years	1,232	3.67 (0.07)	0.03	-0.04	to	0.09	51.5%	1,079	2.89 (0.07)	0.05	-0.01	to	0.11	72.9%
≥ median 20 years	2,050	3.55 (0.05)	0.02	-0.03	to	0.07	NS	1,509	2.61 (0.06)	0.04	-0.04	to	0.13	86.6%

Table 4-11 *continued from previous page*

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Organic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.69*							*p-trend<0.05**				
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
< median 20 years	819	3.50 (0.20)	-0.06	-0.16	to	0.03	78.4%	1,227	2.87 (0.06)	0.04	0.00	to	0.09	62.4%
≥ median 20 years	987	3.46 (0.05)	0.01	-0.09	to	0.12	81.5%	1,471	2.61 (0.04)	0.05	-0.04	to	0.14	92.0%
HICs (never-smokers)			*p of trend <0.05**							*p-trend=0.13*				
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
< median 20 years	248	4.00 (0.08)	0.00	-0.10	to	0.10	NS	298	2.79 (0.06)	0.03	-0.03	to	0.09	NS
≥ median 20 years	82	3.66 (0.12)	-0.24*	-0.47	to	-0.02	67.2%	136	2.73 (0.10)	0.09	-0.12	to	0.30	91.4%
LMICs (never-smokers)			*p-trend=0.59*							*p-trend=0.17*				
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
< median 20 years	571	3.42 (0.22)	-0.08	-0.21	to	0.05	84.9%	929	2.89 (0.07)	0.05	-0.01	to	0.12	73.9%
≥ median 20 years	905	3.44 (0.06)	0.10	-0.01	to	0.20	80.5%	1,335	2.59 (0.05)	0.04	-0.06	to	0.13	92.5%

Table 4-11 *continued from previous page*

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Inorganic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All			*p-trend=0.18*							*p-trend=0.09*				
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
< median 6 years	550	4.05 (0.05)	-0.02	-0.14	to	0.10	88.4%	77	2.87 (0.08)	0.04	-0.19	to	0.27	98.6%
≥ median 6 years	606	3.95 (0.11)	0.05	-0.03	to	0.12	66.4%	54	2.80 (0.08)	0.01	-0.15	to	0.16	95.7%
HICs			*p-trend=0.34*							*p-trend=0.06*				
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
< median 6 years	344	4.38 (0.07)	-0.04	-0.19	to	0.10	80.5%	43	3.03 (0.06)	0.01	-0.38	to	0.41	98.3%
≥ median 6 years	235	4.18 (0.07)	0.05	-0.06	to	0.15	NS	14	3.17 (0.15)	0.23	-0.11	to	0.57	97.5%
LMICs			*p-trend=0.33*							*p-trend<0.001****				
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
< median 6 years	206	3.65 (0.10)	-0.01	-0.19	to	0.16	91.1%	34	2.29 (0.26)	0.07	-0.18	to	0.33	98.2%
≥ median 6 years	371	3.88 (0.14)	0.05	-0.05	to	0.14	73.5%	40	2.52 (0.09)	-0.13*	-0.26	to	0.00	88.8%

Table 4-11 *continued from previous page*

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Inorganic dusts	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.22*							*p-trend<0.05**				
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
< median 6 years	154	3.90 (0.06)	-0.03	-0.19	to	0.13	90.4%	43	2.83 (0.01)	0.04	-0.25	to	0.33	99.2%
≥ median 6 years	191	3.91 (0.17)	0.06	-0.02	to	0.14	71.3%	33	2.64 (0.02)	0.03	-0.17	to	0.24	96.6%
HICs (never-smokers)			*p-trend<0.05**							*p-trend=0.17*				
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
< median 6 years	83	4.49 (0.10)	0.01	-0.20	to	0.21	78.6%	18	2.97 (0.02)	0.02	-0.61	to	0.64	99.4%
≥ median 6 years	52	4.11 (0.12)	0.11	-0.01	to	0.23	56.8%	5	3.50 (0.03)	**0.60*****	**0.53**	to	**0.66**	**NS**
LMICs (never-smokers)			*p-trend=0.75*							*p-trend<0.001**				
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
< median 6 years	71	3.55 (0.15)	-0.05	-0.29	to	0.18	93.5%	25	2.45 (0.03)	0.08	-0.21	to	0.38	98.6%
≥ median 6 years	139	3.87 (0.20)	0.03	-0.07	to	0.13	76.8%	28	2.35 (0.03)	-0.15*	-0.29	to	0.00	87.4%

Table 4-11 *continued from previous page*

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Fumes	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All			*p-trend=0.77*							*p-trend<0.05**				
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
< median 11 years	951	3.97 (0.06)	-0.02	-0.08	to	0.05	57.6%	229	3.15 (0.06)	0.11	-0.01	to	0.23	89.7%
≥ median 11 years	1,002	3.86 (0.08)	0.00	-0.06	to	0.06	54.6%	170	2.97 (0.11)	-0.01	-0.14	to	0.11	95.2%
HICs			*p-trend=0.84*							*p-trend=0.82*				
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
< median 11 years	595	4.37 (0.05)	-0.04	-0.14	to	0.05	56.8%	159	3.17 (0.05)	0.10	-0.06	to	0.25	85.5%
≥ median 11 years	479	4.05 (0.05)	0.00	-0.07	to	0.08	NS	76	2.96 (0.09)	0.03	-0.08	to	0.15	80.5%
LMICs			*p-trend=0.98*							*p-trend<0.05**				
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
< median 11 years	356	3.67 (0.09)	0.01	-0.09	to	0.10	57.1%	70	3.13 (0.15)	0.12	-0.06	to	0.30	91.5%
≥ median 11 years	523	3.80 (0.10)	-0.01	-0.09	to	0.07	63.2%	94	2.98 (0.16)	-0.05	-0.25	to	0.15	96.4%

Table 4-11 *continued from previous page*

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Fumes	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
Never-smokers			*p-trend=0.63*							*p-trend<0.01***				
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
< median 11 years	266	3.77 (0.07)	-0.05	-0.27	to	0.18	96.0%	104	3.12 (0.11)	0.11	-0.03	to	0.24	92.8%
≥ median 11 years	311	3.70 (0.12)	-0.01	-0.10	to	0.08	75.8%	114	2.98 (0.13)	0.03	-0.11	to	0.18	95.9%
HICs (never-smokers)			*p-trend=0.45*							*p-trend<0.05**				
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
< median 11 years	163	4.31 (0.11)	-0.07	-0.21	to	0.08	63.1%	56	3.02 (0.10)	0.08	-0.11	to	0.28	92.5%
≥ median 11 years	133	4.11 (0.07)	0.06	-0.11	to	0.22	55.5%	41	2.97 (0.12)	0.13*	0.01	to	0.26	85.0%
LMICs (never-smokers)			*p-trend=0.96*							*p-trend<0.01***				
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
< median 11 years	103	3.46 (0.08)	-0.04	-0.39	to	0.30	97.5%	48	3.18 (0.15)	0.13	-0.06	to	0.31	90.9%
≥ median 11 years	178	3.56 (0.16)	-0.03	-0.14	to	0.07	80.6%	73	2.99 (0.17)	-0.08	-0.27	to	0.11	95.6%

HIC: high-income countries; LMICs low- and middle-income countries classified by the World Bank; never-smokers stratification included only participants reporting 'never-smoking'.

All Means (SE) were from all 41-site participants; HIC Means (SE) were from 14 high-income site participants; LMIC Means (SE) were from 27 low- and middle-income site participants.

The coefficients (β) were adjusted for age (years), height (cm) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

4.5 Discussion

Overall in this large, international, population-based study, after adjustment for confounders, I found positive associations between all respiratory symptoms and work in each of the pre-specified hazardous occupations. In contrast, there were no consistent associations between either the occupational exposure categories or the high-risk occupations and measures of lung function expressed by FEV_1/FVC ratio or FVC alone.

These findings are in agreement with a recent systematic review reporting significant relationships between occupational exposures to organic dusts, inorganic (mineral) dusts or fumes and both chronic bronchitis and breathlessness. (47) Specifically, participants exposed to organic dust jobs had independently higher risks of respiratory symptoms, particularly cough, wheeze and dyspnoea. The same was true for those in three specific organic dust occupations namely farming, flour, feed or grain milling and cotton or jute processing. Among flour, feed or grain millers the risks of all respiratory symptoms were doubled compared to the unexposed group, with phlegm and dyspnoea showing clear exposure-response trends. Workers in this sector tend to be exposed to complex and high level of dusts (308); a longitudinal study in Canada reported an increase in the odds of all chronic respiratory symptoms with increasing years of working in the grain industry. (309) In my analysis, participants exposed to inorganic dust jobs tended to report more of all chronic respiratory symptoms. The associations between each specific inorganic dust job with each respiratory symptom were also similar. I also highlighted that the greater the time spent working with asbestos the greater the odds of reporting more respiratory symptoms. Sandblasting exposure had the highest effect on dyspnoea. Workers in these jobs are prone to chronically inhale high level of asbestos and silica respectively, which strongly irritate both airways and have a long-term effect to lung tissues. (310) There were varying associations between the groups with exposures to fumes and respiratory symptoms, although in most cases the associations were positive. Chemical and plastic manufacturing associated with cough, phlegm and wheeze in a dose-response manner. The effects on the respiratory tract of chemical and plastic fumes are varied and depend on types and magnitudes of exposure which are typically not well-defined. (311-313) Similarly, I found that foundry or steel milling jobs were also associated with a doubling in the risk of all respiratory symptoms with exposure-response odds for phlegm and dyspnoea. During steel milling processing, metal fumes are formed when vaporized metal condenses into very small particulates. A previous extensive review on human and laboratory animal studies summarised the broad spectrum of airway irritations caused by metal fumes. (314)

I found no consistent associations between occupations and measures of lung function. Lung function was low in miners and chemical or plastic processors with long durations of exposure, compared to the unexposed group, but this difference was not statistically significant. A frequent explanation that is given for several significant associations with respiratory symptoms without significant lung function changes might be due to occupational asthma (OA). OA commonly presents with wheeze and shortness of breath without affecting post-bronchodilator spirometric measures. Substances in workplaces such as agricultural dusts, flour, chemicals and metals are able to induce OA. (315, 316) In addition, this explanation is supported by the population-based European Community Respiratory Health

Survey (ECRHS) study on OA in 12 countries reporting the association of high exposure to biological (organic) dusts, mineral (inorganic) dusts and fumes with excess OA risk. (130)

Stratified analyses by sex, gross national income and smoking status, (35) as sensitivity analyses of lung function, among male participants in HICs indicated that working in an organic dust job for at least 20 years significantly decreased FEV_1/FVC by 0.34% and significantly decreased FVC by 0.18L. While these decrements are unlikely to be clinically significant at the individual level, they may have public health implications. A similar population-based study in Denmark reported an increased prevalence of COPD, defined by the lower limit normal (LLN) of FEV_1/FVC, among workers exposed to high levels (at least 15 years) of organic dust. (62) In LMICs, I found that men working in an organic dust job for at least 20 years had a greater decrement in FEV_1/FVC, 1.01%; however, this finding was not statistically significant and there was high heterogeneity across the LMIC sites. Among never-smokers, although there were no statistically significant associations of FEV_1/FVC in men exposed to organic dust jobs for at least 20 years, in either HIC or LMIC sites, in both there were trends of diminishing FEV_1/FVC by duration of exposure. There is a potential explanation for these results. Farming is the most prevalent industry sector among organic dust jobs in both HICs and LMICs that could explain the associations found in this group. I considered the global distribution of agricultural practices as one of the potential explanations. HICs have similar commercial agriculture systems in terms of organic dust exposure; in contrast, LMICs are characterised by diverse agriculture practices which might cause the significant heterogeneity in the LMIC analyses. (112) (appendix C-5)

Nevertheless, no significant association was observed in overall or sensitivity analyses of the relationships between FEV_1/FVC and inorganic dust jobs exposure. The 20-year ECRHS cohort study also reported no significant association of inorganic (mineral) dust exposure with incident COPD using FEV_1/FVC LLN. (242) However, there were differences between the BOLD and the ECRHS studies in terms of study designs (cross-sectional vs longitudinal) and the scale of studies (the BOLD study was more diverse and had a far larger number of participants than the ECRHS). For FVC, I found the only significant association was among never-smoking women in HICs exposed to inorganic dust for at least six years for whom there was an increase in FVC of 0.6L; in contrast, among women with long durations of exposure in LMICs there was a decrease by 0.15L, although this was not statistically significant. (table 4-11) The women exposed in HICs were few (n=5) and diverse; two from the USA had worked with asbestos for 19 years and in hard-rock mining for eight years respectively; one from Estonia worked with asbestos for 24 years; one from Germany had worked in sandblasting for 11 years and the other from Norway worked with asbestos for 10 years. To check this, I reran an analysis by using the specific medians of each stratum; there was no significant change in the findings. Therefore, the increase in FVC in this group might have occurred by chance or might reflect a healthy worker effect. (240, 317)

The ECRHS study, which was conducted in 12 high-income European countries, reported an increased risk of COPD based on LLN of FEV_1/FVC among workers with occupational gas and fume exposure. (242) In this analysis of the BOLD study, I found no association between fumes and FEV_1/FVC among men exposed to fumes for at least 11 years in HICs. In contrast, there was a significant small effect on FEV_1/FVC (decreased by 0.29%) among men in LMICs. An explanation for my study's contradictory findings might be related to different standards of industrial control between HICs and LMICs, where working conditions remain poor (46). However, this association among men exposed to fumes in LMICs is not present among never smokers. Disappearance of the statically significant association among never smokers can be partly explained by a small sample size in the smoking status strata. Considering a possible modification effect from smoking, I analysed the association among a subgroup of LMIC fume workers with histories of ever- or current smoking (n=345). I found a similar non-significant association with a wide confidence interval (β=0.31, 95%CI -2.27 to 2.90; I^2=94%). Therefore, smoking is unlikely to be an effect modifier in this case. The most recent UK Biobank's publication on lifetime job-histories reported no significant increase in risk of COPD using spirometric measures among never-smokers working in high-fume jobs including chemical processing, metal processing and firefighting. (318)

4.5.1 Strengths and limitations

This study has several strengths. First, most of the previous population-based studies on occupational exposure and respiratory effects, particularly chronic lung disease, have been undertaken in western, high-income countries. (45, 47, 62, 242, 318-320) To the best of my knowledge, this is the first large population-based cross-sectional study to examine the relationship between occupational exposure and respiratory outcomes in both developed and developing countries across almost all world regions (321) This study also emphasised the difference of respiratory outcomes caused by socioeconomic factors, in this case, low- and middle-income versus high-income settings. (322) Second, BOLD has a rigorous protocol for survey and data collection. This study used a standardised protocol for collecting questionnaires and spirometry across 41 sites. Data collection was undertaken by certified technicians and trained interviewers. Moreover, the design of this population-based study focusing on occupational exposure has a value over industry-specific studies in terms of generalisability. Third, this study conducted post-bronchodilator spirometric measurements with central quality control.

Nevertheless, there are a number of limitations. This study is of cross-sectional design which makes it difficult to infer temporality and to distinguish causal relationships. Although the study is large and of community populations, it does not necessarily imply representativeness of the population in each country. In addition, there were variable response rates across sites and missing occupational history data; I included in the analyses only data from participants who completed all questionnaires with acceptable spirometry but low response rates in some sites (e.g., in the USA) might reflect selection bias. Another limitation is regarding self-reported occupational exposure and respiratory symptoms which may be influenced by recall bias. (298) Self-reporting can lead to misclassification of occupational histories and poor precision on duration (years) of exposure might introduce random error and an under- or over-estimation of the associations. Furthermore, the questionnaire did not enquire into the intensity of each occupational exposure which might limit analyses of the exposure-response relationship. (323) The use of the same cut-point for time spent in a certain occupation across all analyses (e.g., median six years for exposure-response analyses across all 'inorganic dust' analyses) might have given rise to random misclassification of exposures. Regarding sensitivity analyses of lung function, I restricted these to only three main groups of dusty jobs (organic, inorganic and fumes) instead of the specific 11 occupations in some of which there were too few subjects, particularly among female participants which I found no significant association between occupational exposure stratifications with lung function measurements. Furthermore, it is also noted that industrial workplaces are generally exposed to combinations of respiratory hazards which affects grouping of dusty jobs. For example, working on farm mainly entails exposure to organic dusts with lower exposure to inorganic dust from soils and also diesel fume. (318) Workers in steel manufacture are chiefly exposed to metal fume but also potentially to inorganic silica dust during foundry processes. (115)

4.5.2 Suggestions

I suggest a further longitudinal study on the association of occupational exposure with respiratory outcomes which would infer causal relationship. In addition, to evaluate high quality occupational exposure assessment, comprehensive data on exposure magnitude (e.g., dose, frequency and intensity) is suggested. Therefore, personal monitoring of a larger global prospective cohort and application of a job-exposure matrix (JEM), disease-specific matrices developed by experts, are recommended to reduce any bias arising from self-reported exposures. (298, 321) I also found clear evidence that occupational dusty jobs were related to chronic respiratory symptoms and with, in some cases, effects on lung function. Therefore, further laboratory studies to understand the mechanism of how workplace exposures to dusts and fumes affect lung function is also suggested. Finally, although there was no significant association of specific occupations and inorganic dust jobs with lung function measures, it does not mean that these exposures are not harmful to health, particularly chronic lung disease; and nor that occupational exposures to them should not be regulated. As most occupational hazards are preventable, interventions including respiratory protection, improving ventilation in the workplace in some industries and regulations to reduce exposures ought to be implemented. Respiratory surveillance should be encouraged among high-risk dusty job workers, especially those living in LMICs.

4.6 Conclusion

In conclusion, I found that exposure to high-risk jobs increases the risk of several chronic respiratory symptoms. In HICs men exposed for longer durations to organic dust jobs are more likely to have decreased lung function but in LMICs this does not seem to be the case. In LMICs, men working with fumes for longer durations had a small increased risk of poorer lung function. To avoid potential lung disease, I recommend preventive measures and respiratory health surveillance should be enhanced among exposed workers.

CHAPTER 5

Overall discussion

CHAPTER 5 Overall discussion

5.1 What skills did I learn?

In undertaking and completing this doctoral work, I learned many essential skills in occupational respiratory epidemiology and public health research, including how to apply biostatistics to address real-world research questions. Equally important, I have developed my skills in critical thinking and academic writing. These skills will help me achieve my goal of becoming an independent researcher in the field of occupational and environmental medicine.

At the beginning of my doctoral study, in CHAPTER 1, I identified several important gaps in the field of occupational health epidemiology, and notably that there is a significant lack of evidence on the relationship between high-risk workplace exposures, particularly farming, and chronic respiratory disease in developing countries. In CHAPTER 2, I learned how to conduct a systematic review and meta-analysis. I learned how to formulate search terms, effectively search electronic databases, register the review protocol on the international prospective register of systematic reviews (PROSPERO) and group information from the searched results. In order to conduct the meta-analysis, I learned how to program and run a script using the statistical software Stata. CHAPTER 3 made me more confident in being an epidemiologist through undertaking, from beginning to end, my own cross-sectional study in Nan, Thailand. Prior to my doctoral study in the UK, I had visited rural areas in Nan and held discussions with local healthcare providers. There was concern over chronic respiratory disease among farming villagers which I subsequently developed as my research theme. Before embarking on my cross-sectional study, I reviewed available national statistics and studies of a similar type. I learned how to design a cross-sectional study and develop a new web-based tool (questionnaire) for collecting information in the field (an agricultural questionnaire, specific to Nan villagers). I learned how to write a research protocol, write all relevant documents including a participant information sheet and consent form, obtain ethical approvals and plan all expenses for undertaking the cross-sectional survey. In early 2019, I was trained in how to design electronic forms for fieldwork data collection using Open Data Kit (ODK) and was professionally instructed in the use of portable spirometry and the interpretation of spirograms, which will be critical in my future medical career in Thailand. During the fieldwork in the Nan villages, I learned important skills in project management including time and budget management, staff recruitment and unexpected problem-solving. I learned that communication skills are a crucial part of research success: high response rates; good cooperation between the provincial executives, health research team, local healthcare providers, rural staff and villagers; and low financial expenses with high research outputs (value for money). After I came back from Thailand, I learned how to perform data management and how to conduct univariable and multivariable regression analyses to answer the research questions concerning the associations between farming exposures and respiratory health. Finally, in CHAPTER 4, to scale up my survey to a global level, I learned how to design an international research project from the example of the multinational Burden of Obstructive Lung (BOLD) Study protocol. I learned how to manage and analyse 'big data' and became confident in using Stata statistical software to analyse them. Specifically, I discovered how to address complex issues such as multiple sources of data collection including numerous occupational history data and spirometry parameter results. My experience in this BOLD data analysis made me understand the totality of research methods and prepared me to initiate my own large-scale research study once I return to be a full-time academic in Thailand.

5.2 Occupational exposures and respiratory health

Using the multinational BOLD data, I found consistent relationships between 11 high risk jobs[5] and several chronic respiratory symptoms. The greater the time spent working in most of these occupations, the greater the odds of reporting respiratory symptoms. In analyses of three main occupational categories (jobs with exposure to organic dusts, inorganic dusts or fumes) and lung function, men exposed to organic dusts for at least 20 years have a decrease in FEV_1/FVC and FVC in high-income country (HIC) sites. In low- and middle-income country (LMIC) sites where the working standards and conditions are probably poorer, men working with organic dusts, mainly in farming, for at least 20 years, had a greater decrement in FEV_1/FVC although this was not statistically significant and there was high heterogeneity across sites. In LMIC sites, men with occupational exposures to fumes for at least 11 years (the median) had a small but significant decline in FEV_1/FVC.

These findings support the belief that high-risk occupational exposures, particularly to organic dusts and fumes, are related to chronic respiratory outcomes. However, since the BOLD study was cross-sectional, it cannot assess the 'direction' of any potentially causal relationship by distinguishing the possibility that 'these high-risk jobs cause impaired lung function measures' from the alternative that 'those with poor lung function, perhaps reflective of early-life poverty, are prone to work in high-risk industries.'. This would require longitudinal data. To fill this research gap, one such study would be an occupation-specific (jobs with exposure to organic dusts or fume jobs), prospective cohort study of the relationships between these high-risk occupational exposures and respiratory outcomes, particularly lung function changes. Indeed, this could be undertaken within the population of male participants in the BOLD study.

5.3 Farming and chronic lung disease

There were a limited number of studies on chronic respiratory disease in agricultural workers in LMICs (table 1-3, CHAPTER 1) and it was, and remains, important to undertake an epidemiological study in an LMIC like Thailand where the large majority of the working population are farmers. (251) I undertook the first community-based cross-sectional study in the Northern region of Thailand and examined the relationship between both pre- and post-bronchodilator spirometry and a comprehensive set of farming factors, with a particular focus on specific pesticides most commonly used in Nan region.

The results suggested that respiratory health was not a common problem among farming villagers in the region. Chronic respiratory symptoms were uncommon and the prevalence of airflow obstruction was no higher than would be expected in a healthy population (5.5% among farming villagers). There are several explanations for these findings. First, similar to

[5] 11 high-risk occupations: farming; flour, feed or grain milling; cotton or jute processing; hard-rock mining; coal mining; sandblasting; working with asbestos; chemical or plastics manufacturing; foundry or steel milling; welding; and firefighting.

other studies in LMICs, farming villagers in Nan province had a low prevalence of smoking reflected in the low prevalence of airflow obstruction. Second, the result might be affected by a healthy worker 'survivor' bias. Those who had poor lung function or a chronic respiratory condition might have left high-risk farming jobs or tasks earlier; it is likely, however, that most of these would have remained in their home villages and so would have been included in the survey. Those with respiratory conditions may have been less likely to complete spirometry adequately, and so would not have been included in the analyses of lung function, although this appears not to have been the case (appendix B-11). In addition, crop farming on open farmland is the main type of farming in Nan province and in comparison with high-density livestock farming (324) (previously studied in most HICs e.g., in Europe) has greater ventilation and potentially low exposures to respiratory hazards.

5.4 Pesticides and effect on lung function

Due to the rapid development of intensive agriculture for commercialisation, Thailand, as well as other developing countries in South East Asia (i.e. Indonesia, Malaysia, the Philippines and Vietnam), have experienced an increasing level of agrochemical use, and is among the highest users of complex pesticide per unit area in the world. (252) In 2016, about 82,000 tons of pesticides (worth £362 million) were imported to Thailand. (168)

Among both local healthcare providers and farming villagers in Nan, pesticide exposure was the main farming-related factor they were concerned about in terms of health effects. In multivariable analyses, I found that most farming practices, particularly pesticide applications, were unlikely to be a major cause of respiratory problems there. Nonetheless, it does not mean that pesticides are not harmful to human health. There is growing evidence reporting associations of pesticide exposures with several non-respiratory health issues e.g. carcinogenic, neurological, immunological effects. (142, 156) Several popular pesticides (paraquat, glyphosate and chlorpyrifos) used in Thailand have been associated with serious health effects. Paraquat has high toxicity to lung tissue via oral ingestion, (163) and there is a wide literature on both accidental and intentional paraquat ingestion worldwide. (325-329) Glyphosate was identified by the World Health Organization's International Agency for Research on Cancer (IARC) as a probable human carcinogen (Group 2A) in 2015. (330) Exposure to glyphosate has been reported to increase the risk of non-Hodgkin's lymphoma in humans. (331) Chlorpyrifos, an organophosphate insecticide, has been found to exert multiple acute effects on the nervous system (e.g. headache, hypersecretion, muscle weakness or tremors), (332) and is also associated with neurodevelopmental effects. (333)

In 2019, the Thai government set up a National Hazardous Substances Committee (NHSC) with the aim of banning the use of three pesticides widely used in Thailand (paraquat, glyphosate and chlorpyrifos) by 2020. (334) The process has caused conflict between the government body and farmers. The NHSC issued laws to limit the use of the three chemicals with penalties of up to ten years imprisonment or fines of up to one million THB (£25,200). In response, in May 2020 the Safe Farming Confederation, on behalf of a group of farmers, filed a petition with the Central Administrative Court. They listed the necessity of continuing the use of these pesticides: the unavailability of effective agrochemical replacements; the economic costs through loss of crops; and limited scientific information. (335) Nonetheless, on 28 September 2020, the NHSC voted to keep them banned. (336) There has been widespread criticism about inconsistent local scientific support and over cost-effectiveness.

In this thesis, I examined and added some new evidence on pesticide exposures and their effects on lung function. My systematic review found no significant association of occupational paraquat exposure with decrements in lung function, a finding supported by my cross-sectional study in Nan. Another interesting herbicide was atrazine; in Nan, I found a significant association between the use of atrazine (duration, intensity and cumulative lifetime hours) and a higher FEV_1/FVC ratio consistent with a lower FVC. These associations could reflect early lung restriction. However, the finding must be interpreted cautiously, since there is very little other information on the relationship between atrazine (or other triazine group agrochemicals) and adverse respiratory health effect. (156, 159) For the most common insecticide of use, organophosphates, the meta-analysis reports a significant association between ChE-inhibiting pesticides (mainly organophosphates) and a decline in FEV_1/FVC. In contrast, I found no statistically significant association of spraying organophosphates with significant changes in lung function among Nan farmers. I did, however, find that a longer duration (≥10 years) and higher cumulative lifetime hours of spraying organophosphates (≥144 hours) were associated with small declines in all spirometric parameters (FEV_1/FVC, FVC and FEV_1) despite no statistical significance.

Both my systematic review and cross-sectional study examined the relationships between 'chronic' pesticide exposures and changes in lung function. There remains a lack of data on the acute effects of pesticide application. (appendix A-2) To address this, short-term (e.g., in-between farming seasons) panel studies among groups of farmers spraying specific pesticides (i.e. atrazine or a group of organophosphates) – perhaps even the group I identified in Nan – could be undertaken. These would require high-quality spirometry and adjustment for potentially confounding exposures such as dust from crop residues. The pesticide exposures in the Nan study were based on self-reported information, open to recall bias. This might lead to imprecision on duration (years) and hours of exposure which affect dose-response relationships. Therefore, for a short-term panel study of organophosphate exposure (e.g., chlorpyrifos), a biological monitoring technique (e.g. the use of urinary dialkylphosphate) for assessing organophosphate metabolite concentrations (187, 188)) would be advisable to assess the actual 'dose' of pesticide exposure.

5.5 The use of national sources of data

It became apparent that there were discrepancies between national sources of data and what I actually found in the field. While designing my survey, and in deciding on a sample size, I relied on national statistics that reported that 46% of Nan adult population were farmers. (253) (table 3-1, CHAPTER 3) I then selected Tha Wang Pha district where 47% of the population were reported to be farmers. At survey, however, I found that 87% of recruited villagers were farmers. (table 3-11, CHAPTER 3). Subsequently, I discussed this apparent discrepancy with a local Public Health officer and heads of the study villages. A possible explanation might be due to different jobs between age groups. The younger labourers in Nan province tend not to work on farms but immigrate to larger provinces in Thailand where they have broader employment options, many paying better than farming. I selected a group aged between 40 and 65, most of whom remain in their home villages and continue to farm.

In addition, prior to my survey, I found that Nan province had the highest death and mortality rates of chronic respiratory disease in Thailand according to national statistics from 2016. (255) As shown in table 5-1, the province had an approximately five-times higher mortality rate than overall national statistics. This seems at odds with the low prevalence of airflow obstruction in my community-based survey. To explore this discrepancy, I discussed the matter with Nan provincial hospital staff. They suggested it might be explained by lack of robustness of the provincial data where cause of death certification relies on previous doctor diagnoses. In Nan province, it is only at the provincial hospital that spirometry and access to a pulmonologist to confirm a COPD diagnosis are available; the provincial statistics are collected from not only the provincial hospital but also other 14 community (district) hospitals without such provision.

As the provincial hospital is the only one equipped to provide COPD specialised care in the province, I later asked permission to access its own statistics. Tables 5-2 to 5-4 present these for COPD outpatients, inpatients and deaths in 2016. Noticeably, more than half of all COPD cases in the hospital were aged ≥70 years old, whereas my survey recruited participants aged between 40 and 65 years. The specific age group in my study design might have been too young to detect the manifestations of COPD including chronic respiratory symptoms and lung function abnormalities.

Table 5-1 Deaths and mortality rates per 100,000 population caused by chronic respiratory disease in 2016

	*N**	mortality rate	mid-year population
Thailand	7,421	11.27	65,830,324
Public Health region 1 (Northern region)	1,930	32.96	5,855,581
Nan province	253	52.74**	479,717

*Classified by the use of ICD-10 code for bronchitis, emphysema and COPD diagnosis (J40-J44) (337)

**The highest rate in Thailand

Table 5-2 Nan provincial hospital's COPD outpatient statistics in 2016

Age group (year)	All		Male		Female	
	n	percent	*n*	percent	*n*	percent
<40	4	0.3%	4	0.6%	0	0.0%
40-49	13	1.1%	8	1.1%	5	1.1%
50-59	118	10.1%	87	12.0%	31	7.0%
60-69	275	23.5%	187	25.8%	88	19.8%
70-79	410	35.0%	231	31.8%	179	40.2%
80-89	296	25.3%	182	25.1%	114	25.6%
≥90	55	4.7%	27	3.7%	28	6.3%
total	1,171	100.0%	726	100.0%	445	100.0%

*Classified by the use of Hospital Numbers (HN) with an ICD-10 code for COPD diagnosis (J44: J44.0; J44.1; J44.8; or J44.9) (337)

Table 5-3 Nan provincial hospital's COPD inpatient statistics in 2016

Age group (year)	All		Male		Female	
	n	percent	*n*	percent	*n*	percent
<40	0	0.0%	0	0.0%	0	0.0%
40-49	3	0.5%	3	0.8%	0	0.0%
50-59	42	7.0%	31	8.6%	11	4.5%
60-69	131	21.7%	87	24.2%	44	18.1%
70-79	227	37.7%	122	33.9%	105	43.2%
80-89	162	26.9%	97	26.9%	65	26.8%
≥90	38	6.3%	20	5.6%	18	7.4%
total	603	100.0%	360	100.0%	243	100.0%

*Classified by the use of Hospital Numbers (HN) with an ICD-10 code for COPD diagnosis (J44: J44.0; J44.1; J44.8; or J44.9) (337)

Table 5-4 Nan provincial hospital's COPD death statistics in 2016

Age group (year)	All		Male		Female	
	n	percent	*n*	percent	*n*	percent
<40	0	0.0%	0	0.0%	0	0.0%
40-49	0	0.0%	0	0.0%	0	0.0%
50-59	5	6.0%	4	7.4%	1	3.3%
60-69	13	15.5%	8	14.8%	5	16.7%
70-79	37	44.1%	25	46.3%	12	40.0%
80-89	21	25.0%	13	24.1%	8	26.7%
≥90	8	9.5%	4	7.4%	4	13.3%
total	84	100.0%	54	100.0%	30	100.0%

*Classified by the use of Hospital Numbers (HN) with an ICD-10 code for COPD diagnosis (J44: J44.0; J44.1; J44.8; or J44.9) (337)

5.6 Key messages and Public Health implications

In summary, this doctoral thesis provides key findings on the relationships between occupational exposures specific to agricultural contexts and chronic respiratory outcomes. Chronic respiratory health was not a common problem among farming villagers in the region of study in northern Thailand and I found no association between farming activities and pesticide use. Findings from the multinational BOLD study show that high-risk occupational exposures, particularly to organic dusts and fumes, are related to chronic respiratory outcomes in male workers.

Reducing the burden of chronic respiratory diseases by implementing effective preventive interventions and policies are essential priorities. In my opinion, more attention should be focussed on the contribution of high-risk occupations to chronic respiratory health. Respiratory surveillance and primary preventive strategies should be enhanced among at risk workers. Cost-effective initiatives, interventions and policies on worker's respiratory health protections are crucial, particularly in LMICs.

Interestingly, I also found that more than half of pesticide applicators in Nan reported that at least a part of their body was usually in direct contact with pesticides during application. Moreover, there was generally an inadequate use of personal protective equipment (PPE) by the participating farmers (table 3-13, CHAPTER 3). Many wore a substandard face covering (balaclavas) that they thought was sufficient protection and that was sold as such in the local marketplaces. In informal interviews during my fieldwork study, some participants mentioned that it was uncomfortable and too hot to wear full PPE while spraying in the open field, where the temperature was in the range of 35°C to 40°C. This issue was similarly reported in other studies (338-340). I also found that some farming villagers mixed and applied pesticides without prior instruction. Local agrochemical sales allowed farmers to buy pesticides without controls or adequate trainings. Furthermore, there is a general lack of appropriate health education and self-protection training for farmers in Thailand as a whole. (52) On my return to Thailand, I plan to reflect the findings from this doctoral work to the local public health executives and relevant healthcare providers in Nan. There will be also an opportunity to work with these local authorities together to plan the most effective methods to inform and make local farming villagers aware of these issues (e.g., inappropriate pesticide practices and PPE use).

As pesticides remain crucial for modern agricultural practices, in my opinion, I support the view that local authorities including healthcare providers (i.e. medical doctors, nurses and public health officers) and agricultural scientific officers should play a major role in providing agricultural health and safety training for farming villagers, including pesticide exposure control measures in the farming area, eliminating or reducing pesticide use and improving the provision of adequate PPE. Moreover, occupational health surveillance among exposed workers is suggested. From my own experience, although it has been decreed by Thai Medical Council as one of the medical competency assessment criteria that medical doctors practising in Thailand must know the basic knowledge of chemical poisoning and therapy including agricultural hazards (341), there was very limited medical training on this issue when I was a medical student there. Raising diagnostic awareness among medical doctors in rural areas is a potential component in preventing farmers from occupational disease. Finally, there is a Thai metaphor for farmers as 'the backbone of the nation'. Despite this, farmers are a group of workers who attract very little attention by policy makers at national level. Farmers in Thailand are considered an informal sector and are not protected by the Labour Protection Act, (342) or covered by the Thai Social Security Scheme. (343) Policy makers and all stakeholders should consider the farming population as a top priority for preventive measures and health promotion campaigns.

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Appendices

Appendix A Pesticide exposure and lung function: a systematic review and meta-analysis

A-1 The international prospective register of systematic reviews (PROSPERO) registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

The association between pesticide exposure and lung function: a systematic review

Jate Ratanachina, Sara De Matteis, Paul Cullinan, Peter Burney

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Review question

Is there any association between pesticide exposure and lung function?

Searches

We will search MEDLINE, EMBASE, and Web of Science electronic databases through October 2017. The search strategy will include both free text and controlled vocabulary in MEDLINE and EMBASE but only free text searching in Web of Science. We will include only studies in humans. There are neither date nor language restrictions. We will consider only papers containing a title and adequate abstract information.
The search will comprise terms related to pesticide exposure and to lung function tests.
1. The first search string will cover pesticide exposures, and will include the terms: Insecticide, Herbicide, Fungicide, Rodenticide, Fumigant, Biocide, Sheep dip, Avicide, Nematicide, Nematocide, Acaricide, Molluscicide, Molluscacide, Agrochemical, and Agrichemical.
2. The outcome section will cover results from lung function tests including synonyms such as pulmonary function test and respiratory function test. This section also includes specific spirometric outcomes, oximetry, bronchial provocation test, bronchial hyperresponsiveness, and diffusing capacity of the lung for carbon monoxide. (Pulmonary function; Respiratory function; Lung function; Spirometry; Spirometer; FEV1; FVC; FEV1/FVC; Forced Expiratory Volume; Vital Capacity; Tiffeneau-Pinelli index; PEEF; PEF; MEF; Peak Expiratory flow; Peak Expiration Flow; Peak Flow Rate; Oximetry; provocation test; Bronchial challenge; Bronchial hyperresponsiveness; DLCO; TLCO; Diffusing capacity.)
The search strategy will be rerun before the commencement of the final analysis. The full search strategy can be found in the attachment.

Types of study to be included

We will include all observational (cohort, case-control and cross-sectional) and experimental studies assessing the relationship between pesticide exposure and lung function outcomes. The selected studies must include at least one control group.

Condition or domain being studied

Our search comprises two main domains: Pesticide exposure and lung function test.

Participants/population

We will include only articles reporting studies in human. There are no other exclusion criteria for the study populations.

Intervention(s), exposure(s)

We will include studies indicating pesticides as the sole or part of studied exposures. All pesticide exposure data collection techniques or measures (e.g. including questionnaire, interview, job exposure-matrix, or biomarkers) will be included. Pesticide exposure assessment may include pesticide type, time and frequency of exposure and method of application.

Comparator(s)/control

A comparable group of people not exposed to pesticides used as a control group in each reviewed study.

Main outcome(s)

Our primary focus is on lung function measurements obtained through spirometry (FEV1, FVC, Tiffeneau-Pinelli index, peak expiratory flow rate). We are interested in values of the ratio between exposed and non-exposed groups estimated by odds ratio (OR) or relative risk (RR) or by comparison of continuous measures.

* Measures of effect

FEV1, FVC, Tiffeneau-Pinelli index, peak expiratory flow rate.

Additional outcome(s)

All other measures of lung function (e.g. DLCO, blood gas analysis (oximetry), airway responsiveness, exercise test).

* Measures of effect

As specified.

Data extraction (selection and coding)

Endnote X7 will be used as our reference management software. After automatic removal of duplicate records, an additional manual screening for residual duplicates will be performed.
The extracted titles and abstracts will be screened for eligibility by one of the reviewers. A second reviewer will re-check a random sample of 200 articles independently. If there is any disagreement, a consensus between reviewers with a third reviewer's comments will be performed. The inclusion/exclusion criteria will be set for full-text screening selection. We will choose only titles and abstracts including pesticide exposure, human study, lung function test outcomes, primary data with control groups, and will exclude pesticide exposure by ingestion. We will note a reason for each rejected article. Non-English articles with English titles and abstracts are eligible and we will use accredited translation services for the full papers when necessary.

When screening full papers we will devise and pilot a data extraction template which will cover:
Study details: first author; title key title; location (city/country); year of study; year of publication;
Study design: population (e.g. general population, farmers etc.); age; sample detail; control group detail; sample sizes; type of study
Data collection: methods (e.g. questionnaire, JEMs, biomarkers, spirometry, forced expiratory flow etc.)
Exposure: pesticide group and subgroup; pesticide type; route of pesticide exposure; pesticide application; exposure assessment; duration and frequency, use of protective clothing.
Other exposure and confounders: lists of other variables
Primary outcome: spirometry and its values – FEV1, FVC and Tiffeneau-Pinelli index (pre- and post-exposure); forced expiratory flow rates and their details (pre- and post-exposure)
Other outcome: other indices of lung function test
Crude and adjusted odds ratio (OR) or relative risk (RR) ratio or comparison of continuous measures (e.g. difference in FEV1/FVC ratio).

Risk of bias (quality) assessment

We will assess the risk of bias of each study by using the Newcastle – Ottawa Quality Assessment Scale (NOS).

Strategy for data synthesis

If appropriate, we will summarize the findings by conducting meta-analysis using either odds ratio (OR), relative risk (RR) or risk differences reported as standardised effect sizes. STATA version 15 software will be used for these calculations.

Analysis of subgroups or subsets

We will analyse the following subgroups: classes and types of pesticides, intensity of pesticide exposure (heavy users/light users/bystander groups), children/adults, genders, high income vs low-to middle-income countries, types of farming and use of personal protective equipment.

Contact details for further information

Dr Jate Ratanachina
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Organisational affiliation of the review

Population Health and Occupational Disease, National Heart and Lung Institute (NHLI), Imperial College

London
http://www.imperial.ac.uk/nhli/research/respiratory/population-health-and-occupational-disease/

Review team members and their organisational affiliations
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Dr Sara De Matteis. National Heart and Lung Institute, Imperial College London, UK.
Professor Paul Cullinan. National Heart and Lung Institute, Imperial College London, UK.
Professor Peter Burney. National Heart and Lung Institute, Imperial College London, UK.

Type and method of review
Systematic review

Anticipated or actual start date
16 October 2017

Anticipated completion date
15 March 2018

Funding sources/sponsors
The Thai Red Cross Society, Bangkok, Thailand

Conflicts of interest
None known

Language
English

Country
England

Stage of review
Review Completed not published

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Occupational Exposure; Pesticides

Date of registration in PROSPERO
09 November 2017

Date of first submission
08 June 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

We have already finished and submitted this systematic review to the journal.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

27 September 2017
21 June 2019

A-2 Characteristics and pesticide exposure metrics of included studies

a) Paraquat

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Paraquat	Paraquat (n = 8)	Castro-Gutierrez, 1997	Nicaragua	LMIC	cross-sectional	134 (186)	self-reported/questionnaire	✓		n/a	n/a	age, sex, smoking
		Cha, 2012	South Korea	HIC	cross-sectional	2,508 (2,882)	self-reported/questionnaire	✓		69	53	age, gender, height, distance from the oil spill site, smoking, alcohol consumption, education, cumulative exposure of pesticides
		Dalvie, 1999	South Africa	LMIC	cross-sectional	56 (126)	JEM	✓		n/a	n/a	age, weight, smoking, alcohol, DIFFHR
		Fieten, 2009	Costa Rica	LMIC	cross-sectional	69 (134)	self-reported/questionnaire	✓		0	0	age, height, smoking
		Howard, 1981	Malaysia	LMIC	cross-sectional	27 (74)	job title	✓		100	100	none
		Lings, 1982	Denmark	HIC	cross-sectional	110 (181)	self-reported/questionnaire	✓		100	100	none
		Schenker, 2004	Costa Rica	LMIC	cross-sectional	219 (338)	self-reported/questionnaire	✓		n/a	n/a	none
		Senanayake, 1993	Sri Lanka	LMIC	cross-sectional	85 (240)	job title	✓		100	100	none

A-2 *continued from previous page*

b) ChE-inhibiting pesticides

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
ChE inhibiting pesticides	ChE inhibiting (n = 1)	Chakraborty, 2009	India	LMIC	cross-sectional	376 (724)	self-reported/questionnaire	✓		100	100	age, sex and smoking matched
	Organophosphate (n = 9)	Abu Sham'a, 2010	India	LMIC	cross-sectional	115 (195)	self-reported/questionnaire	✓		100	100	none
		Al-Shatti, 1997	Kuwait	HIC	longitudinal	38 (76)	job title	✓		n/a	n/a	none
		Fareed, 2013	India	LMIC	cross-sectional	166 (243)	self-reported/questionnaire	✓		100	79	none
		Peiris-John, 2005	Sri Lanka	LMIC	cross-sectional	47 (87)	job title	✓		n/a	n/a	none
		Raanan (1), 2016	USA	HIC	longitudinal (cohort)	279 (279)	Biological monitoring: Urine DAP metabolites	✓		all = 46.2		age, age squared, sex log height, maternal smoking, season of birth, PM2.5, breast feeding, mould at home, distance from highway, pets, food insecurity score, maternal education, season of spirometry and technician
		Sutoluk, 2011	Turkey	LMIC	cross-sectional	50 (100)	job title	✓		100	100	none
		Ye (3), 2016	Canada	HIC	cross-sectional	4,446 (4,446)	biological monitoring: urine DAP metabolites	✓		12-19 years: 51.2 20-79 years: 49.5		age, sex, height, weight, smoking

A-2 *continued from previous page*

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
ChE inhibiting pesticides	Organophosphate (n = 9)	Koilpakov, 1987, in Russian	Russia	LMIC	cross-sectional	46 (260)	job title	✓		0	0	none
		Konieczny, 1990, in Polish	Poland	HIC	cross-sectional	41 (71)	job title	✓		100	100	none
	Chlorpyrifos (n = 2)	Catherine, 2014	Egypt	LMIC	longitudinal	38 (62)	job title	✓	✓	100	100	none
		Fieten, 2009	Costa Rica	LMIC	cross-sectional	69 (134)	self-reported/questionnaire	✓		0	0	age, height, smoking
	Fenthion (n = 1)	Taylor, 1963	Nigeria	LMIC	experimental	39 (n/a)	spray zone (inside & outside)		✓	n/a	n/a	none
	Terbufos (n = 1)	Fieten, 2009	Costa Rica	LMIC	cross-sectional	69 (134)	self-reported/questionnaire	✓		0	0	age, height, smoking

A-2 *continued from previous page*

c) Pyrethroid

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Pyrethroid	Pyrethroid (n = 1)	Ye (2), 2016	Canada	HIC	cross-sectional	5,436 (5,436)	biological monitoring: urine pyrethroid metabolites	✓		6-11 years: 51 12-19 years: 51 20-79 years: 50		age, sex, ethnicity, height, weight, smoking
	Cyfluthrin (n = 1)	Satpathy, 1997	India	LMIC	experimental	5 (5)	pre- & post-exposure measurement		✓	n/a	n/a	none
	Pyrethrin (n = 2)	Kilburn (1), 2004	n/a (in flight)	n/a	cross-sectional	33 (235)	job title	✓		n/a	n/a	none
		Salome, 2000	Australia	HIC	experimental	25 (25)	test aerosol in chamber		✓	n/a	n/a	none

A-2 *continued from previous page*

d) Other specified pesticides

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Other	Insecticide (household) (n = 1)	Werner, 1969	USA	HIC	cross-sectional	93 (142)	self-reported/questionnaire	✓		n/a	n/a	none
	2,4,5-T (n = 1)	Suskind, 1984	USA	HIC	cross-sectional	203 (365)* *with spirometry	job title	✓		100	100	smoking
	DDT/DDE (n = 1)	Ye (1), 2015	Canada	HIC	cross-sectional	1,696 (1,696)	biological monitoring: plasma *p,p'*-DDT & *p,p'*-DDE	✓		all = 49		age, sex, ethnicity, height, smoking, energy expenditure
	Sulphur (n = 1)	Raanan (2), 2017	USA	HIC	longitudinal (cohort)	237 (279)* *with spirometry	geographic information system: distribution of Sulphur used	✓		all = 46		age, sex, height, smoking (maternal), season of birth, PM2.5, breast feed, mould, highway, pets, urine DAP, food insecurity, runny nose, season of spirometry, technician
	TCPN (n = 1)	Huang, 1995	Japan	HIC	cross-sectional	28 (46)	job title	✓		68	80	none
	B.thuringiensis (Biological pesticide) (n = 1)	Pearce, 2002	Canada	HIC	experimental	29 (118)	spray zone (inside & outside)		✓	64	64	none

A-2 *continued from previous page*

e) Unspecified pesticides

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Unspecified pesticides	Pesticide (n = 28)	Abu Sham'a, 2010	Palestine*	LMIC	cross-sectional	250 (250)	self-reported/questionnaire	✓		100	100	none
		Abu Sham'a, 2015	Palestine*	LMIC	longitudinal	115 (195)	self-reported/questionnaire		✓	n/a	n/a	none
		Alif, 2017	Australia	HIC	cross-sectional (nested in a cohort study)	1,335 (1,335)	JEM	✓		n/a	n/a	sex, smoking, pack-year, socioeconomic status (child- & adulthood), asthma (child- & adulthood)
		De Jong (1), 2014	the Netherlands	HIC	longitudinal (cohort 1965-90)	460 (2,527)	JEM	✓		all = 53		age, sex, smoking (pack-year), lung function at the 1st measurement, VGDF
		De Jong (2), 2014	the Netherlands	HIC	longitudinal (cohort)	LifeLines= 11,851 (11,851); Vlagtwedde-Vlaardingen= 2,364 (2,364)	JEM	✓		all = 41		age, sex, height, weight, smoking, pack-year
		Desalu, 2014	Nigeria	LMIC	cross-sectional	228 (228)	self-reported/ questionnaire	✓		96	n/a	none
		Fieten, 2009	Costa Rica	LMIC	cross-sectional	69 (134)	self-reported/ questionnaire	✓		0	0	none

A-2 *continued from previous page*

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Unspecified pesticides	Pesticide (n = 28)	Garcia-Garcia, 2016	Spain	HIC	longitudinal (cohort) *spirometry only in low exposure period	189 (280)	self-reported/questionnaire	✓		56	19	age, sex, BMI
		Hansell, 2014	New Zealand	HIC	cross-sectional	2,978 (2,978)	self-reported/questionnaire	✓		61	26	age, age squared, sex, smoking (pack-year), ethnicity, deprivation
		Hernandez, 2008	Spain	HIC	cross-sectional	89 (114)	self-reported/questionnaire	✓		70	16	none
		Janzen, 2017	Canada	HIC	cross-sectional	940 (1,552)	self-reported/questionnaire	✓		61	26	none
		Jones, 2003	USA	HIC	longitudinal (case-control)	P1: 135 (253); P2: 39 (99)	job title	✓	✓	91	85	none
		Kesavachandran (1), 2009	India	LMIC	cross-sectional	14 (32)	job title	✓		100	100	none
		Kesavachandran (2), 2006	India	LMIC	cross-sectional	34 (51)	job title	✓		100	100	none
		Kossmann, 1997	Poland	HIC	cross-sectional	54 (91)	job title	✓		69	59	none
		Mathew, 2015	India	LMIC	cross-sectional	70 (136)	job title	✓		n/a	n/a	none

A-2 *continued from previous page*

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Unspecified pesticides	Pesticide (n = 28)	Mekonnen (1), 2002	Ethiopia	LMIC	cross-sectional	151 (231)	job title	✓		100	100	none
		Mekonnen (2), 2004	Ethiopia	LMIC	cross-sectional	102 (171)	job title	✓		100	100	none
		Negatu, 2016	Ethiopia	LMIC	cross-sectional (second survey)	807 (1,491)	self-reported/questionnaire	✓		69	63	none
		Pathak, 2013	India	LMIC	experimental	18 (27)	pre- & post-exposure measurement		✓	100	n/a	none
		Rastogi, 1989	India	LMIC	cross-sectional	489 (697)	job title	✓		n/a	n/a	none
		Salameh, 2005	Lebanon	LMIC	cross-sectional	19 (62)	job title	✓		100	77	age, sex, weight, BMI, smoking
		Zubair, 2017	Pakistan	LMIC	cross-sectional	122 (517)	self-reported/questionnaire	✓		n/a	n/a	none
		Zuskin (1), 2008	Croatia	LMIC	cross-sectional	82 (82)	job title	✓		63	58	none
		Barczyk, 2006, in Polish	Poland	HIC	cross-sectional	114 (180)	job title	✓		68	82	none

A-2 *continued from previous page*

Group of Exposure	Exposure of study	Author, year of publication	Country	Income	Study design	Sample size (study (total))	Pesticide exposure metrics (data collection technique)	Long-term exposure	Short-term exposure	Sex (%male)		Final model adjustment
										Exposed group	Unexposed group	
Unspecified pesticides	Pesticide (n = 28)	Barthel, 1977, in German	Germany	HIC	Longitudinal: 4 surveys (exposed & non-exposed periods)	70 (100)	job title	✓		100	100	none
		Lehnigk, 1985, in German	Germany	HIC	cross-sectional	69 (324)	job title	✓		100	100	none
		Thiele, 1973, in German	Germany	HIC	longitudinal (before/during/after exposure period)	30 (80)	job title	✓		100	100	none

* Palestine: West Bank and Gaza GNI per capita = £2,141.50 in 2016 (https://data.worldbank.org/indicator/NY.GNP.PCAP.CD?locations=PS)

n/a: not applicable; JEM: job exposure matrix

A-3 Extraction form

1. Article	1.1. Author			
	1.2. Year of study/ year of publication			
2. Background	2.1. Study design			
	2.2. Country			
	2.3. Population			
	2.4. Study design			
	2.5. Total number		2.6. Response rate	
	2.7. Population	2.7.1. Study group		
		2.7.2. n =		
		2.7.3. Age (Mean (SD) or Median (range))		
		2.7.4. Sex (%Male)		
		2.7.5. Reference group	2.7.5.1. Internal	
			2.7.5.2. External	
		2.7.6. n =		
		2.7.7. Age (Mean (SD) or Median (range))		
		2.7.8. Sex (%Male)		
3. Method (Exposure)	3.1. Self-reported			
	3.2. Air monitoring			
	3.3. Job Exposure Matrix			
	3.4. Biomarkers			
	3.5. Others			
	3.6. Agent (Pesticide)			
	3.7. Pesticide Exposure Metric			
4. Method (Outcome)	4.1. Symptoms Questionnaire			
	4.2. Spirometry			
	4.3. Peak flow			
	4.4. Others			
5. Co-exposure /Confounding factors	5.4. Co-exposure	5.4.1. Farm types		
		5.4.2. Biomass Fuel		
		5.4.3. Dust		
		5.4.4. Animal exposure		
		5.4.5. Others		
	5.5. Confounding factors	5.5.1. Age		
		5.5.2. Sex		
		5.5.3. Smoking		
		5.5.4. Alcohol		
		5.5.5. Height		
		5.5.6. Weight		
		5.5.7. Body Mass Index		
		5.5.8. Education		
		5.5.9. Race/Ethnicity		
		5.5.10. Others		
6. Statistical Analysis	6.1. Statistical Model			
	6.2. Data presentation			
7. Outcome (Pulmonary function test result)	7.1. Spirometry	7.1.1. FVC (study)		
		7.1.2. FVC (control)		
		7.1.3. p-value/95%CI		
		7.1.4. FEV_1 (study)		
		7.1.5. FEV_1 (control)		
		7.1.6. p-value/95%CI		
		7.1.7. FEV_1/FVC (study)		
		7.1.8. FEV_1/FVC (control)		
		7.1.9. p-value/95%CI		
	7.2. PEFR (study)		7.4. p-value/ 95%CI	
	7.3. PEFR (control)			
	7.5. Other PFTs (study)		7.7. p-value/ 95%CI	
	7.6. Other PFTs (control)			
8. Main finding				
9. Bias (NOS scale)	9.1. Selection	9.1.1. (1)		
		9.1.2. (2)		
		9.1.3. (3)		
	9.2. Compatibility	9.2.1. (1a)		
		9.2.2. (1b)		
	9.3. Outcome/ Exposure	9.3.1. (1)		
		9.3.2. (2)		
		9.3.3. (3)		

Appendix B Farming and respiratory health: a cross-sectional study in Nan province, Thailand

B-1 Ethical approval (ICREC reference: 19IC5098)

Imperial College London

Imperial College Research Ethics Committee
Imperial College London
Room 221
Medical School Building
St Marys Campus
London
W2 1PG
Tel: +44 (0)207 594 1872

researchethicscommittee@imperial.ac.uk

30 April 2019

Dear Professor Peter Burney

Study Title: The association of agricultural exposures with chronic lung disease among farmers in Nan province, Thailand: a cross-sectional study

ICREC reference: 19IC5098

The above study was reviewed by the Imperial College Research Ethics Committee on 09/04/19.

Following the review of your documents, the Joint Research Compliance Office would like to grant full approval of the study on the basis that once written permission has been received by each school it is then submitted to the JRCO. Once the permission letter has been acknowledged, research may be conducted within that school.

Documents

The documents reviewed were:

- ICREC application form (v1.1 05/03/19)
- Protocol (v1.1 05/03/19)
- 190102 Chula IRB Information Sheet (AF 09-05/5.0)
- 190102 Chula IRB Consent (AF 09-05/5.0)
- Thai Ethics Approval IRB766_61
- Questionnaires 1-7
- JRCO Sponsorship and Insurance Request Form

Membership of the Committee

The members of the Ethics Committee who reviewed the study were:

Michael Dixon	Ruth Nicholson
Biddy Passmore	Jeff Kramer
Christopher Brierley	

Yours sincerely,

Michael Dixon

Michael Dixon,
Chair, Imperial College Ethics Committee

Imperial College of Science, Technology and Medicine

B-2 Ethical approval (Med Chula IRB 766/61)

IRB No. 766/61

บันทึกข้อความ

ส่วนงาน งานจริยธรรมการวิจัย ฝ่ายวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร.0-2256-4493

ที่ Med Chula IRB 011/2562 **วันที่** 3 มกราคม 2562

เรื่อง แจ้งผลการพิจารณาจริยธรรมการวิจัย (Full Board)

เรียน นพ.เจตน์ รัตนจีนะ

จากการประชุมคณะกรรมการพิจารณาจริยธรรมการวิจัย ครั้งที่ 1 ในวันพฤหัสบดีที่ 3 มกราคม พ.ศ. 2562 ได้พิจารณาโครงการวิจัย เรื่อง การศึกษาความสัมพันธ์ระหว่างการสัมผัสปัจจัยทางการเกษตรต่อโรคปอดเรื้อรังในกลุ่มเกษตรกรในจังหวัดน่าน ประเทศไทย: การวิจัยแบบตัดขวาง

ผู้วิจัยหลัก นพ.เจตน์ รัตนจีนะ

สังกัด ภาควิชาเวชศาสตร์ป้องกันและสังคม

คณะกรรมการมีมติให้ปรับปรุงแก้ไขเพื่อรับรองดังนี้

- Protocol
  1. ขอให้เพิ่มรายละเอียดเกี่ยวกับการตรวจสมรรถภาพปอดตามที่ระบุในเอกสารข้อมูล ระบุสถานที่ที่ใช้ในการตรวจ และควรระบุผู้มีความเสี่ยงต่อการใช้ salbutamol ในเกณฑ์คัดออก
  2. การตรวจสมรรถภาพปอดควรทำในโรงพยาบาลที่สามารถดูแลอาสาสมัครหากเกิดภาวะแทรกซ้อนได้
- Patient / Participant Information Sheet
  1. ขอให้ระบุจำนวนข้อของแบบสอบถาม และระบุว่ามีสิทธิ์ไม่ตอบคำถามข้อใดข้อหนึ่ง
  2. ขอให้เพิ่มรายละเอียด วิธีการตรวจสมรรถภาพปอด พร้อมภาพประกอบ
  3. หัวข้อ ประโยชน์ที่อาจได้รับ ขอให้แก้ไขเป็น "ท่านจะไม่ได้รับประโยชน์ใดๆจากการเข้าร่วมในการวิจัยนี้ แต่ผลของการศึกษาวิจัยในครั้งนี้ จะ......"
- Consent Form
  1. ขอให้ตัดข้อความที่ไม่เกี่ยวข้องและปรับข้อความให้สอดคล้อง

คณะกรรมการมีความเห็นให้ผู้วิจัยส่งรายงานความก้าวหน้าอย่างน้อย 1 ครั้ง/ปี หรือส่งรายงานฉบับสมบูรณ์หากดำเนินโครงการเสร็จสิ้นก่อน 1 ปี

โครงการวิจัยของท่านอาจได้รับการตรวจติดตามโดยคณะกรรมการจริยธรรมการวิจัย

จึงเรียนมาเพื่อทราบ และโปรดดำเนินการตามเงื่อนไขข้างต้น ทั้งนี้ขอให้ส่งบันทึกข้อความชี้แจงการแก้ไขมาเป็นข้อๆ พร้อมเอกสารฉบับที่มีการแก้ไข โดยเปลี่ยน Version... Date... ของเอกสารฉบับที่มีการแก้ไขและ Highlight ตรงส่วนที่มีการปรับแก้ไข ส่งเอกสารฉบับที่มีการแก้ไขมายังสำนักงานคณะกรรมการพิจารณาจริยธรรมการวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย จำนวน 3 ชุด ภายใน 30 วันทำการ นับจากที่ท่านได้รับผลการพิจารณา เมื่อพ้นกำหนดนี้แล้ว จะต้องชี้แจงเหตุผลที่ล่าช้ามาในบันทึกข้อความด้วย ทั้งนี้เพื่อให้เป็นไปตามมาตรฐานที่ Med Chula IRB ได้รับการรับรองจาก SIDCER/FERCAP

(ศาสตราจารย์กิตติคุณ แพทย์หญิงธาดา สืบหลินวงศ์)

ประธานคณะกรรมการพิจารณาจริยธรรมการวิจัย

B-3 Information sheet

Institutional Review Board AF 09-04/5.0

Faculty of Medicine Chulalongkorn University

Participant Information Sheet

Title **The association of agricultural exposures with chronic lung disease among farmers in Nan province, Thailand: a cross-sectional study**

Sponsor National Heart and Lung Institute, Imperial College London, United Kingdom

Principle Investigator

Name	Dr Jate Ratanachina
Address	1) Department of Preventive and Social Medicine, King Chulalongkorn Memorial Hospital, Rama IV Road, Pathumwan, Bangkok 10330 2) National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, 1b Manresa Road, London SW3 6LR, United Kingdom
Tel (office)	+66 (0) 2252 7864
24-hour contact	*...local mobile phone number on the site...*

Dear Research Participant,

You are invited to participate in this research project because you are qualified as a person aged between 40 and 65 years old living in Nan province. Please read this document carefully before you decide to participate in the study. This is to inform you of the ideas, reasons and details of this research study. If you have any additional questions, please ask the researcher who will be able to answer your questions.

Before making a final decision whether or not to participate in this research study, you can ask for advice from your family, friends or personal medical doctors. You will have enough time to make your decision. If you decide to participate in this research study, please finally sign the consent form.

Background

The province of Nan, in northern Thailand, is largely agricultural and one of the poorest in the country. In Nan, in 2558/2559 BE (2015/2016) COPD was the commonest recorded cause of death, and the 9th most common in-patient diagnosis in adults. Smoking has been shown to be the most common cause of chronic airflow obstruction in the international Burden of Obstructive Lung Disease (BOLD) Study, though there is substantial variation in prevalence that is not explained by smoking prevalence; other identified risk factors include a history of tuberculosis, poverty, a low level of education, a low body mass index and work in a dusty environment. Of the individual occupations examined in the BOLD Study, farming was by far the most common and appears to be associated with airflow obstruction. The reasons for farmers having low lung function are poorly understood but probably include high rates of non-occupational risks such as tobacco, poverty and tuberculosis as well as specific occupational hazards.

Among the important occupational exposures faced by farmers are pesticides. There is a growing literature on the risks to lung health and to lung function in particular posed by pesticide use. A systematic review of the subject is under way; preliminary findings suggest that lung function is reduced in those who have regularly used some pesticides, most prominently organophosphates. The literature is however limited. Many studies are small, the assessment of pesticide use often does not specify the pesticides used or the amount, frequency and duration of exposure and there is inadequate account taken of other potentially important exposures.

Research objectives

This research study aims to assess the association of lung function (FEV_1; FVC and FEV_1/FVC ratio), with exposure to occupational hazards with a focus on farmers in Nan province, Thailand.

• <u>You are invited to participate in this research project because</u>

You are in the population aged between 40 and 65.

• <u>You will be excluded from this research study if</u>

You are a vulnerable person consisting of prisoners, pregnant women or those with identified cancer or who are terminally or mentally ill. You will also not be able to participate in the research study if you are allergic to Salbutamol drug OR have one of the contraindications for spirometry tests comprising:

1. recent surgical procedures on eyes, abdomen or chest in past three months
2. a history of a detached retina
3. a history of a heart attack in past three months
4. hospitalisation due to any other heart problem within the past month
5. the last trimester of pregnancy
6. tachycardia (pulse rate > 120 bpm)

7. currently taking medication for tuberculosis

• Research site		Villages in Nan Province

• Number of participants	400

Research Methods

After you consent to participate in this research study, the researcher will ask for information about the disease, drug allergy history, contraindications whether you are appropriate to participate in the research (all participants).

If you meet the criteria for the study, you will be invited to see the researcher on the date of appointment below.

(Date………………… Month.. 2562 BE Time ....)
(Venue...)

You will be asked a several questions on general and respiratory symptoms, smoking, occupational and other known risk factors. You will also be asked questions from a detailed farming questionnaire including general information, agricultural work history, agricultural circumstance, pesticide use information and use of personal protective equipment (PPE).

The questionnaires are composed of:

• Spirometry questionnaire	27	questions
• Core questionnaire	58	questions
• Occupational questionnaire	6	questions (with 15 optional occupations)
• Environmental questionnaire	24	questions
• Agricultural questionnaire	14	questions

In each question, you have rights to not answer any question without giving any reason.

Your weight, height, waist circumference, length measurements including arms and legs (ulna and fibula) will be measured. You will be invited to undergo pre- and post-bronchodilator spirometry using a ndd spirometer and inhaled salbutamol (a bronchodilating agent) via a spacer device. The duration of the research project is 1.5 to 2 hours. You will be contacted to you once.

Responsibilities of participants

To accomplish this research study, the researcher would like to ask for your cooperation by strictly following the researcher's instructions and informing them of any unusual symptoms.

Risks

These procedures carry no major health risk for participants. All participants will be interviewed by questionnaires and perform spirometry both before and after administration of an inhaled bronchodilating agent. However, the breathing test (spirometry) may cause some participants to feel dizzy or lightheaded; some may faint. To minimize the risk of injury associated with fainting, the maneuver will be performed with participants seated in a stationary chair. The technicians administering the test will be trained to watch for signs of faintness and to stop the test if the participant appears unusually breathless or uncomfortable.

The bronchodilating medication (salbutamol) participants will inhale as part of the breathing test is designed to help people with airflow limitation breath more easily. It is very safe, and should cause the airways in the lungs to open up if constricted. The side effects from the use of this drug are minor and may include increased heart rate, nervousness, shakiness, dizziness, weakness, sweating, and chest pains. These effects, if they occur, last for only a few minutes. The staff administering the lung function tests will be monitoring participants for side effects and will manage them if necessary. Questions are also asked to screen out those people who have or recently had conditions that place them at risk when doing spirometry (including recent myocardial infarction; eye, chest, or abdominal surgery; and tachycardia).

In the case of any emergency, participants will be immediately referred to the nearest collaborative Nan district or provincial hospital.

Please inform the researcher if the above symptoms or others are found during the research study as soon as possible.

Uncertain risks

You may have side effects or discomfort in addition to those shown in this document. For your safety, please inform the researcher immediately if any abnormalities occur.If you have any questions about the risks that may arise from participating in this research study, you are welcome to ask the researcher at any time. The researchers will inform you immediately if they discover new information that may affect your safety during your participation. The researcher will allow you to decide whether to stay in the research project or to withdraw from this research study.

Seeing a medical doctor outside the schedule in case of side effects

If any side effects occur to you outside the appointment schedule, please contact your local doctor immediately (the researcher will help you coordinate in advance). If such symptoms are the result from participating in the research study, you will not be charged.

Benefits of taking part

You will be given a free lung function testing. Information we get from this study will be used to improve public health.

Other treatment methods

You do not need to join this research study for the benefit of treating the disease you have. Therefore, you should consult with your doctor before deciding to participate in this research study.

You have to do:

You have to inform us of any drug allergy history and contraindications for spirometry tests comprising:

1. recent eyes, abdominal or thoracic surgical procedures in past three months
2. a detached retina history
3. a history of heart attack in past three months
4. hospitalisation due to any other heart problem within the past month
5. the last trimester of pregnancy
6. tachycardia (pulse rate > 120 bpm)
7. currently taking medication for tuberculosis

If you have at least one contraindication, you will be excluded from the study. Please inform the researcher of any adverse event occurring while you participate in this research study.

Adverse events that may arise from participating in this research study and the responsibility of the researchers/research sponsor

If you have any adverse event arising from participation in this research study, you will receive appropriate treatment immediately. If you follow the advice of the research team, the researchers/ research sponsor will be responsible for your medical expenses. In addition, both loss of time and income will be compensated as appropriate.

In the incidence occurred you can 24-hour contact with a researcher, Dr Jate Ratanachina, Telephone number ...(local mobile phone number on the site)...

Your expenses for participating in research

There is no charge to participate in this research study. You will be performed free lung function testing.

Compensation for participants

You will not receive compensation from participating in the research. You will receive a travel fee in case of traveling for THB 100 per time, once.

Participation and withdrawal

Participation in this research project is voluntary. If you do not voluntarily participate in the study, you can withdraw at any time. Requests for withdrawal from the research project will not affect the treatment of your disease in any way.

Researchers may withdraw you from participating in this research study for your safety OR when the research sponsor ceases to conduct research OR in the following cases:

- You cannot follow the advice of the researcher.
- You have side effects OR abnormalities from the tests in this research.
- You are allergic to drugs used in this research study.

Protecting confidentiality

Information that may lead to your identity will be concealed and will not be disclosed to the public. In case the research results are published, your name and address must always be concealed.

Signing the consent of the researcher and research sponsor, Institutional Board Review and the regulatory agency can check your medical records even after the research study has finished. However, it must not violate your rights to maintain confidentiality beyond the legal and regulatory limits allowed.

From signing your consent, the researcher can give details about your participation in this research study to your medical doctor.

Cancellation of consent

If you wish to cancel your consent, you can inform OR write a note requesting to cancel the consent and send to Dr Jate Ratanachina, Department of Preventive and Social Medicine Chulalongkorn Hospital, 19th Floor, Or Por Ror Building, Rama IV Road, Pathumwan, Bangkok 10330.

If you request to cancel the consent after you have joined the research project, your personal information will not be recorded. However, other information about you may be used to evaluate research results. In addition, you will not be able to participate in this project again.

Rights of participants

As a participant in the research study you will have the following rights.

1. You will be informed of the details and objectives of this research.
2. You will have the methods including drugs and equipment used in research explained.
3. You will have the risks and discomforts that can arise from the research explained.
4. You will receive an explanation of the benefits you may receive from the research.
5. You will be informed of the treatment guidelines in case of any complication found after participating in the research project
6. You will have opportunities to ask questions about research or steps related to research.
7. You can request to withdraw from the project at any time without any effect to the participant.
8. You will receive an information sheet and a copy of the consent form containing both signature and date.
9. You have the right to decide whether or not to participate in the research project without intimidation or deception

If you are not appropriately compensated for injuries or illnesses occurring as a result of this research study OR you are not been treated as shown in the information sheet, you can complain to Institutional Review Board, Faculty of Medicine Chulalongkorn University, the 3rd floor of Anandamahidol Building, Rama IV Road, Pathumwan, Bangkok 10330 Tel./Fax +66 (0) 22564493 (at office hours) or e-mail: medchulairb@chula.ac.th.

Testing your lungs by Spirometry

What is the spirometry?

Spirometry is a test to know how healthy of your lungs, which can help diagnose or monitor the condition of the lungs. During the test, you will have to blow your breath out as much as possible in the spirometer. This tool will know the volume of all the blowing air and the amount of wind blowing in the first second. The test is painless and will take up to 10 minutes.

Figure showing the spirometry test

What will happen during the test?

The researcher will ask you about your risks of performing spirometry and inform you all the test method including how to blow the spirometer. You may have to wear a soft nose clip to prevent air leakage from your nostrils during the test.

<u>Before beginning the test</u>: You must breathe deeply and breathe out into the spirometer. The researcher will ask you to blow the air for 3 times, but not more than 10 times.

<u>During the test</u>: We ask for your cooperation.

- Breathe as deep as you can and tighten your lips around of the mouthpiece.
- Blow the breath out through the mouth through the mouthpiece and as quickly as possible.
- Keep blowing out the breath until your lungs are empty and the researcher tells you to stop blowing.

How to prepare before the test?

The researcher asks you to "abstain" smoking, drinking coffee, strenuous working or exercising and eating a large meal before the appointment date for testing.

Problems that may arise during the test?

This test is a low-risk test. However, the hard blows needed for this test are difficult for some people. If you feel dizzy during the test, ask the researcher to rest the test for a moment before continuing the test. If you want to cough, stop the test and clear your chest before you try again.

Signing the consent form does not mean that you give up any legal rights which you have.

Thank you for your cooperation.

B-4 Consent form

Institutional Review Board **AF 09-05/5.0**

Faculty of Medicine Chulalongkorn University

Consent Form for Participants

Title **The association of agricultural exposures with chronic lung disease among farmers in Nan province, Thailand: a cross-sectional study**

Date of Consent Date…………… Month.......................... 2562 BE (2019)

I, Mr/Mrs/Miss ....

Address .... have already read the details from the Information sheet for participants on date .... and I voluntarily consent to participate in this research study.

I received a copy of the participant information sheet along with the consent form, which I signed. Before signing the consent form for this research, I have been explained by the researcher about research objectives, the duration of research, research methods and benefits of research. I have also been explained risks, symptoms, protocols to the effects for dealing with effects that may arise from the research or from drugs used. I have had enough time and opportunity to ask questions until I have already understood. The researcher willingly responded without concealment until I was satisfied.

I acknowledge from the researcher that if there is any danger from the research, I will receive free medical treatment; however, there is no compensation from the sponsor.

I have the right to withdraw my participation in this research study without any reason at any time. It will my current treatment of any disease or other rights.

The researcher certifies that my personal information will be kept confidential. My personal information will only be disclosed when receiving my consent. Other people including the university/hospital on behalf of this research sponsor may be permitted to access my personal information only for the purpose of verifying the accuracy of the information. By agreeing to participate in this study, I also consent to the researchers accessing my medical history if any.

This research is partly supervised from Imperial College London. Information from the study will be shared with them using a secure network but your name will not be shared with anyone outside the research team in Nan Province without your explicit permission.

The researcher assures me that there will not be any additional data collected after I withdraw from this research study. All information able to refer to me must be destroyed.

I understand that I have a right to check or edit my personal information. I have a right to cancel the right to use my personal information after informing the researcher.

I realised that the research data including my concealed medical information will be collected through various processes such as data collection recording in computers, monitoring, analysis and reporting for academic purposes.

I have read and understood the above information. I willingly participate in this research study and therefore sign this consent form.

.... Signature

(..) Name of Participant

Date....................................

I have explained research objectives, research methods, adverse effects, risks and benefits that may arise from research. I also clearly explained to the participant above and willingly signed this consent.

.... Signature

(..) Name of Researcher taking consent

Date....................................

.... Signature

(..) Name of Witness

Date....................................

B-5 Spirometry questionnaire

Spirometry questionnaire

Site		…….……
Fieldworker number		…….……
Participant number		…….……
1. Pulse (bpm)		…….……
2.1. Systolic blood pressure (mmHg)		………….
2.2. Diastolic blood pressure (mmHg)		………….
3. Height (cm)		………….
4. Weight (kg)		………….
5.1. Hip circumference 1st measurement (cm)		………….
5.2. Hip circumference 2nd measurement (cm)		………….
6.1. Waist circumference 1st measurement (cm)		………….
6.2. Waist circumference 2nd measurement (cm)		………….
7. Ulna length (cm)		………….
8. Fibula length (cm)		………….
9.1. Neck circumference 1st measurement (cm)		………….
9.2. Neck circumference 2nd measurement (cm)		………….

10. Comments ……..

11. In the past three months have you had any surgery on your chest or abdomen?	Yes	No
12. Have you had a heart attack within the past three months?	Yes	No
13. Do you have a detached retina or have you had eye surgery within the past three months?	Yes	No
14. Have you been hospitalized for any other heart problem within the past month?	Yes	No
15. Are you in the last trimester of pregnancy?	Yes	No
16. Are you currently taking medication for tuberculosis?	Yes	No
17. Is there some other reason why this participant should not perform the spirometry manoeuvre?	Yes	No
18. Have you had a respiratory infection (cold) in the last three weeks?	Yes	No
19. Have you taken any medications for breathing in the last 24 hours?	Yes	No
Recent medications	Yes	No
20. Record name/type of medication(s) used:	Yes	No
20.1. Did participant use a short acting beta agonist (e.g. albuterol, salbutamol) or anticholinergic inhaler (e.g. atrovent, iprtropium), either alone or in combination with some other product, in the last six hours?	Yes	No
20.2. Did participant use a long acting beta agonist (e.g. Serevent, Advair, Formoterol, Symbicort) or oral beta 2 agonist (e.g. salbutamol tablets), either alone or in combination with some other product, in the last 12 hours?	Yes	No
20.3. Did participant use an oral theophyllin/ long acting anticholinergic (e.g. spiriva, tiotropium), either alone or in combination with some other product, in the last 24 hours?	Yes	No
21. Have you smoked in the last 30 days?	Yes	No
21.1. When did you last smoke?	………….	

22.1. Acceptable pre-bronchodilator test completed? Yes No

22.2. Acceptable post-bronchodilator test completed? Yes No

23. Why were you unable to obtain satisfactory spirometry?

- The participant did not understand instructions
- The participant was medically excluded
- The participant was unable to physically cooperate
- The participant refused
- Doesn't apply

24. Were any adverse events related to the spirometry maneuver observed by the evaluator? Yes No

25. Was this a major event (was the participant hospitalised or did the participant die)? Yes No

26. Please briefly describe event: ………………………………………………………………………………………………………

27. If the participant had a condition that would affect the result of their spirometry test (e.g., kyphosis, missing limbs, etc.) note that condition here: ……………………………………………………………….

Completed by: ____ ____ ____ ____

B-6 Core questionnaire

<u>Core questionnaire</u>

Site	……..……
Fieldworker number	……..……
Participant number	……..……
1. What is the participant's sex?	Male Female
2. What is your date of birth?	……..……

Education

3.1. What is the highest level of schooling you have completed?

- o Primary School
- o Middle school
- o High school
- o Some college (Trade/Professional/Community)
- o Four-Year College/University
- o None
- o Unknown

3.2. What is the highest level of schooling your mother has completed?

- o Primary School
- o Middle school
- o High school
- o Some college (Trade/Professional/Community)
- o Four-Year College/University
- o None
- o Unknown

Household assets

4.1. Please tell me whether this household or any person who lives in the household has/owns the following items:

4.1.1. Electricity?	Yes	No	Don't know
4.1.2. Flush toilet?	Yes	No	Don't know
4.1.3. Fixed telephone?	Yes	No	Don't know
4.1.4. Cell telephone?	Yes	No	Don't know
4.1.5. Television?	Yes	No	Don't know
4.1.6. Radio?	Yes	No	Don't know
4.1.7. Refrigerator?	Yes	No	Don't know
4.1.8. Car?	Yes	No	Don't know
4.1.9. Moped/scooter/motorcycle?	Yes	No	Don't know
4.1.10. Washing machine?	Yes	No	Don't know
4.1.11. Own their own home?	Yes	No	Don't know
4.1.12. Indoor bath or shower?	Yes	No	Don't know
4.1.13. Indoor tap?	Yes	No	Don't know
4.1.14. Outdoor tap of their own?	Yes	No	Don't know

4.2. When you were 5 years old did any person who lived in your household have/own the following items:

4.2.1. Electricity?	Yes	No	Don't know
4.2.2. Flush toilet?	Yes	No	Don't know

4.2.3. Fixed telephone?	Yes	No	Don't know
4.2.4. Television?	Yes	No	Don't know
4.2.5. Radio?	Yes	No	Don't know
4.2.6. Refrigerator?	Yes	No	Don't know
4.2.7. Car?	Yes	No	Don't know
4.2.8. Moped/scooter/motorcycle?	Yes	No	Don't know
4.2.9. Washing machine?	Yes	No	Don't know
4.2.10. Own their own home?	Yes	No	Don't know
4.2.11. Indoor bath or shower?	Yes	No	Don't know
4.2.12. Indoor tap?	Yes	No	Don't know
4.2.13. Outdoor tap of their own?	Yes	No	Don't know

5. In the last year did you or any person who lives in the household ever go hungry for lack of money?
Yes No Don't know

5.1. How often did you or any person who lives in the household ever go hungry for lack of money?

- Most days
- Most weeks
- Most months
- Certain times of the year
- Occasionally
- Never

6. How many people live in your house with you? (including you) …….……

7. How many rooms are there in your house? (excluding kitchen and bathroom/s) …….……

Respiratory symptoms

These questions pertain mainly to your chest. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.

8. Do you usually cough when you don't have a cold? Yes No

8.1. Are there months in which you cough on most days? Yes No

8.2. Do you cough on most days for as much as three months each year? Yes No

8.3. For how many years have you had this cough?

- Less than 2 years
- 2-5 years
- More than 5 years

9. Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? Yes No

9.1. Are there months in which you have this phlegm on most days? Yes No

9.2. Do you bring up this phlegm on most days for as much as three months each year? Yes No

9.3. For how many years have you had this phlegm?

- Less than 2 years
- 2-5 years
- More than 5 years

9.4. Is the phlegm worse when you lie in certain positions (on one side or the other)? Yes No

10. Have you had wheezing or whistling in your chest at any time in the last 12 months? Yes No

10.1. In the last 12 months, have you had this wheezing or whistling only when you have a cold? Yes No

10.2. In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath?
Yes No

11. Are you unable to walk due to a condition other than shortness of breath? Yes No

11.1. Nature of condition(s): ……

Exertional Dyspnoea

12. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?
Yes No

12.1. Do you have to walk slower than people of your age on level ground because of shortness of breath?

Yes No Does not apply

12.2. Do you ever have to stop for breath when walking at your own pace on level ground?

Yes No Does not apply

12.3. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground?

Yes No Does not apply

12.4. Are you too short of breath to leave the house or short of breath on dressing or undressing?

Yes No Does not apply

Respiratory diagnoses

13. Has a doctor or other health care provider ever told you that you have emphysema? Yes No

14. Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis?
Yes No

14.1. Do you still have asthma, asthmatic bronchitis or allergic bronchitis? Yes No

15. Has a doctor or other health care provider ever told you that you have chronic bronchitis? Yes No

15.1. Do you still have chronic bronchitis? Yes No

16. Has a doctor or other health care provider ever told you that you have chronic obstructive pulmonary disease (COPD)?
Yes No

17. In the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion)?
Yes No

Medications

17.1. How many medicines have you taken for your breathing (including medications for nasal congestion) in the past 12 months?
……..……

Medications: Details

17.2. Medication Name(s): ……..……

17.2.1. Formulation:

- Pills
- Inhaler
- Nebulizer
- Liquid
- Suppository
- Injection
- Other

17.2.2. Is the medicine taken on most days, or just when you have symptoms, or both?

- On most days
- Just when I have symptoms
- Both

17.2.3. When you are taking the medication, how many days a week do you take it? ……..……

17.2.4. When you are taking the medication, how many months in the past 12 months have you taken it?

0-3 4-6 7-9 10-12

17.3. Please tell me about any other products that you take or things you do to help your breathing that you have not already told me about: ..………………………………………………………………………………………

Spirometry and breathing problems

18. Has a doctor or other health care provider ever had you blow into a machine or device in order to measure your lungs (i.e., a spirometer or peakflow meter)? Yes No

18.1. Have you used such a machine in the past 12 months? Yes No

19. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work? Yes No

19.1. How many such episodes have you had in the past 12 months? ………….

19.2. For how many of these episodes did you need to see a doctor or other health care provider in the past 12 months? ………….

19.3. For how many of these episodes were you hospitalized overnight in the past 12 months? ………….

19.3.1. All together, for how many total days were you hospitalized overnight for breathing problems in the past 12 months?……..…

Sleep

20. How many hours of sleep do you estimate that you get on average each night? ………….

21. Do you snore? Yes No Don't know

21.1. Your snoring is:

- Slightly louder than breathing
- As loud as talking
- Louder than talking
- Very loud (can be heard in adjacent rooms)

21.2. How often do you snore?

- Almost every day
- 3-4 times per week
- 1-2 times per week
- 1-2 times per month
- Rarely or never
- Don't know

21.3. Has your snoring ever bothered other people? Yes No Don't know

22. Has anyone noticed that you quit breathing during your sleep?

- Almost every day
- 3-4 times per week
- 1-2 times per week
- 1-2 times per month
- Rarely or never
- Don't know

23. Do you gasp for air or choke while sleeping? Yes No Don't know

23.1. In the last month on how many nights per week did you gasp for air or choke while sleeping?

- Never
- Less than once a week
- 1-2 times a week
- 3-4 times a week
- 5-7 times a week
- Don't know

24. In the past month, how often have you felt sleepy during the day?

- Never
- Less than once a week
- 1-2 times a week
- 3-4 times a week
- 5-7 times a week
- Don't know

25.1. How likely are you to doze off while sitting in a public place (for instance in a theatre or meeting)?

- Would never doze
- Slight chance of dozing
- Moderate chance of dozing
- High chance of dozing

25.2. How likely are you to doze off while sitting down and talking to someone?

- o Would never doze
- o Slight chance of dozing
- o Moderate chance of dozing
- o High chance of dozing

25.3. How likely were you to doze off while sitting quietly after a meal without alcohol?

- o Would never doze
- o Slight chance of dozing
- o Moderate chance of dozing
- o High chance of dozing

26. In the past month, how often have you had heartburn after lying down?

- o Never
- o Less than once a week
- o 1-2 times a week
- o 3-4 times a week
- o 5-7 times a week
- o Don't know

27. In the past month, how often have you sweated or perspired excessively during the night?

- o Never
- o Less than once a week
- o 1-2 times a week
- o 3-4 times a week
- o 5-7 times a week
- o Don't know

28. During your waking time, how often do you feel tired, fatigued or not up to par?

- o Almost every day
- o 3-4 times per week
- o 1-2 times per week
- o 1-2 times per month
- o Rarely or never
- o Don't know

29. In the past three months, how often have you woken up at least 30 minutes earlier in the morning and been unable to get back to sleep? ………….

30. In the past three months, how often have you woken from sleep several times during the night? Never

- o Less than once a week
- o 1-2 times a week
- o 3-4 times a week
- o 5-7 times a week
- o Don't know

31. In the past three months, how often have you had difficulties falling asleep (taken more than 30 minutes)?

- o Never
- o Less than once a week
- o 1-2 times a week
- o 3-4 times a week
- o 5-7 times a week
- o Don't know

Smoking

32. Now I am going to ask you about smoking. First, I will ask about cigarettes, including hand rolled cigarettes, and then I will ask about other items that are smoked.

32.1. Have you ever smoked cigarettes? Yes No

32.1.1. How old were you when you first started regular cigarette smoking? ………….

32.1.2. Have you stopped smoking? Yes No

32.1.2.1. How old were you when you last stopped? ………….

32.1.3. On average over the entire time that you smoke(d), how many cigarettes per day/week do (did) you smoke?

32.1.3.1. cigarettes/day ………….

32.1.3.2. cigarettes/week ………….

32.1.4. On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured or hand-rolled cigarettes?

- o Manufactured
- o Hand-rolled

32.2. Have you ever smoked beedi? Yes No

32.2.1. How old were you when you first started regular beedi smoking? ………….

32.2.2. Have you ever stopped smoking beedi? Yes No

32.2.2.1. How old were you when you last stopped? ………….

32.2.3. On average over the entire time that you smoke(d), about how many beedi per day/per week do (did) you smoke?

32.2.3.1. beedi/day ………….

32.2.3.2. beedi/week ………….

32.3. Have you ever smoked kreteks? Yes No

32.3.1. How old were you when you first started regular kreteks smoking? ………….

32.3.2. Have you ever stopped smoking kreteks? Yes No

32.3.2.1. How old were you when you last stopped? ………….

32.3.3. On average over the entire time that you smoke(d), about how many kreteks per day/per week do (did) you smoke?

32.3.3.1. kreteks/day ………….

32.3.3.2. kreteks/week ………….

32.4. Have you ever smoked pipes of tobacco? Yes No

32.4.1. How old were you when you first started regular pipe smoking? ………….

32.4.2. Have you ever stopped smoking tobacco pipes? Yes No

32.4.2.1. How old were you when you last stopped? ………….

32.4.3. On average over the entire time that you smoke(d), about how many grams per day/per week do (did) you smoke?

32.4.3.1. grams/day ………….

32.4.3.2. grams/week ………….

32.5. Have you ever smoked cigars, cheroots, or cigarillos? Yes No

32.5.1. How old were you when you first started regular cigar/cheroot/cigarillo smoking? ………….

32.5.2. Have you stopped smoking cigars, cheroots, or cigarillos? Yes No

32.5.2.1. How old were you when you last stopped smoking a cigar, cheroot or cigarillo? ………….

32.5.3. On average over the entire time that you smoke(d), about how many cigar/cheroot/cigarillo per day/per week do (did) you smoke?

32.5.3.1. cigars, etc/day ………….

32.5.3.2. cigars, etc/week ………….

32.6. Have you ever smoked a water pipe? Yes No

32.6.1. How old were you when you first started regular water pipe smoking? ………….

32.6.2. Have youstopped smoking water pipe? Yes No

32.6.2.1. How old were you when you last stopped smoking a water pipe? ………….

32.6.3. On average over the entire time that you smoke(d), about how many water pipes per day/per week do (did) you smoke?

32.6.3.1. water pipe/day ………….

32.6.3.2. water pipe/week ……..……

32.7. Have you ever smoked cannabis? Yes No

32.7.1. How old were you when you first started regular cannabis smoking? ……..……

32.7.2. Have you stopped smoking cannabis? Yes No

32.7.2.1. How old were you when you last stopped cannabis smoking? ……..……

32.7.3. On average over the entire time that you smoke(d), about how many joints/splifs/pipes of cannabis per day/per week do (did) you smoke?

32.7.3.1. joints/day ……..……

32.7.3.2. joints/week ……..……

32.8. Have you ever vaped/smoked e-cigarettes? Yes No

32.8.1. How old were you when you first started regular vaping/e-cigarette smoking? ……..……

32.8.2. Have you ever stopped vaping/smoking e-cigarettes? Yes No

32.8.2.1. How old were you when you last stopped? ……..……

32.8.3. On average over the entire time that you vaped/smoke(d), about how many e-cigarettes cartridges per day/per week do (did) you use?

32.8.3.1. e-cigarette cartridges/day ……..……

32.8.3.2. e-cigarette cartridges/week ……..……

32.8.4. Have you ever vaped/smoked e-cigarettes with aroma(s)? Yes No

32.9. Have you ever smoked or inhaled any other substance? (e.g. local, recreational smoked substances) Yes No

32.9.1. specify type: ……..……

32.9.2. specify unit. e.g. pipes, joints ……..……

32.9.3. How old were you when you first started regularly smoking this? ……..……

32.9.4. On average over the entire time that you smoke(d), about how many units per day/per week do (did) you smoke?

32.9.4.1. units/day ……..……

32.9.4.2. units/week ……..……

33. Are you currently smoking anything? (not correlate with current cigarette smoking)

Yes No

34. How soon after you wake up do you smoke your first cigarette/e-cigarette/beedi/kretek/pipe of tobacco/cigar, cheroot, or cigarillo/water pipe?

- 0-5 min
- 6-30 min
- 31-60 min
- After 60 min

35. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., church, library, cinema, restaurant)?

Yes No

36. Which cigarette/e-cigarette/beedi/kretek/pipe of tobacco/cigar, cheroot, or cigarillo/water pipe would you be the most unwilling to give up?

- First in the morning
- Any of the others

37. Do you smoke more frequently during the first hours after waking than during the rest of the day?

Yes No

38. Do you smoke if you are so ill that you are in bed most of the day? Yes No

39. In the last year, how many times have you quit smoking for at least 24 hours? ……..…

39.1. Are you seriously thinking of quitting smoking? Yes No

39.2. Has a doctor or other health care provider ever advised you to quit smoking? Yes No

39.3. Have you received medical advice to stop smoking within the past 12 months? Yes No

39.4. Have you used any medication (prescription or non-prescription), including a nicotine patch, to help you stop smoking? Yes No

39.4.1. What kind of medication did you take to help you stop smoking?

Nicotine Replacement Bupropion Tofranil Cytisine VareniclineOther

39.4.2. Have you used or done anything else to help you stop smoking? Yes No

39.4.2.1. What did you do?

Hypnosis Acupuncture Biofeedback Other

40. Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past two weeks? Yes No

40.1. Not counting yourself, how many people in your household smoke regularly? …….……

40.2. Do people smoke regularly in the room where you work? Yes No

40.3. How many hours per day, are you exposed to other people's tobacco smoke in the following locations?

40.3.1. In the home? …….……

40.3.2. In the workplace? …….……

40.3.3. In bars, restaurants, cinemas or similar social settings? …….……

40.3.4. Elsewhere? …….……

Intro: The following questions refer only to cigarettes and tobacco

40.4. Based on what you know or believe, does smoking tobacco cause serious illness? Yes No

40.5. Based on what you know or believe, does smoking tobacco cause the following…

40.5.1. Stroke (blood clots in the brain that may cause paralysis) Yes No Don't know

40.5.2. Heart attack Yes No Don't know

40.5.3. Lung cancer Yes No Don't know

40.5.4. Chronic bronchitis Yes No Don't know

40.5.5. Emphysema/COPD Yes No Don't know

41. Have you ever worked for a year or more in a dusty job? Yes No

41.1. For how many years have you worked in dusty jobs? …….……

42. Has a doctor or other health care provider ever told you that you had:

42.1. Heart disease Yes No

42.1.1. Heart failure Yes No

42.2. Hypertension Yes No

42.3. Diabetes Yes No

42.4. Lung cancer Yes No

42.5. Stroke Yes No

Tuberculosis

43. Have you ever been diagnosed with tuberculosis? Yes No

43.1. How many times have you been treated for tuberculosis? ……..……

Please answer these questions for the most recent episode.

43.2. When were you last diagnosed as having tuberculosis? (year) ……..……

43.3. What part of the body did the tuberculosis affect?

- Lungs
- Glands/Lymph nodes
- Brain/Meninges
- Abdomen
- Heart
- Other
- Unknown

43.4. Were the doctors/clinic sure that you had tuberculosis? Yes No Unknown

43.4.1. Which tests showed that you had tuberculosis?

- Sputum (Phlegm)
- Sputum (Xpert TB testing)
- Chest X-ray
- Bone Marrow
- Lumbar Puncture
- Fine Needle Aspirate (FNA)
- Not sure
- Other

43.5. Did you ever stay in hospital for treatment of tuberculosis? Yes No Unknown

43.5.1. How long for were you in the hospital (sleeping in the hospital)?

- Less than 1 week
- 1 week to 1 month
- More than 1 month

43.6. Where did you get your pills or injections for tuberculosis (which clinic)? ……..……

43.7. How long (in months) did you take treatment for? ……..……

43.8. Did you finish the treatment? Yes No

43.8.1. Why did you not complete the treatment?

- Financial burden (loss of work)
- Financial burden (travel costs)
- Side effects
- Felt medication not working
- Felt recovered
- Poor service
- Stigma

43.8.2. Did you feel partly or completely well again (better) after ending treatment?

- Yes, completely
- Yes, partially
- No

43.8.3. Did the clinic doctor say you were cured? Yes No

43.8.4. Did you stop attending the clinic before the treatment was meant to stop? Yes No Unknown

Other

44. Have you ever had an operation on your chest in which a part of your lung was removed?

Yes No Unknown

45. In the past 12 months did you get a flu shot? Yes No Unknown

46. Has a doctor or other health care professional told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD? Yes No Unknown

Quality of Life

The following questions ask for your views about your health—how you feel and how well you are able to do your usual activities. There are no right or wrong answers; please choose the answer that best fits your life right now.

47. In general, would you say your health is: (Check one)

Excellent Very good Good Fair Poor

48. Does your health now limit you in these activities? If so, how much?

48.1. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling or playing golf.

- Yes, limited a lot
- Yes, limited a little bit
- No, not limited at all

48.2. Climbing several flights of stairs.

- Yes, limited a lot
- Yes, limited a little bit
- No, not limited at all

49. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

49.1. Accomplished less than you would like.

- No, none of the time
- Yes, a little of the time
- Yes, some of the time
- Yes, most of the time
- Yes, all of the time

49.2. Were limited in the kind of work or other activities.

- No, none of the time
- Yes, a little of the time
- Yes, some of the time
- Yes, most of the time
- Yes, all of the time

50. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

50.1. Accomplished less than you would like.

- No, none of the time
- Yes, a little of the time
- Yes, some of the time
- Yes, most of the time
- Yes, all of the time

50.2. Didn't do work or other activities as carefully as usual.

- No, none of the time
- Yes, a little of the time
- Yes, some of the time
- Yes, most of the time
- Yes, all of the time

51. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

52. How much of the time during the past 4 weeks…

52.1. Have you felt calm and peaceful?

- All the time
- Most of the time
- A good bit of the time
- Some of the time
- A little bit of the time
- None of the time

52.2. Did you have a lot of energy?

- o All the time
- o Most of the time
- o A good bit of the time
- o Some of the time
- o A little bit of the time
- o None of the time

52.3. Have you felt downhearted and blue?

- o All the time
- o Most of the time
- o A good bit of the time
- o Some of the time
- o A little bit of the time
- o None of the time

52.4. Have you felt tired?

- o All the time
- o Most of the time
- o A good bit of the time
- o Some of the time
- o A little bit of the time
- o None of the time

53. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- o All the time
- o Most of the time
- o A good bit of the time
- o Some of the time
- o A little bit of the time
- o None of the time

53.1. Compared to one year ago, how would you rate your physical health in general now?

- o Much better
- o Slightly better
- o About the same
- o Slightly worse
- o Much worse

53.2. Compared to one year ago, how would you rate your emotional problems (such as feeling anxious, depressed or irritable) now?

- o Much better
- o Slightly better
- o About the same
- o Slightly worse
- o Much worse

Work

The next questions ask about work and about times when you may have missed work due to health problems.

54. At any time in the past 12 months, did you work for income? Yes No

Paid Employment

54.1. During how many of the past 12 months did you work for income? …….……

54.2. During the months that you worked, how many days per week did you work for income?
…….……

54.3. What is the usual number of hours per day you work for income? …….……

54.4. During the past 12 months, did health problems ever stopped you from working for income?
Yes No

54.4.1. During the past 12 months, how many total days were you unable to work for income due to your health problems?
…….……

54.4.2. During the past 12 months, how many total days were you unable to work for income specifically due to breathing problems?
…….……

54.5. During the past 12 months, did you not work for income mainly due to breathing problems?
Yes No

54.6. During the past 12 months, did you not work for income because you were a full-time homemaker or caregiver?
Yes No

54.7. During the past 12 months, did health problems prevent you from participating in one or more non-work related activities?
Yes No

54.7.1. During the past 12 months, how many total days did you not participate in non-work related activities due to your health problems? …….……

54.7.2. During the past 12 months, how many total days did you not participate in non-work related activities specifically due to breathing problems? …….……

54.7.3. During the past 12 months, did health problems stop you from performing your usual homemaking/caregiving tasks?
Yes No

54.7.3.1. During the past 12 months, how many total days were you unable to perform your homemaking/caregiving tasks due to your health problems? …….……

54.7.3.2. During the past 12 months, how many total days were you unable to perform your homemaking/caregiving tasks specifically due to breathing problems? …….……

Physical activity

Next, I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

55. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?
…….……

55.1. How much time (hours) did you usually spend doing vigorous physical activities on one of those days?
…….……

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

56. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking. …….……

56.1. How much time (hours) did you usually spend doing moderate physical activities on one of those days?
…….……

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

57. During the last 7 days, on how many days did you walk for at least 10 minutes at a time? …….……

57.1. How much time (hours) did you usually spend walking on one of those days? …….……

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

58. During the last 7 days, how much time (hours) did you spend sitting on a week day? …….……

Completed by: ____ ____ ____ ____

B-7 Occupational questionnaire

<u>Occupational questionnaire</u>

Site ……..…

Fieldworker number ……..…

Participant number ……..…

1. Have you ever worked to earn money? Yes No

Past employment in high-risk occupations

2. Have you ever worked for <u>3 months or more</u> at any of the following occupations?

- Hard-rock mining
- Coal mining
- Sandblasting or stonemasonry
- Working with asbestos
- Chemical or plastics manufacturing
- Flour, feed or grain milling or baking
- Cotton or jute processing
- Foundry or steel milling
- Welding
- Firefighting
- Farming
- Construction
- Cleaning
- Cement manufacturing
- Waste recycling

Hard Rock Mining

2.1.1. How many years did you work/have you been working in hard rock mining? ……..…

2.1.2. Are you still working in hard rock mining? Yes No

2.1.3. Did you leave this job because it caused you breathing problems? Yes No

2.1.4. What sort of work are/were you doing in hard rock mining?

- o Senior manager
- o Professional
- o Technical
- o Clerical
- o Skilled manual
- o Unskilled

2.1.5. Are you or were you:

- o A manager working for an employer?
- o A foreman or supervisor working for an employer?
- o Working for an employer, but neither a manager, supervisor or foreman?
- o Self-employed?

Senior manager: directing the policy of a company, institution or government department

Professional: generally requiring a university degree and a chartered qualification

Technical: generally requiring an apprenticeship or college qualification

Clerical: requires literacy and some general training but mostly receives specific training on the job

Skilled manual: requires an apprenticeship or extensive on the job training with transferrable skills

Unskilled: manual work with no specific training required other than local direction

Coal mining

2.2.1. How many years did you work/have you been working in coal mining? ……..…

2.2.2. Are you still working in coal mining? Yes No

2.2.3. Did you leave this job because it caused you breathing problems? Yes No

2.2.4. What sort of work are/were you doing in coal mining?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.2.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Sandblasting or stonemasonry

2.3.1. How many years did you work/have you been working in Sandblasting or Stonemasonry?	…….…	
2.3.2. Are you still working in Sandblasting or Stonemasonry?	Yes	No
2.3.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.3.4. What sort of work are/were you doing in Sandblasting or Stonemasonry?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.3.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Working with asbestos

2.4.1. How many years did you work with asbestos?	…….…	
2.4.2. Are you still working with asbestos?	Yes	No
2.4.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.4.4. What sort of work are/were you doing with asbestos?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.4.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Chemical or plastics manufacturing

2.5.1. How many years did you work/have you been working in Chemical or plastics manufacturing?	…….…	
2.5.2. Are you still working in Chemical or plastics manufacturing?	Yes	No
2.5.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.5.4. What sort of work are/were you doing in Chemical or plastics manufacturing?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual

- Unskilled

2.5.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Flour, feed or grain milling or baking

2.6.1. How many years did you work/have you been working in flour, feed or grain milling or baking? ……..…

2.6.2. Are you still working in flour, feed or grain milling or baking? Yes No

2.6.3. Did you leave this job because it caused you breathing problems? Yes No

2.6.4. What sort of work are/were you doing in flour, feed or grain milling or baking?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.6.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Cotton or jute processing

2.7.1. How many years did you work/have you been working in cotton or jute processing? ……..…

2.7.2. Are you still working in cotton or jute processing? Yes No

2.7.3. Did you leave this job because it caused you breathing problems? Yes No

2.7.4. What sort of work are/were you doing in cotton or jute processing?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.7.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Foundry or steel milling

2.8.1. How many years did you work/have you been working in foundry or steel milling? ……..…

2.8.2. Are you still working in foundry or steel milling? Yes No

2.8.3. Did you leave this job because it caused you breathing problems? Yes No

2.8.4. What sort of work are/were you doing in foundry or steel milling?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.8.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Welding

2.9.1. How many years did you work/have you been working in welding? ……..…

2.9.2. Are you still working in welding? Yes No

2.9.3. Did you leave this job because it caused you breathing problems? Yes No

2.9.4. What sort of work are/were you doing in welding?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.9.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Firefighting

2.10.1. How many years did you work/have you been working in firefighting? ……..…

2.10.2. Are you still working in firefighting? Yes No

2.10.3. Did you leave this job because it caused you breathing problems? Yes No

2.10.4. What sort of work are/were you doing in firefighting?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.10.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Farming

2.11.1. How many years did you work/have you been working in farming? ……..…

2.11.2. Are you still working in farming? Yes No

2.12.3. Did you leave this job because it caused you breathing problems? Yes No

2.12.4. What sort of work are/were you doing in farming?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.12.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Construction

2.12.1. How many years did you work/have you been working in construction? ……..…

2.12.2. Are you still working in construction? Yes No

2.12.3. Did you leave this job because it caused you breathing problems? Yes No

2.12.4. What sort of work are/were you doing in construction?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.12.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Cleaning

2.13.1. How many years did you work/have you been working in cleaning?	……..…	
2.13.2. Are you still working in cleaning?	Yes	No
2.13.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.13.4. What sort of work are/were you doing in cleaning?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.13.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Cement manufacturing

2.14.1. How many years did you work/have you been working in Cement manufacturing?	……..…	
2.14.2. Are you still working in Cement manufacturing?	Yes	No
2.14.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.14.4. What sort of work are/were you doing in Cement manufacturing?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual
- Unskilled

2.14.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Waste recycling

2.15.1. How many years did you work/have you been working in Waste recycling?	……..…	
2.15.2. Are you still working in Waste recycling?	Yes	No
2.15.3. Did you leave this job because it caused you breathing problems?	Yes	No

2.15.4. What sort of work are/were you doing in Waste recycling?

- Senior manager
- Professional
- Technical
- Clerical
- Skilled manual

- Unskilled

2.15.5. Are you or were you:

- A manager working for an employer?
- A foreman or supervisor working for an employer?
- Working for an employer, but neither a manager, supervisor or foreman?
- Self-employed?

Longest held job

3. From all the jobs you had in your life, was this/one of these the job you have worked at the longest? Yes No

The next questions are about the job you have worked at the longest during your working life.

3.1. What year did you start your longest held job? ……..…

3.2. What year did you end your longest held job? ……..…

3.3. Is/Was your job in…

- Agriculture, horticulture, fishing, other work with animals (including managers)
- Construction, building, demolition or maintenance (including managers)
- Transport (road, rail, air, water), work with other mobile machinery (including managers)
- Routine factory-based manufacturing (including managers)
- Mining, quarrying, energy production, water treatment (including managers)
- Skilled manual work (including managers)
- Cleaning, caretaking, waste collection, pest control (including managers)
- Science, research, engineering, computer technology (including managers)
- Health (human or animal), residential/social/religious care, undertaking (including managers)
- Sport, culture, arts, media, entertainment (including managers)
- Office-based work: professional, managerial, administrative or general office/clerical
- Selling and shop work (retail/wholesale), storage and distribution (including managers)
- Personal services, travel/tourism, hospitality (including managers)
- Education, school-related work (including managers)
- Armed Forces, emergency services, security, health & safety (including managers)

3.3.1. More specifically, is/was it…

- Farming fishing
  - Agricultural work, farming, work with farm animals
  - Work with plants, trees and other landscape (including conservation)
  - Work in fishing
  - Work with non-farm animals
- Construction
  - Outside work in construction, building, demolition or maintenance
  - Inside work in construction, building or maintenance
  - Inside finishing or renovation work such as plastering, tiling, flooring, painting and decorating: sign writing
  - Work on or from scaffolding or rigging, steel erecting or on tall buildings such as industrial chimneys or steeples
  - Manual work in road or rail or ship construction
  - Other outdoor construction or maintenance work
  - Managerial work, including surveyors and inspectors, designers, instructors
- Transports
  - Road transport
  - Drivers and operators of other mobile machinery
  - Rail transport (overground and underground)
  - Air transport
  - Sea/water transport
  - Vehicle (car, bus, train, ship/boat, aircraft) body builders, fitters and repairers, including electricians, auto engineers, spray painters, etc.
  - Managerial/administrative work in transport/distribution
- Manufacturing
  - Engineers and factory maintenance
  - Managerial work, inspectors, instructors
  - Routine factory work in the production of food, drink or tobacco
  - Routine factory work in the production of textiles, clothes, or shoes
  - Routine factory work in the production of leather, hides, pelts
  - Routine factory work in the production of glass or ceramics
  - Routine factory work in the production of plastics or plastic products
  - Routine factory work in the production of rubber
  - Routine factory work in the production of chemicals or petrochemicals
  - Routine factory work in the production of paper, pulp or wood products
  - Routine factory work in the production of concrete, asphalt, lime, asbestos
  - Routine factory work in the production of electrical/electronic products and equipment
  - Routine factory work in the production of vehicles or vehicle components
  - Routine factory work in the production of metal goods such as cookers, bed frames, jewellery, rifles, bicycles etc.
  - Routine factory work in the production of any other goods or products

    - Routine factory work in making, treating or scrapping metals
- Mining energy water
    - Work in mining, quarrying, utilities and power generating industry, or water treatment
    - Managerial work, including engineers, surveyors and inspectors
- Skilled manual
    - Textiles, leather, upholstery
    - Printing
    - Food, drink
    - Glass, ceramics, bricks
    - Furniture, other wood trades, musical instruments
    - Precious metals or stones
    - Work with metal, welding
    - Vehicle (car, bus, train, ship, aircraft) body building or repairing
    - Electrics, electronics, telecommunications, computers
    - Instrument making
    - Other
- Cleaning waste pest control
    - Factory and industrial cleaners
    - Cleaner, laundry or dry-cleaning worker, including manager/owner
    - Caretaker or housekeeper, including porters
    - Waste collector, recycler, including manager
    - Pest control worker, including manager
- Science technology
    - Science/research professional, including managers
    - Science/research technician, including librarian
    - Engineering professional
    - Engineering technician
    - Information & communication technology (ICT) or information technology (IT) professional or technician, including managers
- Healthcare
    - Medical doctor, psychologist, pharmacist, ophthalmic optician, dentist
    - Nurse and auxiliary, paramedic, therapist, other medical/allied professional
    - Medical/allied assistant/technician and other staff, including administrators
    - Manager in healthcare (hospitals, clinics etc.) or residential care
    - Residential care worker (with children, the elderly, young offenders)
    - Social and community worker or manager, including clergy/any religious officer/leader
    - Undertaker, mortuary assistant, including funeral director and manager
    - Animal health professional or assistant and related jobs
- Sports arts
    - Work in sport and fitness, sports players
    - Visual artist, graphic designer, other designer (clothing, fashion, commercial, furniture, interior, textile)
    - Author or writer, journalist, broadcaster; photographer or audiovisual operator; public relations professional
    - Actor, singer, dancer, musician, or other performers
    - Arts or entertainment manager
    - Arts or entertainment assistants
    - Other entertainment assistants and related jobs
- Office based
    - Official in national/local government including chief executive, administrator, manager, supervisor, officer; civil and public service professional, assistant or clerical officer
    - Official in private organisation or NGO, including chief executive, administrator, manager, supervisor, officer, etc.
    - Manager or senior official in sales and marketing, advertising, public relations, human resources, customer care; property/housing manager
    - Clerk/officer in sales and marketing, advertising, public relations, human resources, or customer care; estate agent, auctioneer
    - Manager, office manager or clerk in financial institution (banks, post office, insurance)
    - Other professional or support work in business or finance
    - Work in law, accountancy or business analysis/management consultancy
    - Work in architecture, town planning or surveying
    - Secretary, receptionist, or typist
    - General office worker, telephonist, radio operator, postal worker, messenger
    - Librarian, filing and database clerk
- Retail
    - Selling or other work in all kind of shops (retail or wholesale)
    - Other work in selling, including: door-to-door sales, credit agent, market trader, telephone salesperson, advertising worker
    - Work in storage, distribution or transport of goods
- Services personal
    - Personal services, including beauty
    - Work in travel and tourism
    - Work in restaurants, bars, pubs, hotels and other accommodation
- Education
    - Teaching professional
    - Educational/school assistant or other childcare workers
    - Manager or administrator in educational establishment
- Military emergency

- Armed Forces (excluding civilians working in this sector)
- Ambulance service, fire service, police service
- Prison and probation services, customs and excise, border control
- Private and other security work
- Inspector of factories, utilities and trading standards; occupational hygiene or health/safety officer, building inspector, environmental health officer

3.3.2. Which one would you say your job is/was? ……[ISCO88 lists]……

3.4. On average, how many hours a week do/did you work?

- Less than 20 hours
- 20 to 40 hours
- More than 40 hours

3.5. Were/are you regularly exposed to dust? Yes No

3.6. Were/are you regularly exposed to fumes? Yes No

3.7. Did/do you usually wear a mask or other breathing protection? Yes No

Completed by: ____ ____ ____ ____

B-8 Environmental questionnaire

Environmental questionnaire

Site ………

Fieldworker number ………

Participant number ………

Heating

This section is about the way you heat your home

1.1. Do you heat your home? Yes No

1.2. In the period since the last survey, what fuels have you used to heat your home?

- Coal
- Coke
- Charcoal
- Wood
- Kerosene
- Liquefied Petroleum Gas
- Dung
- Straw and other crop residues
- Electricity
- Other

1.3. How many months of the year do you heat your home on most days? ………

1.4. Is the boiler/stove/fire inside your home? Yes No

1.4.1. Is it vented to the outside by a chimney Yes No

1.4.2. Does the room with the boiler/stove/fire have open windows/doors Yes No

Cooking

This section is about the main stoves/devices that are used at your home (including cooking food, making tea, and boiling drinking water)

2. In the period since the last survey, what fuels has your household used to cook on?

- Coal
- Coke
- Charcoal
- Wood
- Kerosene
- Liquefied Petroleum Gas
- Dung
- Straw and other crop residues
- Electricity
- Other

Coal:

2.1.1. Has your household used coal to cook for more than 6 months in your life? Yes No

2.1.2 For how many years since the last survey has your household used coal for cooking? ………

2.1.3. Is your household still using coal now for cooking? Yes No

2.1.4. Do you yourself cook (with coal)? Yes No

2.1.5. During the period in which coal was used, on average how many days a week have you cooked? ………

2.1.6. On the days during this period when you were cooking on coal, on average how many hours a day have you cooked? ………

2.1.7. Do/Did your eyes tear or smart while cooking on coal because of smoke from the fire? No Sometimes Often

2.1.8. How many hours a day do you spend in the room where the meals are cooked? ………

2.1.9. Is your coal fire…

- Outside

- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of coal fire

2.1.10. Does your coal stove have a separate chimney? Yes No

2.1.10.1. Is your outhouse ventilated through open doors or windows? Yes No

2.1.10.2. Is your kitchen ventilated through open doors or windows? Yes No

2.1.10.3. Is your living room ventilated through open doors or windows? Yes No

Charcoal:

2.2.1. Has your household used charcoal to cook for more than 6 months in your life? Yes No

2.2.2. For how many years since the last survey has your household used charcoal for cooking? ……..…

2.2.3. Is your household still using charcoal now for cooking? Yes No

2.2.4. Do you yourself cook (with charcoal)? Yes No

2.2.5. During the period in which charcoal was used, on average how many days a week have you cooked? ……..…

2.2.6. On the days during this period when you were cooking on charcoal, on average how many hours a day have you cooked? ……..…

2.2.7. Do/Did your eyes tear or smart while cooking on charcoal because of smoke from the fire? No Sometimes Often

2.2.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.2.9. Is your charcoal fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of charcoal fire

2.2.10. Does your charcoal stove have a separate chimney? Yes No

2.2.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.2.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.2.10.3. Is your living room ventilated through open doors and windows? Yes No

Coke:

2.3.1. Has your household used coke to cook for more than 6 months in your life? Yes No

2.3.2. For how many years since the last survey has your household used coke for cooking? ……..…

2.3.3. Is your household still using coke now for cooking? Yes No

2.3.4. Do you yourself cook (with coke)? Yes No

2.3.5. During the period in which coke was used, on average how many days a week have you cooked? ……..…

2.3.6. On the days during this period when you were cooking on coke, on average how many hours a day have you cooked? ……..…

2.3.7. Do/Did your eyes tear or smart while cooking on coke because of smoke from the fire? No Sometimes Often

2.3.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.3.9. Is your coke fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of coke fire

2.3.10. Does your coke stove have a separate chimney? Yes No

2.3.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.3.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.3.10.3. Is your living room ventilated through open doors and windows? Yes No

Wood:

2.4.1. Has your household used wood to cook for more than 6 months in your life? Yes No

2.4.2. For how many years since the last survey has your household used wood for cooking? ……..…

2.4.3. Is your household still using wood now for cooking? Yes No

2.4.4. Do you yourself cook? Yes No

2.4.5. During the period in which wood was used, on average how many days a week have you cooked? ……..…

2.4.6. On the days during this period when you were cooking on wood, on average how many hours a day have you cooked? ……..…

2.4.7. Do/Did your eyes tear or smart while cooking on wood because of smoke from the fire? No Sometimes Often

2.4.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.4.9. Is your wood fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of wood fire

2.4.10. Does your wood stove have a separate chimney? Yes No

2.4.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.4.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.4.10.3. Is your living room ventilated through open doors and windows? Yes No

Kerosene:

2.5.1. Has your household used kerosene to cook for more than 6 months in your life? Yes No

2.5.2. For how many years since the last survey has your household used kerosene for cooking? ……..…

2.5.3. Is your household still using kerosene now for cooking? Yes No

2.5.4. Do you yourself cook (with kerosene)? Yes No

2.5.5. During the period in which kerosene was used, on average how many days a week have you cooked? ……..…

2.5.6. On the days during this period when you were cooking on kerosene, on average how many hours a day have you cooked? ……..…

2.5.7. Do/Did your eyes tear or smart while cooking on kerosene because of smoke from the fire? No Sometimes Often

2.5.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.5.9. Is your kerosene fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of kerosene fire

2.5.10. Does your kerosene stove have a separate chimney? Yes No

2.5.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.5.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.5.10.3. Is your living room ventilated through open doors and windows? Yes No

Liquefied Petroleum Gas (LPG):

2.6.1. Has your household used LPG to cook for more than 6 months in your life? Yes No

2.6.2. For how many years since the last survey has your household used LPG for cooking? ……..

2.6.3. Is your household still using LPG now for cooking? Yes No

2.6.4. Do you yourself cook (with LPG)? Yes No

2.6.5. During the period in which LPG was used, on average how many days a week have you cooked? ……..…

2.6.6. On the days during this period when you were cooking on LPG, on average how many hours a day have you cooked? ……..…

2.6.7. Do/Did your eyes tear or smart while cooking on LPG because of smoke from the fire? No Sometimes Often

2.6.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.6.9. Is your LPG stove…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of LPG fire

2.6.10. Does your LPG stove have a separate chimney? Yes No

2.6.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.6.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.6.10.3. Is your living room ventilated through open doors and windows? Yes No

Dung:

2.7.1. Has your household used dung to cook for more than 6 months in your life? Yes No

2.7.2. For how many years since the last survey has your household used dung for cooking? ……..…

2.7.3. Is your household still using dung now for cooking? Yes No

2.7.4. Do you yourself cook (with dung)? Yes No

2.7.5. During the period in which dung was used, on average how many days a week have you cooked? ……..…

2.7.6. On the days during this period when you were cooking on dung, on average how many hours a day have you cooked? ……..…

2.7.7. Do/Did your eyes tear or smart while cooking on dung because of smoke from the fire? No Sometimes Often

2.7.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.7.9. Is your dung fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of dung fire

2.7.10. Does your dung stove have a separate chimney? Yes No

2.7.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.7.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.7.10.3. Is your living room ventilated through open doors and windows? Yes No

Straw and other crop residues:

2.8.1. Has your household used straw or other crop residues to cook for more than 6 months in your life? Yes No

2.8.2. For how many years since the last survey has your household used straw or crop residues for cooking? ……..…

2.8.3. Is your household still using straw or crop residues now for cooking? Yes No

2.8.4. Do you yourself cook (with straw or crop residues)? Yes No

2.8.5. During the period in which straw or crop residues were used, on average how many days a week have you cooked? ……..…

2.8.6. On the days during this period when you were cooking on straw or crop residues, on average how many hours a day have you cooked? ……..…

2.8.7. Do/Did your eyes tear or smart while cooking on straw because of smoke from the fire? No Sometimes Often

2.8.8. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.8.9. Is your straw fire…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room
-

Ventilation of straw fire

2.8.10. Does your straw stove have a separate chimney? Yes No

2.8.10.1. Is your outhouse ventilated through open doors and windows? Yes No

2.8.10.2. Is your kitchen ventilated through open doors and windows? Yes No

2.8.10.3. Is your living room ventilated through open doors and windows? Yes No

Electricity:

2.9.1. Has your household used electricity to cook for more than 6 months in your life? Yes No

2.9.2. For how many years since the last survey has your household used electricity for cooking? ……..…

2.9.3. Is your household still using electricity now for cooking? Yes No

2.9.4. Do you yourself cook (with electricity)? Yes No

2.9.5. During the period in which electricity was used, on average how many days a week have you cooked? ……..…

2.9.6. On the days during this period when you were cooking on electricity, on average how many hours a day have you cooked? ……..…

2.9.7. How many hours a day do you spend in the room where the meals are cooked? No Sometimes Often

2.9.8. Is your electric stove…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of electric stove

2.9.9. Does your electric stove have a separate chimney? Yes No

2.9.9.1. Is your outhouse ventilated through open doors and windows? Yes No

2.9.9.2. Is your kitchen ventilated through open doors and windows? Yes No

2.9.9.3. Is your living room ventilated through open doors and windows? Yes No

Other Cooking Fuels:

2.10.1. What "other" fuel have you used to cook for more than 6 months in your life? …….………..

2.10.2. Has your household used this other fuel to cook on throughout this entire period? Yes No

2.10.3. For how many years since the last survey has your household used this other fuel for cooking? ……..…

2.10.4. Is your household still using this other fuel now for cooking? Yes No

2.10.5. Do you yourself cook? Yes No

2.10.6. During the period in which this other fuel was used, on average how many days a week have you cooked?……..…

2.10.7. On the days during this period when you were cooking on this other fuel, on average how many hours a day have you cooked? ……..…

2.10.8. Do/Did your eyes tear or smart while cooking on this other fuel because of smoke from the fire?

No Sometimes Often

2.10.9. How many hours a day do you spend in the room where the meals are cooked? ……..…

2.10.10. Is your stove with this other fuel…

- Outside
- In a separate building from the main dwelling
- In a separate room within the main dwelling
- In the main living room

Ventilation of stove with this other fuel

2.10.11. Does your stove with this other fuel have a separate chimney? Yes No

2.10.11.1. Is your outhouse ventilated through open doors and windows? Yes No

2.10.11.2. Is your kitchen ventilated through open doors and windows? Yes No

2.10.11.3. Is your living room ventilated through open doors and windows? Yes No

Lighting

This section is about the way you light your home

3. Do you use lights at home? Yes No

3.1. In the period since the last survey, what fuels has your household used for lighting?

- Candle
- Kerosene
- Electricity or batteries
- Liquefied Petroleum Gas
- Sun (solar lantern)
- Other

Candle:

3.2.1. Has your household used candles for lighting for more than 6 months in your life? Yes No

3.2.2. For how many years since the last survey has your household used candles for lighting? ……..…

3.2.3. Is your household still using candles for lighting? Yes No

3.2.4. During the period in which candles were used for lighting, on average how many days a week have you used them? ……..…

3.2.5. On the days during this period when you were using candles for lighting, on average how many hours a day have you used them? ……..…

Kerosene:

3.3.1. Has your household used kerosenes for lighting for more than 6 months in your life? Yes No

3.3.2. For how many years since the last survey has your household used kerosenes for lighting? ……..…

3.3.3. Is your household still using kerosenes for lighting? Yes No

3.3.4. During the period in which kerosene was used for lighting, on average how many days a week have you used it?……..…

3.3.5. On the days during this period when you were using kerosene for lighting, on average how many hours a day have you used it? ……..…

Electricity or batteries:

3.4.1. Has your household used electricity or batteries for lighting for more than 6 months in your life? Yes No

3.4.2. For how many years since the last survey has your household used electricity or batteries for lighting? ……..…

3.4.3. Is your household still using electricity or batteries for lighting? Yes No

3.4.4. During the period in which electricity or batteries were used for lighting, on average how many days a week have you used them? ……..…

3.4.5. On the days during this period when you were using electricity or batteries for lighting, on average how many hours a day have you used them? ……..…

Liquefied Petroleum Gas (LPG):

3.5.1. Has your household used LPG for lighting for more than 6 months in your life? Yes No

3.5.2. For how many years since the last survey has your household used LPG for lighting? ……..…

3.5.3. Is your household still using LPG for lighting? Yes No

3.5.4. During the period in which LPG was used for lighting, on average how many days a week have you used it?……..…

3.5.5. On the days during this period when you were using LPG for lighting, on average how many hours a day have you used it? ……..…

Solar lanterns:

3.6.1. Has your household used solar lanterns for lighting for more than 6 months in your life? Yes No

3.6.2. For how many years since the last survey has your household used solar lanterns for lighting? ……..…

3.6.3. Is your household still using solar lanterns for lighting? Yes No

3.6.4. During the period in which solar lanterns were used for lighting, on average how many days a week have you used them? ……..…

3.6.5. On the days during this period when you were using solar lanterns for lighting, on average how many hours a day have you used them? ……..…

Other lighting fuels:

3.7.1. What "other" fuel have you used to light on? ……..………..

3.7.2. Has your household used this other fuel for lighting for more than 6 months in your life? Yes No

3.7.3. For how many years since the last survey has your household used this other fuel for lighting? ……..…

3.7.4. Is your household still using this other fuel for lighting? Yes No

3.7.5. During the period in which this other fuel was used for lighting, on average how many days a week have you used it? ……..…

3.7.6. On the days during this period when you were using this other fuel for lighting, on average how many hours a day have you used it? ……..…

Other: This section is about other things of your daily living

Traffic

4.1.1. In the period since the last survey, have you moved home? Yes No

4.1.2. How many years have you lived in your current home? ……..…

4.1.3. Is your home on a major road (this is, a road with heavy traffic of lorries and/or regular buses/minibuses)? Yes No

4.1.4. Was your previous home on a major road? Yes No

4.1.5. How many hours of your average day do you spend standing or working within 20 metres of a major road? ……..…

4.1.6. How many hours of your average day do you spend travelling (including walking) on a major road? ……..…

4.1.7. What is the main mode of travel you use?

- o Walking
- o Bicycle
- o Motorbike or moped
- o Car
- o Bus or minibus
- o Lorry
- o Other

Cleaning

4.2.1. In the period since the last survey, which of the following cleaning products have you personally used in your own home?

- Ammonia
- Bleach (not used for laundry)
- Stain removers or other solvents
- Furniture sprays
- Glass cleaning sprays
- Sprays for mopping the floor

4.2.2. During this period, on average how many days a week have you personally used…

4.2.2.1. ammonia? ……..…

4.2.2.2. bleach? ……..…

4.2.2.3. stain removers or other solvents? ……..…

4.2.2.4. furniture sprays? ……..…

4.2.2.5. glass cleaning sprays? ……..…

4.2.2.6. sprays for mopping the floor? ……..…

Pest control (in house)

4.3.1. In the period since the last survey, which of the following insecticides or repellents have you used in your home?

- Mosquito coils
- Insecticides or other pesticides in spray form
- Insecticides or other pesticides in powder form

4.3.2. During this period, on average how many days a week have you personally used…

4.3.2.1. mosquito coils? ……..…

4.3.2.2. insecticides or other pesticides in spray form? ……..…

4.3.2.3. insecticides or other pesticides in powder form? ……..…

Burning

4.5. Are you ever exposed to smoke from burning refuse (waste, rubbish)? Yes No

4.5.1. How often is there smoke from burning refuse where you are?

- o Every day
- o Most days
- o Most weeks
- o Occasionally
- o Never

4.6. Do you burn incense sticks at home? Yes No

4.6.1. How often do you burn incense?

- o Every day
- o Most days
- o Most weeks
- o Occasionally
- o Never

4.7. Are you ever exposed to smoke from burning crops (for example, sugar cane)? Yes No

4.7.1. How many days per year are you exposed to smoke from burning crops?

- o Every day
- o Most days
- o Most weeks
- o Occasionally
- o Never

Completed by: ____ ____ ____ ____

B-9 Tracking questionnaire

<u>Tracking questionnaire</u>

Site	……..…	
Fieldworker number	……..…	
Participant number	……..…	
1. Age	……..…	
2. Gender	Male	Female
3. Data Collected:	Yes	No

Did you collect?:

1.	Spirometry Questionnaire	Yes	No
2.	Core Questionnaire	Yes	No
3.	Anthropometry	Yes	No
4.	Pre-bronchodilator Spirometry	Yes	No
5.	Post-bronchodilator Spirometry	Yes	No
6.	Occupational Questionnaire	Yes	No
7.	Environmental Questionnaire	Yes	No
8.	Agricultural Questionnaire	Yes	No
9.	Refusal Questionnaire	Yes	No

Non-Response:

- o Refused/No data collected
- o Known to have permanently left area
- o Temporarily out of area
- o Dead
- o Age ineligible
- o Untraceable (e.g., bad address and phone)
- o Unreachable (e.g., never returns mail or answers phone)

Completed by: ____ ____ ____ ____

B-10 Agricultural questionnaire

1. Have you ever lived on a farm? Yes ☐ No ☐

[If "yes" ask question 1A., otherwise skip to question 2.]

1A. Are you still living on a farm? Yes ☐ No ☐

[If "yes" ask question 1A.i., otherwise skip to question 1B.]

1A.i. What size is the farm (in local unit)? _ _ _ Rai _ Ngan

_ _ _ Tarang Wa (Wa^2)

1B. How many years have you lived on a farm? _ _ years

2. Have you ever ploughed the soil or prepared it for planting? Yes ☐ No ☐

[If "yes" ask all question 2A. to 2E., otherwise skip to question 3.]

2A. How many years have you ploughed the soil or prepared it for planting?

_ _ years

2B. In the years that you ploughed the soil or prepared it for planting, how many months of each year did you do it?

_ _ months

2C. In the months that you ploughed the soil or prepared it for planting, how many days of each month did you do it?

_ _ days

2D. On the days that you ploughed the soil or prepared it for planting, how many hours of each day did you do it?

_ _ hours

2E. Are you still ploughing the soil or preparing it for planting? Yes ☐ No ☐

Plants grown

3. Do you grow plants? Yes ☐ No ☐

[If "yes" ask question all 3A. to 3O., otherwise skip to question 4.]

3A. Cereal Yes ☐ No ☐

[If "yes" ask all question 3A.i to 3A.iii, otherwise skip to question 3B.]

3A.i. Which cereal crop(s) do you grow? [SELECT ALL THAT APPLY]

☐ In-season rice
☐ Off-season rice
☐ Maize
☐ Sweet corn
☐ Wheat
☐ Other cereal

3A.i.i. If select "other cereal", please specify:_________________

3A.ii. Are you involved with harvesting the cereal crops? Yes ☐ No ☐

3A.iii. Are you involved with threshing the cereal crops? Yes ☐

No ☐

3B. Vegetables and melons Yes ☐

No ☐

[If "yes" ask all question 3B.i, otherwise skip to question 3C.]

3B.i. Which vegetables and melons do you grow?[SELECT ALL THAT APPLY]

☐ Cauliflower
☐ Cabbage
☐ Chinese kale
☐ Pak Choi
☐ Coriander
☐ Chinese convolvulus
☐ Water convolvulus
☐ Chinese cabbage
☐ Mustard Green
☐ Lettuce
☐ Broccoli
☐ Courgette
☐ Cucumber
☐ Japanese Cucumber, Suhyo
☐ Watermelon
☐ Wax gourd
☐ Pumpkin
☐ Tomato
☐ Thai eggplant
☐ Aubergine
☐ Eggplant
☐ Bitter melon
☐ Garlic
☐ Onion
☐ Shallot
☐ Indian Oyster
☐ Other vegetable and melon

3B.i.i. If select "other vegetable and melon", please specify:_____

3C. Fruit and nuts Yes ☐

No ☐

[If "yes" ask all question 3C.i, otherwise skip to question 3D.]

3C.i. Which fruit and nuts do you grow? [SELECT ALL THAT APPLY]

☐ Pineapple
☐ Santol
☐ Banana
☐ Rambutan
☐ Durian
☐ Guava
☐ Monkey apple
☐ Tamarind
☐ Lime
☐ Mango
☐ Papaya
☐ Langsat
☐ Longan
☐ Lychee
☐ Strawberry
☐ Mulberry
☐ Tangerine
☐ Pomelo
☐ Passion fruit
☐ Avocado
☐ Tung oil, tree China wood-oil tree
☐ Cashew tree
☐ Other fruit and nut

3C.i.i. If select "other fruit and nut", please specify:____________

3D. Oilseed crops Yes ☐

No ☐

[If "yes" ask all question 3D.i, otherwise skip to question 3E.]

3D.i. Which oilseed(s) do you grow? [SELECT ALL THAT APPLY]

- ☐ Sesame
- ☐ Peanut
- ☐ Soybean
- ☐ Oil Palm
- ☐ Other oilseed

3D.i.i. If select "other oilseed", please specify:_________________

3E. Root/tuber crops with high starch or inulin content	Yes	☐
	No	☐

[If "yes" ask all question 3E.i, otherwise skip to question 3F.]

3E.i. Which root/tuber crops with high starch or inulin content do you grow?

[SELECT ALL THAT APPLY]

- ☐ Sweet potato
- ☐ Potato
- ☐ Cassava
- ☐ Other root

3E.i.i. If select "other root", please specify:_____________________

3F. Beverage and spice crops	Yes	☐
	No	☐

[If "yes" ask all question 3F.i, otherwise skip to question 3G.]

3F.i. Which beverage and spice crops do you grow?

[SELECT ALL THAT APPLY]

- ☐ Coffee bean
- ☐ Tea
- ☐ Ginger
- ☐ Bird eye chili
- ☐ Chilli pepper
- ☐ Sweet pepper
- ☐ Bell pepper
- ☐ Makhwaen/Sichuan pepper
- ☐ Other beverage/spice crop

3F.i.i. If select "other beverage", please specify:________________

3G. Leguminous crops	Yes	☐
	No	☐

[If "yes" ask all question 3G.i, otherwise skip to question 3H.]

3G.i. Which leguminous crops do you grow? [SELECT ALL THAT APPLY]

- ☐ Mung bean
- ☐ Black gram, urad bean
- ☐ Cow pea
- ☐ Common bean
- ☐ Asparagus bean
- ☐ Pea
- ☐ Other legume

3G.i.i. If select "other legume", please specify:________________

3H. Sugar cane	Yes	☐
	No	☐
3I. Grasses and other fodder crops	Yes	☐
	No	☐
3J. Fibre crops	Yes	☐
	No	☐

[If "yes" ask all question 3J.i, otherwise skip to question 3K.]

3J.i. Which fibre crops do you grow? [SELECT ALL THAT APPLY]

☐ Cotton
☐ Other fibre
3J.i.i. If select "other fibre", please specify:____________________

3K. Medicinal, aromatic, pesticidal, or similar crops — Yes ☐ / No ☐

[If "yes" ask question 3K.i, otherwise skip to question 3L. and 3M.]

3K.i. Which medicinal, aromatic, pesticidal, or similar crops do you grow?,

please specify:_______________

3L. Rubber — Yes ☐ / No ☐

3M. Flower crops — Yes ☐ / No ☐

[If "yes" ask all question 3M.i, otherwise skip to question 3N.]

3M.i. Which flower crops do you grow?, please specify:_________________

3N. Tobacco — Yes ☐ / No ☐

3O. Other crops — Yes ☐ / No ☐

[If "yes" ask all question 3O.i, otherwise skip to question 4.]

3O.i. Which other crops do you grow? [SELECT ALL THAT APPLY]

☐ Teak
☐ Calameae
☐ Bamboo
☐ Agarwood/Eagle wood
☐ Other crop
3O.i.i. If select "other crop", please specify:__________________

Weedkillers

4. Have you ever used weedkillers to protect your plants? — Yes ☐ / No ☐

[If "yes" ask question 4A.., otherwise skip to question 5.]

4A. When did you start spraying weedkillers? _ _ _ _ (year in B.E.)

4B. Over the past year, have you sprayed weedkillers? — Yes ☐ / No ☐

[If "no" ask question 4C., otherwise skip to question 4B.1. then 4D.]

4B.1. Time since last weedkillers exposure
i. _ _ hours
ii. _ _ days
iii. _ _ months

4C. When did you stop spraying weedkillers? _ _ _ _ (year in B.E.)

[Continue question 4D.]

4D. weedkillers

Now I am going to ask you about *weedkillers* that you have ever used. I would like you to tell me each *weedkiller* that you apply (or applied), and how long do (or did) you spray? If possible, please show the *weedkiller* package(s)/label(s). In case the name(s) of *weedkiller(s)* used is/are not in the lists below, please specify on question 4D.i. in the 'other' cell, and allow the interviewer to take a photo (by a device provided).

i. Which weedkillers have you ever used? [SELECT ALL THAT APPLY]	ii. How many years have you sprayed your crops with weedkillers?	iii. In the years that you sprayed weedkillers, how many months of each year did you spray?	iv. In the months that you sprayed weedkillers, how many days of each month did you spray?	v. On the days that you sprayed weedkillers, how many hours of each day did you spray?	vi. Over the past year, have you used this?	If applicable, take a photo of weedkiller package(s)/label(s). [Only 'other' selected]
☐ 1. glyphosate *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 2. paraquat *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 3. 2,4-D-dimethylammonium *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 4. atrazine *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 5. acetochlor *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 6. alachlor *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 7. pendimethalin *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 8. metsulfuron-methyl *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 9. isoxaflutole *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 10. cyprosulfamide + isoxaflutole *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 11. 2,4-D sodium salt *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 12. quizalofop-P-tefuryl *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 13. fomesafen *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 14. glufosinate-ammonium *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ other: please specify………….. *If selected, answer ii. to vi*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	*Please record a photo no.* …………….

4E. When you spray, which parts of your body usually come into contact with weedkillers? [SELECT ALL THAT APPLY]

Face	☐
Hands	☐
Arms	☐
Trunk	☐
Legs	☐
None of the above	☐

4F. Do you mix these weedkillers yourself?

Yes	☐
No	☐

[If "yes" ask question 4G., otherwise skip to question 4H.]

4G. Did you mix them inside home, outside home or both?

Outside home	☐
Inside home	☐
Both outside and inside home	☐

4H. Do you store the mixed chemicals in your home?

Yes	☐
No	☐

4I. When mixing, loading or applying these weedkillers what protective clothing do you wear? [SELECT ALL THAT APPLY]

Boots	☐
Gloves	☐
Respirator	☐
Goggles/Safety glasses	☐
Mask	☐
Balaklavas or clothes wrapped around the face	☐
Hat	☐
Full face shield	☐
Apron	☐
None of the above	☐

4J. After spraying the weedkillers do you…? [SELECT ALL THAT APPLY]

Wash your hands, in home	☐
Wash your hands, outside home	☐
Have a shower, in home	☐
Have a shower, outside home	☐
Change your clothes	☐
None of the above	☐

<u>Insecticides</u>

5. Have you ever used insecticides to protect your plants?

Yes	☐
No	☐

[If "yes" ask question 5A., otherwise skip to question 6.]

5A. When did you start spraying insecticides? _ _ _ _ (year in B.E.)

5B. Over the past year, have you sprayed insecticides? Yes ☐

No ☐

[If "no" ask question 5C., otherwise skip to question 5B.1. then 5D.]

5B.1. Time since last insecticides exposure
i. _ _ hours
ii. _ _ days
iii. _ _ months

5C. When did you stop spraying insecticides? _ _ _ _ (year in B.E.)

[Continue question 5D.]

<u>5D. insecticides</u>

Now I am going to ask you about *insecticides* that you have ever used. I would like you to tell me each *insecticide* that you apply (or applied), and how long do (or did) you spray? If possible, please show the *insecticide* package(s)/label(s). In case the name(s) of *insecticide(s)* used is/are not in the lists below, please specify on question 5D.i. in the 'other' cell, and allow the interviewer to take a photo (by a device provided).

i. Which insecticides have you ever used? [SELECT ALL THAT APPLY]	ii. How many years have you sprayed your crops with insecticides?	iii. In the years that you sprayed insecticides, how many months of each year did you spray?	iv. In the months that you sprayed insecticides, how many days of each month did you spray?	v. On the days that you sprayed insecticides, how many hours of each day did you spray?	vi. Over the past year, have you used this?	If applicable, take a photo of insecticide package(s)/label(s). [Only 'other' selected]
☐ 1. chlorpyrifos *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 2. cartap hydrochloride *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 3. cypermethrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 4. acetamiprid *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 5. fipronil *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 6. chlorpyrifos + cypermethrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 7. pyridaben *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 8. imidacloprid *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 9. emamectin benzoate *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 10. chlorfenapyr	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes	

If selected, answer ii. to vi.					☐ No	
☐ 11. buprofezin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 12. sulphur *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 13. carbaryl *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 14. abamectin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 15. propargite *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 16. Petroleum oil *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 17. dinotefuran *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 18. *B Thuringiensis* *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 19. thiamethoxam *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 20. indoxacarb *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 21. lambda-cyhalothrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ other: please specify………….. *If selected, answer ii. to vi..*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	*Please record a photo no.* …………….

5E. When you spray, which parts of your body usually come into contact with insecticides? [SELECT ALL THAT APPLY]

Face	☐
Hands	☐
Arms	☐
Trunk	☐
Legs	☐
None of the above	☐

5F. Do you mix these insecticides yourself?

Yes	☐
No	☐

[If "yes" ask question 5G., otherwise skip to question 5H.]

5G. Did you mix them inside, outside home or both?

- Outside home ☐
- Inside home ☐
- Both outside and inside home ☐

5H. Do you store the mixed chemicals in your home? Yes ☐ No ☐

5I. When mixing, loading or applying these insecticides what protective clothing do you wear? [SELECT ALL THAT APPLY]

- Boots ☐
- Gloves ☐
- Respirator ☐
- Goggles/Safety glasses ☐
- Mask ☐
- Balaklavas or clothes wrapped around the face ☐
- Hat ☐
- Full face shield ☐
- Apron ☐
- None of the above ☐

5J. After spraying the insecticides do you…? [SELECT ALL THAT APPLY]

- Wash your hands, in home ☐
- Wash your hands, outside home ☐
- Have a shower, in home ☐
- Have a shower, outside home ☐
- Change your clothes ☐
- None of the above ☐

<u>Fungicides</u>

6. Have you ever used fungicides? Yes ☐ No ☐

[If "yes" ask question 6A., otherwise skip to question 7.]

6A. When did you start spraying fungicides? _ _ _ _ (year in B.E.)

6B. Over the past year, have you sprayed fungicides? Yes ☐ No ☐

[If "no" ask question 6C., otherwise skip to question 6B.1. then 6D.]

6B.1. Time since last fungicides exposure
- i. _ _ hours
- ii. _ _ days
- iii. _ _ months

6C. When did you stop spraying fungicides? _ _ _ _ (year in B.E.)

[Continue question 6D.]

6D. fungicides

Now I am going to ask you about *fungicides* that you have ever used. I would like you to tell me each *fungicide* that you apply (or applied), and how long do (or did) you spray? If possible, please show the *fungicide* package(s)/label(s). In case the name(s) of *fungicide(s)* used is/are not in the lists below, please specify on question 6D.i. in the 'other' cell, and allow the interviewer to take a photo (by a device provided).

i. Which fungicides have you ever used? [SELECT ALL THAT APPLY]	ii. How many years have you sprayed your crops with fungicides?	iii. In the years that you sprayed fungicides, how many months of each year did you spray?	iv. In the months that you sprayed fungicides, how many days of each month did you spray?	v. On the days that you sprayed fungicides, how many hours of each day did you spray?	vi. Over the past year, have you used this?	If applicable, take a photo of insecticide package(s)/label(s). [Only 'other' selected]
☐ 1. mancozeb *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 2. hexaconazole *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 3. carbendazim *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 4. thiram *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 5. copper II hydroxide *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 6. quintozene + Etridiazole *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 7. triforine *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 8. pyraclostrobin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 9. dimethomorph *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 10. etridiazole *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 11. cuprous oxide *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 12. prochloraz *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 13. tetraconazole *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ other: please specify…………… *If selected, answer ii. to vi..*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	*Please record a photo no.* …………….

6E. When you spray, which parts of your body usually come into contact with fungicides? [SELECT ALL THAT APPLY]

Face ☐

Hands ☐

Arms ☐

Trunk ☐

Legs ☐

None of the above ☐

6F. Do you mix these fungicides yourself? Yes ☐

No ☐

[If "yes" ask question 6G., otherwise skip to question 6H.]

6G. Did you mix them inside, outside home or both?

Outside home ☐

Inside home ☐

Both outside and inside home ☐

6H. Do you store the mixed chemicals in your home? Yes ☐

No ☐

6I. When mixing, loading or applying these fungicides what protective clothing do you wear? [SELECT ALL THAT APPLY]

Boots ☐

Gloves ☐

Respirator ☐

Goggles/Safety glasses ☐

Mask ☐

Balaklavas or clothes wrapped around the face ☐

Hat ☐

Full face shield ☐

Apron ☐

None of the above ☐

6J. After spraying the fungicides do you…? [SELECT ALL THAT APPLY]

Wash your hands, in home ☐

Wash your hands, outside home ☐

Have a shower, in home ☐

Have a shower, outside home ☐

Change your clothes ☐

None of the above ☐

Storage of food crops

7. Have you ever used chemicals to protect food crops during storage? Yes ☐
No ☐

[If "yes" ask question 7A., otherwise skip to question 8.]

7A. Which chemicals do you apply to protect food crops during storage?

[SELECT ALL THAT APPLY]

Rodenticide ☐

Fumigant ☐

Animals

8. Do you keep animals? Yes ☐ No ☐

[If "yes" ask question 8A. and 9., otherwise skip to question 10.]

8A. Which of these animals do you keep? [SELECT ALL THAT APPLY]

Insects (bees/silkworms/other worms or insects) ☐
Large ruminants (Cattle/buffaloes/yaks) ☐
Small ruminants (Sheep/goats) ☐
Pigs or swine ☐
Equines ☐
Poultry: hens, ducks, geese etc. ☐
Dogs and cats ☐
Rabbits and hares ☐
Other animal(s) ☐
8A.i. If select "other animal(s)", please specify:________________

Insecticides protecting animals

9. Have you ever used insecticides to protect your animals? Yes ☐ No ☐

[If "yes" ask question 9A., otherwise skip to question 10.]

9A. When did you start dipping insecticides protecting animals? _ _ _ _ (year in B.E.)

9B. Over the past year, have you dipped insecticides protecting animals?

Yes ☐

No ☐

[If "no" ask question 9C., otherwise skip to question 9B.1. then 9D.]

9B.1. Time since last insecticides protecting animal exposures

i. _ _ hours

ii. _ _ days

iii. _ _ months

9C. When did you stop spraying insecticides protecting animals? _ _ _ _ (year in B.E.)

[Continue question 9D.]

9D. insecticides protecting animals

Now I am going to ask you about *insecticides* that you have ever used to protect your animals. I would like you to tell me each *insecticide* that you apply (or applied), and how long do (or did) you dip? If possible, please show the *insecticide* package(s)/label(s). In case the name(s) of *insecticide(s)* used is/are not in the lists below, please specify on question 9D.i. in the 'other' cell, and allow the interviewer to take a photo (by a device provided).

i. Which insecticides have you ever used? [SELECT ALL THAT APPLY]	ii. How many years have you dipped insecticides to protect animals?	iii. In the years that you dipped insecticides, how many months of each year did you dip?	iv. In the months that you dipped insecticides, how many days of each month did you dip?	v. On the days that you dipped insecticides, how many hours of each day did you dip?	vi. Over the past year, have you applied this?	If applicable, take a photo of insecticide protecting animals package(s)/label(s). [Only 'other' selected]
☐ 1. chlorpyrifos *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 2. cartap hydrochloride *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 3. cypermethrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 4. acetamiprid *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 5. fipronil *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 6. chlorpyrifos + cypermethrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 7. pyridaben *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 8. imidacloprid *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 9. emamectin benzoate *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 10. chlorfenapyr *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 11. buprofezin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 12. sulphur *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 13. carbaryl *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 14. abamectin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 15. propargite *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 16. Petroleum oil *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	

☐ 17. dinotefuran *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 18. *B Thuringiensis* *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 19. thiamethoxam *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 20. indoxacarb *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ 21. lambda-cyhalothrin *If selected, answer ii. to vi.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	
☐ other: please specify…………… *If selected, answer ii. to vi..*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Yes ☐ No	*Please record a photo no.* …………….

9E. When you dip, which parts of your body usually come into contact with insecticides? [SELECT ALL THAT APPLY]

Face ☐

Hands ☐

Arms ☐

Trunk ☐

Legs ☐

None of the above ☐

9F. Do you mix these insecticides yourself? Yes ☐

No ☐

[If "yes" ask question 9G., otherwise skip to question 9H.]

9G. Did you mix them inside, outside home or both?

Outside home ☐

Inside home ☐

Both outside and inside home ☐

9H. Do you store the mixed chemicals in your home? Yes ☐

No ☐

9I. When mixing, loading or applying these insecticides what protective clothing do you wear? [SELECT ALL THAT APPLY]

Boots ☐

Gloves ☐

Respirator ☐

Goggles/Safety glasses ☐

Mask ☐

Balaklavas or clothes wrapped around the face ☐

Hat ☐

Full face shield ☐

Apron ☐

None of the above ☐

9J. After dipping the insecticides do you…? [SELECT ALL THAT APPLY]

Wash your hands, in home ☐

Wash your hands, outside home ☐

Have a shower, in home ☐

Have a shower, outside home ☐

Change your clothes ☐

None of the above ☐

10. Have you ever worked in a barn/silo storing grain or fodder? Yes ☐ No ☐

[If "yes" ask question 10A. to 10E., otherwise skip to question 11.]

10A. How many years have you worked in a barn/silo storing grain or fodder? _ _ years

10B. In the years that you worked in a barn/silo storing grain or fodder, how many months of each year did you do it? _ _ months

10C. In the months that you worked in a barn/silo storing grain or fodder, how many days of each month did you do it? _ _ days

10D. On the days that you worked in a barn/silo storing grain or fodder, how many hours of each day did you do it? _ _ hours

10E. Are you still working in a barn/silo storing grain or fodder? Yes ☐

No ☐

11. Have you ever driven farm machines? Yes ☐ No ☐

[If "yes" ask question 11A., otherwise skip to question 12.]

<u>11A. farm machines</u>

Now I am going to ask you about *farm machines and fuels* that you have ever used. I would like you to tell me each *farm machine* that you drive (or drove), how long do (or did) you use, and its fuel? The following are explanations for each *farm machine.* In case of 'other' selected, please specify a name of machine used.

- <u>Farm trucks</u>: Pick-ups, cargo vans, cars and other passenger vehicles used in farm business
- <u>Tractors</u>
- <u>Tillage equipment</u>: Moldboard plow; Disk plow; Subsoiler; Lister; Disk harrow; Spring tooth harrow; Spike; Land roller; Float
- <u>Planting equipment</u>: Spacing drill; Planters; Transplanters; Suger cane planter
- <u>Crop protection equipment</u>: Water pumps; Sprats; Cultivator; Fertiliser distributors; Mowers
- <u>Harvesting equipment</u>: Combine harvester; Sugar harvester; Straw or fodder balers; Root or tuber harvesting; Threshing; Hullers and Mills
- <u>Other</u>: e.g. Livestock machine, Milking machines, Feeding stuffs, Poultry keeping, Crop processing equipment, Grading, Dryers, Conveyors

i. Which of these machines have you driven on the farm? [SELECT ALL THAT APPLY]	ii. How many years have you driven these farm machines	iii. In the years that you drove these farm machines, how many months of each year did you drive it?	iv. In the months that that you drove these farm machines, how many days of each month did you drive it?	v. On the days that that you drove these farm machines, how many hours of each day did you drive it?	vi. Which of these sources of fuel is used for driving your driving farm machinery? [SELECT ALL THAT APPLY]	vii. Over the past year, have you driven these farm machines?
☐ Farm trucks *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No
☐ Tractors *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No
☐ Tillage equipment *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No
☐ Planting equipment *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No
☐ Crop protection equipment *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No
☐ Harvesting equipment *If selected, answer ii. to vii.*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:*………..	☐ Yes ☐ No

☐ Other: please specify…………… *If selected, answer ii. to vii..*	_ _ years	_ _ months	_ _ days	_ _ hours	☐ Diesel ☐ Petrol (gasoline) ☐ Biodiesel ☐ Gasohol ☐ Other fuel *specify:………..*	☐ Yes ☐ No

12. Do you apply natural fertilizer?
Yes ☐
No ☐

13. Do you apply chemical fertilizer?
Yes ☐
No ☐

14. Do you burn forest/previous crops for converting to farm lands?
Yes ☐
No ☐

[If "yes" ask question 14A., otherwise finish this interview]

14A. Over the past year, have you burnt forest/previous crops for converting to farm lands?

Yes ☐
No ☐

[If "yes" ask question 14A.1., otherwise skip to question 14B.]

14A.1. Time since last burning forest/previous crops for converting to farm lands?

i. _ _ hours
ii. _ _ days
iii. _ _ months

14B. How long have you burnt forest/previous crops for converting to farm lands?

_ _ years

14C. How many times a year did you burn forest/previous crops for converting to farm lands?

_ _ _ times

Completed by: ____ ____ ____ ____

B-11 Comparison of respiratory symptoms between participants who did and did not achieve post-bronchodilator spirometry

	acceptable and repeatable post-bronchodilator spirometry result				
	with- (n=358)		without- (n=35)		
Respiratory symptoms†	*n*	Percent	*n*	Percent	p-value
Chronic cough	34	9.5%	7	20.0%	0.05
Chronic phlegm	23	6.4%	2	5.7%	1.00
Shortness of breath	8	2.3%	1	2.9%	0.57
Wheezing	20	5.6%	4	11.4%	0.25
Self-reported chronic bronchitis	3	0.8%	1	2.9%	0.31

†Analysing differences between subject groups by chi-squared test or Fisher's exact test (for n<5).

Appendix C Occupational exposures and respiratory health effects: results from the Burden of Obstructive Lung Disease (BOLD) study

C-1 Association of respiratory symptoms with occupational variables

Occupational variables		Cough†					Phlegm†					Wheeze††					**Dyspnoea††**				
	n	OR	95% CI			I^2 (%)	OR	95% CI			I^2 (%)	OR	95% CI			I^2 (%)	**OR**	**95% CI**			**I^2 (%)**
Unexposed to any dusty job	18,455	ref					ref					ref					ref				
Organic dust	3,979	**1.22***	**1.03**	to	**1.46**	**NS**	1.16	0.99	to	1.37	NS	**1.37*****	**1.21**	to	**1.55**	**NS**	**1.40*****	**1.22**	to	**1.62**	**NS**
Farming	3,826	**1.28****	**1.08**	to	**1.53**	**NS**	1.18	0.99	to	1.40	NS	**1.38*****	**1.20**	to	**1.57**	**NS**	**1.43*****	**1.23**	to	**1.66**	**NS**
Flour, feed or grain milling	219	**2.13****	**1.38**	to	**3.28**	**NS**	**2.27*****	**1.62**	to	**3.17**	**NS**	2.45***	1.76	to	3.42	51.3%	2.49***	1.51	to	4.11	58.8%
Cotton or jute processing	265	1.47	0.85	to	2.54	NS	1.21	0.80	to	1.83	NS	1.68*	1.12	to	2.51	55.3%	**2.07****	**1.27**	to	**3.37**	**NS**
Inorganic dust	660	**1.59*****	**1.24**	to	**2.03**	**NS**	**1.40****	**1.10**	to	**1.79**	**NS**	1.92***	1.47	to	2.52	54.5%	**1.67*****	**1.28**	to	**2.18**	**NS**
Hard-rock mining	171	1.51	0.83	to	2.76	NS	**2.09****	**1.34**	to	**3.26**	**NS**	**2.48*****	**1.73**	to	**3.55**	**NS**	**1.97****	**1.27**	to	**3.06**	**NS**
Coal mining	156	**1.86***	**1.07**	to	**3.23**	**NS**	1.56	0.86	to	2.83	NS	2.35*	1.22	to	4.52	52.5%	2.49***	1.53	to	4.04	**NS**
Sandblasting	108	**3.13****	**1.63**	to	**5.98**	**NS**	**2.11***	**1.14**	to	**3.93**	**NS**	**2.21****	**1.32**	to	**3.70**	**NS**	**3.93*****	**2.15**	to	**7.16**	**NS**
Working with asbestos	310	**2.38*****	**1.59**	to	**3.57**	**NS**	**1.91*****	**1.33**	to	**2.73**	**NS**	**1.94*****	**1.38**	to	**2.73**	**NS**	**2.17*****	**1.45**	to	**3.26**	**NS**
Fume	1,172	1.42*	1.07	to	1.88	53.6%	1.31	0.98	to	1.75	56.5%	**1.42*****	**1.22**	to	**1.66**	**NS**	**1.42****	**1.16**	to	**1.74**	**NS**
Chemical or plastics-manufacturing	449	**1.90*****	**1.45**	to	**2.49**	**NS**	**1.61****	**1.23**	to	**2.12**	**NS**	**1.52*****	**1.26**	to	**1.83**	**NS**	**1.56***	**1.07**	to	**2.28**	**NS**
Foundry or steel milling	365	**1.82***	**1.15**	to	**2.87**	**NS**	**1.70***	**1.09**	to	**2.66**	**NS**	**1.95*****	**1.53**	to	**2.49**	**NS**	**2.51*****	**1.62**	to	**3.90**	**NS**
Welding	562	2.46*	1.07	to	5.70	92.7%	1.26	0.98	to	1.63	NS	**1.42*****	**1.18**	to	**1.72**	**NS**	**1.67*****	**1.29**	to	**2.15**	**NS**
Firefighting	102	**2.65***	**1.05**	to	**6.68**	**NS**	**1.80***	**1.04**	to	**3.10**	**NS**	**2.31*****	**1.55**	to	**3.43**	**NS**	**2.15***	**1.08**	to	**4.28**	**NS**

NS: not statistically significant

C-2 Association of post-bronchodilator spirometric parameters with occupational variables

Occupational variables	FEV$_1$/FVC (%)†					FVC (L)††				
	n	Mean (SE)	β	95% CI	I^2 (%)	*n*	Mean (SE)	β	95% CI	**I^2 (%)**
Unexposed to any dusty job	18,484	79.28 (0.19)	ref			18,484	3.09 (0.02)	ref		
Organic dust	7,612	77.32 (0.32)	-0.16	-0.44 to 0.13	NS	7,612	3.37 (0.03)	0.01	-0.01 to 0.03	NS
Farming	7,078	77.23 (0.32)	-0.05	-0.38 to 0.28	NS	7,078	3.38 (0.03)	0.03	-0.01 to 0.07	78.7%
Flour, feed or grain milling	411	75.68 (1.01)	-0.32	-2.17 to 1.53	93.7%	411	3.79 (0.08)	0.00	-0.08 to 0.08	81.3%
Cotton or jute processing	516	78.03 (0.98)	-0.23	-0.82 to 0.35	NS	516	3.19 (0.14)	-0.02	-0.10 to 0.05	74.0%
Inorganic dust	1,287	76.58 (0.79)	-0.19	-0.76 to 0.38	NS	1,287	3.92 (0.08)	0.02	-0.04 to 0.08	64.1%
Hard-rock mining	335	72.89 (2.62)	-0.96	-2.02 to 0.10	53.2%	335	3.71 (0.13)	0.01	-0.12 to 0.14	87.6%
Coal mining	313	74.44 (0.76)	0.60	-1.22 to 2.42	91.5%	313	3.86 (0.06)	-0.02	-0.17 to 0.13	90.1%
Sandblasting	210	71.79 (3.01)	0.24	-2.04 to 2.52	95.9%	210	3.70 (0.20)	0.00	-0.10 to 0.10	83.5%
Working with asbestos	623	77.53 (0.88)	-1.75	-3.66 to 0.16	90.4%	623	4.01 (0.08)	-0.07	-0.20 to 0.07	90.5%
Fume	2,352	76.42 (0.61)	0.13	-0.65 to 0.92	78.8%	2,352	3.78 (0.05)	0.00	-0.03 to 0.04	NS
Chemical or plastics-manufacturing	892	76.28 (0.79)	-0.63	-1.53 to 0.26	69.6%	892	3.63 (0.06)	0.03	-0.06 to 0.12	84.2%
Foundry or steel milling	700	76.51 (1.29)	-0.12	-1.28 to 1.04	76.3%	700	3.87 (0.18)	-0.04	-0.13 to 0.06	75.4%
Welding	1,068	76.17 (1.16)	0.53	-0.45 to 1.50	78.5%	1,068	3.90 (0.05)	-0.02	-0.07 to 0.03	52.7%
Firefighting	202	76.87 (1.04)	1.25	-0.27 to 2.77	87.0%	202	4.03 (0.08)	-0.05	-0.14 to 0.04	69.9%

Means (SE) were from all 41-site participants together.

† The coefficients (β) were adjusted for sex, age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

†† The coefficients (β) were adjusted for sex, age (years), height (cm) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

C-3 Association of FEV_1/FVC (%) with groups of dusty jobs stratified by sex and sites' country economy

Groups of dusty jobs	Male FEV_1/FVC (%)							Female FEV_1/FVC (%)						
Organic dust	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All														
unexposed to any	7,443	78.48 (0.28)	ref					11,041	79.99 (0.17)	ref				
ever	4,287	76.60 (0.49)	-0.16	-0.63	to	0.31	NS	3,325	78.75 (0.40)	-0.10	-0.50	to	0.29	NS
HICs														
unexposed to any	3,023	78.15 (0.26)	ref					4,280	78.98 (0.17)	ref				
ever	1,005	76.90 (0.66)	0.24	-0.45	to	0.93	NS	737	76.89 (0.36)	-0.29	-0.91	to	0.33	NS
LMICs														
unexposed to any	4,420	78.56 (0.33)	ref					6,761	80.29 (0.21)	ref				
ever	3,282	76.55 (0.55)	-0.41	-1.00	to	0.19	NS	2,588	79.23 (0.49)	-0.05	-0.57	to	0.47	53.2%
Never-smokers														
unexposed to any	3,144	79.78 (0.27)	ref					8,437	80.27 (0.18)	ref				
ever	1,806	76.66 (1.66)	-0.15	-0.68	to	0.38	NS	2,698	79.28 (0.43)	-0.15	-0.56	to	0.27	NS
HICs (never-smokers)														
unexposed to any	1,126	79.94 (0.33)	ref					2,551	80.20 (0.16)	ref				
ever	330	78.50 (0.60)	0.11	-0.88	to	1.10	NS	434	77.74 (0.45)	-0.62	-1.34	to	0.10	NS
LMICs (never-smokers)														
unexposed to any	2,018	79.75 (0.32)	ref					5,886	80.29 (0.21)	ref				
ever	1,476	76.43 (1.83)	-0.27	-0.90	to	0.35	NS	2,264	79.59 (0.50)	0.04	-0.52	to	0.59	NS

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Groups of dusty jobs	Male FEV1/FVC (%)								Female FEV1/FVC (%)							
Inorganic dust	***n***	**Mean (SE)**	**β**	**95% CI**			**I^2 (%)**	***n***	**Mean (SE)**	**β**	**95% CI**			**I^2 (%)**
All														
unexposed to any	7,443	78.48 (0.28)	ref					11,041	79.99 (0.17)	ref				
ever	1,156	76.62 (0.83)	0.00	-0.63	to	0.62	NS	131	75.92 (1.15)	0.55	-1.42	to	2.53	96.5%
HICs														
unexposed to any	3,023	78.15 (0.26)	ref					4,280	78.98 (0.17)	ref				
ever	579	75.61 (0.44)	0.42	-0.50	to	1.35	NS	57	75.47 (1.23)	-0.02	-2.90	to	2.86	79.9%
LMICs														
unexposed to any	4,420	78.56 (0.33)	ref					6,761	80.29 (0.21)	ref				
ever	577	77.12 (1.24)	-0.40	-1.20	to	0.40	NS	74	76.80 (2.39)	0.94	-1.63	to	3.51	97.8%
Never-smokers														
unexposed to any	3,144	79.78 (0.27)	ref					8,437	80.27 (0.18)	ref				
ever	345	81.47 (1.00)	0.62	-0.98	to	2.22	89.3%	76	76.94 (0.52)	0.09	-3.52	to	3.70	99.4%
HICs (never-smokers)														
unexposed to any	1,126	79.94 (0.33)	ref					2,551	80.20 (0.16)	ref				
ever	135	78.22 (0.75)	0.73	-1.54	to	3.01	88.8%	23	78.78 (0.91)	0.48	-6.02	to	6.99	99.1%
LMICs (never-smokers)														
unexposed to any	2,018	79.75 (0.32)	ref					5,886	80.29 (0.21)	ref				
ever	210	82.38 (1.24)	0.58	-1.50	to	2.67	86.5%	53	74.57 (0.28)	-0.18	-4.81	to	4.46	NS

C-3 *continued from previous page*

Groups of dusty jobs	Male FEV_1/FVC (%)					Female FEV_1/FVC (%)				
Fume	***n***	**Mean (SE)**	**β**	**95% CI**	***I²* (%)**	***n***	**Mean (SE)**	**β**	**95% CI**	***I²* (%)**
All										
unexposed to any	7,443	78.48 (0.28)	ref			11,041	79.99 (0.17)	ref		
ever	1,953	76.14 (0.69)	0.23	-0.57 to 1.03	76.4%	399	78.12 (0.89)	-0.96*	-1.78 to -0.15	65.0%
HICs										
unexposed to any	3,023	78.15 (0.26)	ref			4,280	78.98 (0.17)	ref		
ever	1,074	75.86 (0.42)	-0.22	-0.79 to 0.35	NS	235	76.96 (0.78)	-0.43	-1.37 to 0.52	NS
LMICs										
unexposed to any	4,420	78.56 (0.33)	ref			6,761	80.29 (0.21)	ref		
ever	879	76.26 (0.99)	0.57	-0.58 to 1.72	80.2%	164	79.24 (1.46)	-1.24*	-2.43 to -0.05	63.4%
Never-smokers										
unexposed to any	3,144	79.78 (0.27)	ref			8,437	80.27 (0.18)	ref		
ever exposed to	577	79.71 (0.90)	0.48	-0.70 to 1.66	85.5%	218	79.07 (1.02)	-0.68	-1.59 to 0.23	69.1%
HICs (never-smokers)										
unexposed to any	1,126	79.94 (0.33)	ref			2,551	80.20 (0.16)	ref		
ever	296	79.18 (0.56)	0.08	-1.02 to 1.19	NS	97	78.95 (0.75)	-0.24	-1.32 to 0.84	NS
LMICs (never-smokers)										
unexposed to any	2,018	79.75 (0.32)	ref			5,886	80.29 (0.21)	ref		
ever	281	79.94 (1.27)	0.78	-0.87 to 2.44	89.0%	121	79.13 (1.45)	-0.87	-2.16 to 0.43	77.6%

HICs: high-income countries; LMICs low- and middle-income countries classified by the World Bank; never-smokers stratification included only participants reporting 'never-smoking'.

Means (SE) were from all 41-site participants together.

The coefficients (β) were adjusted for age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

C-4 Association of FVC (L) with groups of dusty jobs stratified by sex and sites' country economy

Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Organic dust	*n*	Mean (SE)	β	95% CI			I^2 (%)	*n*	Mean (SE)	β	95% CI			I^2 (%)
All														
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
ever	4,287	3.67 (0.05)	0.01	-0.02	to	0.04	NS	3,325	2.78 (0.03)	0.04	0.00	to	0.09	78.3%
HICs														
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
ever	1,005	3.97 (0.05)	-0.02	-0.07	to	0.03	NS	737	2.84 (0.04)	0.02	-0.02	to	0.07	NS
LMICs														
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
ever	3,282	3.63 (0.05)	0.02	-0.02	to	0.06	NS	2,588	2.76 (0.04)	0.05	-0.01	to	0.11	84.5%
Never-smokers														
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
ever exposed to	1,806	3.48 (0.12)	-0.03	-0.10	to	0.04	66.0%	2,698	2.76 (0.04)	0.05*	0.00	to	0.10	79.1%
HICs (never-smokers)														
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
ever	330	3.92 (0.07)	-0.04	-0.13	to	0.05	NS	434	2.77 (0.05)	**0.05***	**0.00**	to	**0.11**	**NS**
LMICs (never-smokers)														
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
ever	1,476	3.43 (0.13)	-0.03	-0.12	to	0.06	74.9%	2,264	2.76 (0.04)	0.05	-0.01	to	0.11	85.5%

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Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Inorganic dust	***n***	**Mean (SE)**	**β**	**95% CI**			***I*²** **(%)**	***n***	**Mean (SE)**	**β**	**95% CI**			***I*²** **(%)**
All														
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
ever	1,156	3.98 (0.08)	0.026	-0.04	to	0.09	67.9%	131	2.85 (0.06)	0.01	-0.11	to	0.14	95.0%
HICs														
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
ever	579	4.28 (0.05)	0.02	-0.05	to	0.10	NS	57	3.06 (0.06)	0.12	-0.01	to	0.24	69.0%
LMICs														
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
ever	577	3.83 (0.12)	0.02	-0.07	to	0.11	73.3%	74	2.43 (0.12)	-0.05	-0.21	to	0.11	96.6%
Never-smokers														
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
ever exposed to	345	3.90 (0.13)	0.02	-0.06	to	0.11	69.9%	76	2.76 (0.05)	-0.01	-0.24	to	0.22	98.8%
HICs (never-smokers)														
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
ever	135	4.30 (0.09)	0.03	-0.09	to	0.15	50.0%	23	3.06 (0.08)	0.11	-0.57	to	0.78	99.4%
LMICs (never-smokers)														
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
ever	210	3.79 (0.16)	0.02	-0.09	to	0.13	76.0%	53	2.39 (0.05)	-0.10	-0.27	to	0.08	96.4%

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Groups of dusty jobs	Male FVC (L)							Female FVC (L)						
Fume	***n***	**Mean (SE)**	**β**	**95% CI**			***I*²** **(%)**	***n***	**Mean (SE)**	**β**	**95% CI**			***I*²** **(%)**
All														
unexposed to any	7,443	3.60 (0.03)	ref					11,041	2.64 (0.04)	ref				
ever	1,953	3.90 (0.06)	-0.01	-0.04	to	0.03	NS	399	3.08 (0.06)	0.07	-0.04	to	0.19	90.6%
HICs														
unexposed to any	3,023	4.00 (0.04)	ref					4,280	2.84 (0.02)	ref				
ever	1,074	4.22 (0.04)	-0.02	-0.09	to	0.04	NS	235	3.11 (0.05)	0.05	-0.05	to	0.14	62.9%
LMICs														
unexposed to any	4,420	3.51 (0.05)	ref					6,761	2.58 (0.06)	ref				
ever	879	3.76 (0.08)	0.01	-0.04	to	0.06	NS	164	3.04 (0.10)	0.09	-0.08	to	0.26	93.0%
Never-smokers														
unexposed to any	3,144	3.53 (0.04)	ref					8,437	2.60 (0.04)	ref				
ever exposed to	577	3.73 (0.08)	0.00	-0.06	to	0.06	NS	218	3.05 (0.08)	0.11	-0.01	to	0.23	91.2%
HICs (never-smokers)														
unexposed to any	1,126	3.95 (0.07)	ref					2,551	2.69 (0.02)	ref				
ever	296	4.20 (0.06)	0.01	-0.09	to	0.11	NS	97	3.00 (0.09)	0.09	-0.01	to	0.19	65.6%
LMICs (never-smokers)														
unexposed to any	2,018	3.45 (0.04)	ref					5,886	2.58 (0.06)	ref				
ever	281	3.53 (0.11)	-0.01	-0.08	to	0.07	54.0%	121	3.07 (0.10)	0.11	-0.07	to	0.28	92.5%

HICs: high-income countries; LMICs low- and middle-income countries classified by the World Bank; never-smokers stratification included only participants reporting 'never-smoking'.

Means (SE) were from all 41-site participants together.

The coefficients (β) were adjusted for age (years) and smoking status (never, <20 pack-years, ≥20 pack-years).

*p<0.05, **p<0.01, ***p<0.001; NS non-statistically significant (p≥0.05) heterogeneity (I^2); both p<0.05 and I^2=NS in bold.

C-5 Main agricultural practice classification

BOLD sites	Main agricultural practice*
High-income countries (14 sites)	-
Australia (Sydney)	Commercial, commercial gardening
Austria (Salzburg)	Commercial, dairy
Estonia (Tartu)	Commercial, dairy
Germany (Hannover)	Commercial, dairy
Iceland (Reykjavik)	Little agriculture
The Netherlands (Maastricht)	Commercial, dairy
Norway (Bergen)	Commercial, commercial gardening
Portugal (Lisbon)	Commercial, Mediterranean
Sweden (Uppsala)	Commercial, dairy
UK (London)	Commercial, dairy
Trinidad and Tobago (Port of Spain)	Commercial, plantation
Saudi Arabia (Riyadh)	Commercial, commercial gardening
Canada (Vancouver)	Commercial, commercial gardening
USA (Lexington)	Commercial, mixed crop and livestock
Low- and middle-income countries (27 sites)	
China (Guangzhou)	Subsistence, intensive subsistence (wet rice dominant)
Malaysia (Penang)	Subsistence, shifting cultivation
The Philippines (Manila)	Subsistence, intensive subsistence (wet rice dominant)
The Philippines (Nampicuan and Talugtug)	Subsistence, intensive subsistence (wet rice dominant)
Albania (Tirana)	Commercial, Mediterranean
Kyrgyzstan (Chui)	Commercial, livestock ranching
Kyrgyzstan (Naryn)	Commercial, livestock ranching
Poland (Krakow)	Commercial, mixed crop and livestock
Turkey (Adana)	Subsistence, intensive subsistence (wet rice not dominant)
Jamaica	Commercial, plantation
Algeria (Annaba)	Commercial, Mediterranean
Morocco (Fes)	Commercial, Mediterranean
Tunisia (Sousse)	Commercial, Mediterranean
India (Mumbai)	Subsistence, intensive subsistence (wet rice dominant)
India (Mysore)	Subsistence, intensive subsistence (wet rice dominant)
India (Pune)	Subsistence, intensive subsistence (wet rice dominant)
India (Srinagar)	Subsistence, intensive subsistence (wet rice not dominant)
Pakistan (Karachi)	Subsistence, pastoral nomadism
Sri Lanka	Commercial, plantation

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BOLD sites	Main agricultural practice
Low- and middle-income countries (27 sites)	
Benin	Subsistence, shifting cultivation
Cameroon (Limbe)	Commercial, plantation
Malawi (Blantyre)	Commercial, plantation
Malawi (Chikwawa)	Commercial, plantation
Nigeria (Ife)	Subsistence, shifting cultivation
South Africa (Cape Town)	Commercial, Mediterranean
Sudan (Gezira)	Commercial, plantation
Sudan (Khartoum)	Commercial, plantation

*Agricultural practice was classified by the Whittlesey's 11 main agricultural regions using each site's geographic coordinate.