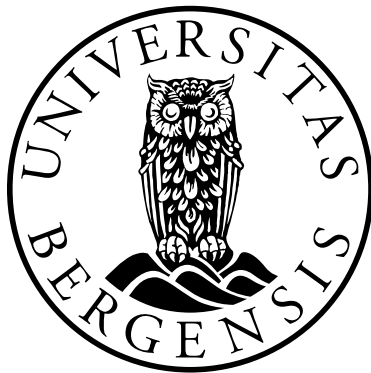

Respiratory health among Tanzanian cement workers

Effects of Improved Dust Control Measures?

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Scientific environment

This study involved researchers from the following institutions;

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List of abbreviations

AM (SD)	Arithmetic Mean (Standard Deviation)
ATS	American Thoracic Society
BMRC	British Medical Research Council
COPD	Chronic Obstructive Pulmonary Disease
ERS	European Respiratory Society
FE _{NO}	Fractional Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in 1 second
FEV ₁ %	Percentage predicted Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FVC%	Percentage predicted Forced Vital Capacity
FEV ₁ /FVC	Forced Expiratory Volume in 1 second to Forced Vital Capacity ratio
GOLD	Global Initiative for Obstructive Lung Diseases
GM (GSD)	Geometric Mean (Geometric Standard Deviation)
IL	Interleukin
IOM	Institute of Occupational Medicine
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
ppb	Parts per billion
PNOS	Particles Not Otherwise Specified
RPE	Respiratory Protective Equipment
SKC	Side Kick Casella pump
SPSS	Statistical Package for Social Science
TLV	Threshold Limit Value
tpa	Tons per annum
TPCC	Tanzania Portland Cement Company
µm	Micrometre
vs	Versus

Abstract

Background: Previous studies have reported associations between dust exposure and adverse chronic respiratory health effects, but there are only a few follow-up studies among cement workers. None of the previous studies have reported on the possible health effects following improvement of dust control measures in the cement factory. Airway inflammation has recently been reported as a possible underlying mechanism of dust-related respiratory health effects. Only one study has examined FE_{NO} as a possible non-invasive marker of inflammation among cement workers.

Objectives: We aimed at assessing changes in personal total dust exposure levels, chronic respiratory symptom, lung function and COPD among Tanzanian cement production workers, following improvement of dust control measures. In addition, we aimed at exploring possible associations between total dust exposure and FE_{NO} .

Method: This thesis consists of four papers. In Paper I, we compared summarized group data for total dust exposure reported in 2002 with data collected in 2010–11 in the same cement factory (before vs after improvement) (n: 79 vs. 179 dust samples). Similarly, summarized group data for chronic respiratory symptoms, FEV_1 , FVC, FEV_1/FVC ratio, COPD and % predicted values for FEV_1 and FVC obtained in 2002 were compared with analogous data in 2010, among exposed workers and controls (n:120 vs. 171, and 107 vs. 98, respectively). In Paper II, a one-year follow-up on chronic respiratory symptoms was conducted among the exposed workers and controls from 2010 to 2011.

Paper III compared FE_{NO} levels between exposed workers and controls (n: 127 vs 28). The FE_{NO} levels in Paper III were also compared between the exposed workers with high (GM \geq 5 mg/m³) and low total dust exposure (GM < 5 mg/m³), and between the exposed workers in the first and second stage of cement production (n: 64 vs. 64, and 65 vs. 62, respectively).

Paper IV examined possible cross-shift changes in FE_{NO} for three consecutive days among exposed workers and for two consecutive days among controls (n: 55 vs. 31). Associations between individually measured total dust exposure levels and the cross-shift change in FE_{NO} were also evaluated.

Results: In Paper I, total dust exposure among exposed workers was reduced in 2010–11 compared to 2002, GM: 5.8 mg/m³ vs. 10.6 mg/m³. Similarly, the proportion of total dust exposure exceeding the threshold limit value of 10 mg/m³ was lower in 2010–11 and 2002, 31%, vs. 58%.

The exposed workers had higher symptom prevalence and impaired lung function compared to controls in 2002, whereas no such differences were observed in 2010. Among the exposed workers, the prevalence of chronic cough, chronic sputum production, chronic bronchitis and COPD was lower in 2010 compared to 2002. The exposed workers in 2010 had higher FEV₁, FEV₁% and FVC% than the exposed workers in 2002.

In Paper II, the exposed workers had higher chronic respiratory symptom prevalence and overall symptoms score at baseline (2010) compared to controls, but these differences were not significant. One year later in 2011, there was significantly lower

prevalence of cough, cough with sputum, dyspnoea and wheezing among the exposed workers compared to controls.

In Paper III, there were similar FE_{NO} levels among exposed workers and controls (GM; 16 ppb for each group), among the exposed workers with high total and low total dust exposure (GM: 17 ppb and 16 ppb, respectively), and among workers in the first and second stage of cement production (GM: 17 ppb vs. 16 ppb, respectively).

In Paper IV, we observed a statistically significant cross-shift decrease in FE_{NO} on each of the three days of examination among exposed workers, but not for the two days among controls. The cross-shift decrease in FE_{NO} among the exposed workers was not correlated with personal total dust exposure levels, correlation coefficient; -0.175, and 95% confidence interval:-0.36 to 0.04.

Conclusions: We found a reduction in personal total dust exposure, prevalence of chronic respiratory symptoms and COPD among Tanzanian cement production workers, after improvement of dust control measures, from 2002 to 2010.

After one year from 2010, there was a significant reduction in the prevalence of chronic respiratory symptoms among Tanzanian cement production workers.

There was no significant difference in FE_{NO} between exposed workers and controls.

However, there was a significant cross-shift decrease in FE_{NO} among exposed workers. The reason for this decrease is unknown.

List of publications

- I. Tungu AM, Bråtveit M, Mamuya SD, Moen BE. Reduced dust exposure: Chronic respiratory symptoms, lung function and COPD in a Tanzanian cement factory. Submitted for publication.
- II. Tungu AM, Bråtveit M, Mamuya SH, Moen BE. Reduction in respiratory symptoms among cement workers: A follow-up study. Submitted for publication.
- III. Tungu AM, Bråtveit M, Mamuya SH, Moen BE. Fractional exhaled nitric oxide among cement factory workers: A cross-sectional study. *Occup Environ Med.* 2013;70:289-95.
- IV. Tungu AM, Bråtveit M, Mamuya SH, Moen BE. Cross-shift decrease in fractional exhaled nitric oxide among cement worker. Submitted for publication.

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1. Introduction

1.1 Historical perspectives of cement

The discovery of cement, an important adhesive component in construction and civil engineering today (1), goes back to the ancient periods in Egypt, Greece and the Roman Empire (2, 3). The mixture of gypsum and lime was used for building constructions in Egypt. Further advances in cement technology were made by Greeks and Romans. A Roman engineer Marcus Vitruvius described cement as “a fascinating powder obtained from natural causes which provides strength to buildings” (3). Vitruvius described this powder as a mixture of lime and crushed volcanic ash capable of hardening over time even when the construction was under the sea. This powder was named “Pozzolanic” because it was obtained from Pozzuoli, a place where volcanic ash was obtained. The name “Portland” cement was given to an artificial cement by Joseph Aspdin in 1824, because this cement resembled stones quarried in the Isle of Portland (1, 2). Aspdin used a pulverized mixture of limestone and clay, which was heated and reground to form cement. In the Roman period, the discovery of cement was important for expansion of Roman Empire, and the heating process occurred due to volcanic action (3). The Aspdin method is the origin of the modern methods used nowadays in the manufacture of Portland cement (2). There are two main types of cement, natural and artificial (1). Natural cement is obtained by only heating natural materials which resemble cement. Artificial cement (Portland cement and aluminous) is obtained by heating materials to form cement with a different chemical composition.

1.2 Main stages in the manufacture of Portland cement

Cement manufacturing today mainly involves two stages, “clinker” formation (stage I) and clinker grinding (stage II) (1). In stage I, the bulky raw materials from the quarry, limestone (calcium carbonate) and aluminium silicates (clay and sand) (4), are crushed (Figure 1). The crushed raw materials are transported for storage in the gantry. From the gantry, the raw materials are transported to the raw mill hoppers with the aid of either cranes or automated machines. The raw materials are then transported to the raw mills where they are ground to a required fineness and stored in the raw mill silos, forming the raw feed. The raw feed is either dried (dry process) or mixed with water to form a slurry (wet process) (1) and transported to the kiln using pressurized air systems. In the kiln, the raw feed is heated under high temperature (1500 °C to 1800 °C) to form (lumps of) clinker. The formed clinker is cooled immediately when leaving the kiln to prevent decomposition of tricalcium silicate, an important component of Portland cement, into dicalcium silicate and calcium oxide. The cooled clinker is stored in the clinker gantry. In stage II, the cooled clinker is mixed with gypsum, iron ore and sand in proportions depending on the setting time and properties of concrete needed (1, 4). The mixture is ground in the cement mills to form cement as a final product, which is in powder form. The powder is transported for storage in the silos using pressurized air systems. The stored cement is then packed in cement bags using rotary packing machines or is delivered in larger quantities to designated areas.

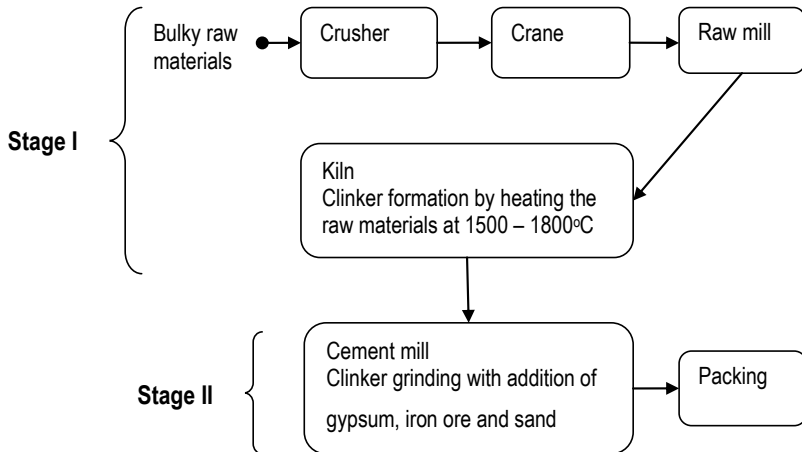


Figure 1: Sections and the two main stages in the manufacture of Portland cement

1.3 Physical properties and chemical composition of cement

Portland cement is a grey powder-like substance whose main physical properties depend on factors such as the fineness of the grind and the setting time (4). The pH of cement when dissolved in water is 12.5. Portland cement contains two essential constituents (4), tricalcium silicate (3CaOSiO_2) (50-70%) and dicalcium silicate (2CaOSiO_2) (15-30%). The two essential constituents control setting time, strength and other properties of the concrete formed (3, 4). Tricalcium silicate controls early strength of concrete due to rapid hydration while dicalcium silicate hydrates slowly (from 7 days to 1 year). Other constituents of Portland cement include tricalcium aluminate ($3\text{CaOAl}_2\text{O}_3$) (5-10%), tetracalcium aluminoferrite ($4\text{CaOAl}_2\text{O}_3\text{Fe}_2\text{O}_3$) (5-15%), magnesium oxide (MgO) (5%) and crystalline silica (0.01-0.78%) (5-7). Hexavalent chromium (Cr^{6+}) is also present in small amounts in the final product (1, 4).

1.4 The worldwide cement industry

Globally, cement is one of the synthetic materials used in abundance (3). The cement industry employs approximately 850,000 workers worldwide (2). The worldwide cement industry is dominated by Portland cement. In 1994, Portland cement contributed 94% and 43% in the cement industry in the USA and Europe, respectively (2).

Global production and consumption of cement has increased progressively from 2001 to 2012 (2, 8, 9). In 2011, and the leading producers of global cement were reported to be China followed by India, Iran and the USA (8, 9). Countries with high economic growth had high cement consumption due to increasing investments in infrastructures (2).

In Africa, cement consumption was reported to be 5% of the global consumption (2, 8). In East Africa, the consumption of cement has risen by 14% over the last decade (10). It has been estimated that the increase in cement production in this region will continue at a rate of 8% per annum, expanding from 8.2 million tpa in 2010 to about 14 million tpa by 2017. Likewise, cement production capacity is expected to rise by more than 60% from 2010 to about 17 million tpa in 2017.

1.5 The cement industry in Tanzania

Currently, there are three functional cement factories in Tanzania. The estimated annual production capacity is 3.8 million tpa against a demand of 4 million tpa (11). Approximately 12% of cement is imported to meet the national demand. By 2015, cement production in the country is estimated to be 6.8 million tpa, due to the

installation of new cement plants in Dar es Salaam, Mtwara and Lindi. The current producers of cement are located in Dar es Salaam, Tanga and Mbeya.

1.6 General information on occupational dust exposure

Dust can be defined as dispersed solid particles suspended in air (12). In the cement industry, the dust particles are suspended in the air during crushing, craning, grinding and transport of cement-related materials. *Particle size* is usually defined based on the aerodynamic diameter which is the diameter of a unity density sphere (water) that settles at the same velocity as the particle in question (13). The *aerodynamic diameter* influences penetration, deposition and health effects of dust particles inhaled in the respiratory airways. The *inhalable fraction* is the mass fraction of total airborne particles that are inhaled through the nose and/or mouth (50% cut-off aerodynamic diameter of 100 μm). The term *total dust* has loosely been used to refer to a fraction of all particles suspended and the total dust samplers had no performance criteria for the 50% cut-off point. The *thoracic fraction* is the mass fraction of inhaled particles reaching the tracheobronchial region of the airways (beyond the larynx) (50% cut-off aerodynamic diameter of 10 μm). The *respirable* fraction is the mass fraction of inhaled particles which penetrate deeper reaching the gaseous exchange region of the lung (alveoli) (50% cut-off an aerodynamic diameter of 4 μm) (13).

Personal dust sampling can be used to estimate the concentration of dust of the different size fractions. Inhalable dust can be sampled using the IOM inhalable sampler, whereas total dust can be sampled by the three-piece closed-faced Millipore sampler. However, the closed Millipore sampler may underestimate the amount of

inhalable dust by a factor of 1.5 to 3.0 compared to the inhalable convention (14). It has been shown that by mass the total dust fraction among cement workers contains approximately 40% respirable particles (7, 15).

However, variability in dust exposure may occur in the two main stages of cement production. In stage I, workers might be exposed to coarser dust particles resulting from disintegrating bulky raw materials which possibly contain a larger concentration of silica compared to workers in stage II. In stage II, clinker and cement dust may contain finer dust particles that have more irritative effects due to clinker and the cement alkalinity (4) compared to the dust in stage I. However, there are no studies that have documented differences in health outcomes between these main stages of cement production so far.

Evaluation of the variability in dust exposure and proper grouping schemes is important in reducing misclassification of exposure (16-18). Variability in the dust exposure between-groups, between-workers and from day-to-day may depend on a number of factors such as sections, work tasks, distance from the machines and time spent when performing such tasks (6).

Study groups may be classified using two principles of grouping, *a priori* or *a posteriori* (17). The *a priori* grouping scheme is based on existing occupational groups such as sections and work tasks in the production line and anticipated dust levels. In *a posteriori* grouping schemes, the groups are established according to measured exposure levels.

The two main principles used in the control of workplace exposures are engineering and administrative control measures (19). *Engineering control* involves appropriate designing, installation and maintenance of the control measures such as local and general ventilation systems.

Administrative control measures involve provision of administrative and financial support for enforcement of appropriate exposure control measures and training of the workforce on occupational safety and health related issue.

Other dust controls measures are *authoritative* measures and *personal protection*.

Authoritative dust control measures include the setting of standards such as TLV, for instance, a TLV value of 10 mg/m^3 for particles not otherwise specified (20), and ensuring that the standards set are followed properly (law enforcement).

Personal protection is regarded as the last resort of the control measures due to its ineffectiveness (19). However, a proper use of RPE, for instance, is advisable in situations when engineering controls are not feasible, in emergencies such as major spillages, during maintenance work, and when there is an immediate risk to workers until when other dust control measures have yet to be established (19).

1.7 Occupational dust exposure among cement workers

Occupational dust exposure has been reported to occur among workers in all stages of cement production (4). Studies originating from Europe (21, 22) and the USA (23) have reported relatively low dust exposure levels (Table 1), except among cement plant cleaners in Germany (Inhalable dust, GM; 55 mg/m³) (24). Several studies performed in Africa (6, 18) and in Asia (9, 25) have reported high dust exposure levels among cement workers, exceeding the TLV of 10 mg/m³ for PNOS (20). The highest dust exposure levels have been reported among Ethiopian cleaners (Total dust, GM; 549 mg/m³) (6). In developing countries, lack of efficient dust control measures and old production technology may contribute to the high dust exposures compared to developed countries (4). In Tanzania, the highest exposure levels were reported among crane operators followed by the operators in packing and the crusher, while the lowest exposure was found in the raw mill (Total dust, GM; 38 mg/m³, 21 mg/m³, 13 mg/m³ and 1.9 mg/m³, respectively) (18).

1.8 Occupational dust exposure and respiratory health effects

Occupational dust exposure among cement workers has been associated with acute and chronic respiratory health effects. The commonly reported acute respiratory effects are sneezing, cough, runny nose, difficulty in breathing and impairment of lung function which may occur immediately after exposure to dust (7, 15, 22, 26). Chronic respiratory health effects such as chronic cough, reduced lung function, obstructive pulmonary diseases (21, 25, 27-29), and cancers of the larynx and lung (30) may develop after repeated and/or prolonged exposure to dust among cement workers. The acute respiratory symptoms, acute lung impairment and cancers of the respiratory system are beyond the scope of this thesis.

Several cross-sectional studies have reported associations between high occupational dust exposure and chronic lung function impairment, increased prevalence of chronic respiratory symptoms and COPD among workers in cement factories (9, 27, 31, 32). COPD is characterized by progressive airway obstruction that is not fully reversible. The obstruction is associated with an abnormal inflammatory process in the lung that occurs after exposure to noxious particles or gases, for instance dust and cigarette smoke (33). Table 1 summarizes studies assessing the adverse effects of exposure to dust among cement workers worldwide and most of them show that these effects are present. Workers exposed to relatively low dust exposure levels did not differ significantly in such adverse respiratory health effects when compared with controls (5, 23), possibly due to better dust control measures in these factories.

There are few follow-up studies among workers in cement factories (15, 29, 34, 35). The follow-up studies from Europe are either very old (28, 29) or include workers

apart from cement production workers (34). In Africa, only one follow-up study has been performed among cement factory workers in Ethiopia (35). The Ethiopian study reported changes in respiratory symptoms, and an accelerated decline in the FEV₁ and FEV₁/FVC ratio among cement workers compared to controls after one year. The dust levels in the Ethiopian study were very high, and no interventions to reduce the dust exposure levels were carried out during follow-up. Thus, similar studies may not reveal such changes at lower dust exposure levels.

Table 1-Studies on dust exposure (mg/m³), prevalence of chronic respiratory symptoms, lung function and COPD among cement workers by continent, country and year of publication

Continent / Country	Author (year) / study design	Workers		Personal dust exposure among exposed workers		Prevalence (%) of chronic respiratory symptoms among exposed vs controls	Lung function among exposed workers vs controls	COPD prevalence
		N	AM(SD)	AM(SD)	GM(GSD)			
AFRICA								
Ethiopia	Zeleke (2011) (35) Prospective follow-up	E=127 C=27	Total dust: Cleaners: 221.5(?) Others: 56(?) (range: 0.7-6710)	Total dust: Cleaners: 432 Others: 8.5 (range: 0.1-6710)	Higher % for all symptoms at baseline and follow-up	Significant decrease in FEV ₁ and FEV ₁ /FVC ratio after 1 year	--	
Sudan	El Badri (2008)(36) Cross-sectional	E=40 C=40	--	--	Reduced FEV ₁ and FVC	Reduced FEV ₁ and FVC	--	
Nigeria	Merenu (2007) (31) Cross-sectional	E=56 C=96	--	--	Reduced FEV ₁ and VC	No difference in FEV ₁ /FVC ratio	--	
Tanzania	Mwaiselage (2004, 2005) (27, 37) Cross-sectional	E=120 C=107	Total dust: 13(10) (range: 0.21-229)	Total dust: 10.6 (range: 0.21+229)	Increased chronic cough (25.8 vs 12.0), chronic sputum production (43.2 vs 10.3), dyspnoea (19.2 vs 6.5), work related shortness of breath (16.7 vs 4.7) and chronic bronchitis (20.0 vs 7.5)	Reduced FEV ₁ , FVC, FEV ₁ %, FVC% and FEV ₁ /FVC ratio	Increased% (18.8 vs 5)	
Nigeria	Oleru (1984) (38) Cross-sectional	E=52 C=24	Total dust: 30.8	--	Increased cough and phlegm (68.5 vs 62.5), chest tightness (60.8 vs 37.5), dyspnoea (53.8 vs 0)	Reduced FEV ₁ and FVC among cement packers only	none	
AMERICA								
Mexico	Alvear-Galindo (1999) (39) Cross-sectional	E=425 C=0	--	--	Increased probability of having chronic bronchitis, dyspnoea and wheezing	No difference in FEV ₁ and FVC	--	
USA	Abrons (1988) (23) Cross-sectional	E=2736 C=755	Total dust:2.9(4.4) Respirable dust :0.6(3.6)	Total dust:2.9(4.4) Respirable dust :0.6(3.6)	No difference in chronic cough (15.4 vs 14.0), chronic phlegm (18.1 vs 16.1), chronic bronchitis with exacerbations (5.8 vs 4.1), chronic bronchitis with obstruction (4.1 vs 3.0), wheezing (8.5 vs 7.7) and asthma (8.7 vs 8.9), except for dyspnoea (5.0 vs 3.0)	No difference in FEV ₁ and FVC	--	
ASIA								
Pakistan	Meo (2013) (40) Cross-sectional	E=50 C=50	--	--	Reduced FEV ₁ and FVC among workers exposed ≥ 5 years	Reduced FEV ₁ and FVC among workers exposed ≥ 5 years	--	
United Arab Emirates	Ahmed (2012) (41) Cross-sectional	E=149 C=78	Total dust: 87.4 (AM range:24-145)	Total dust: 8.9 (GM range:4-9)	Increased cough (19.5 vs 5.1), phlegm (14.8 vs 1.3) and dyspnoea grade II or more (10.7 vs 3.8)	No difference in FEV ₁ /FVC ratio	--	
Iran	Neghab (2007) (32) Cross-sectional	E=88 C=80	Inhalable dust:53(43) Respirable dust:26(14)	--	Increased wheezing (28.0 vs 5.0), phlegm (26.0 vs 15.0), cough (32.0 vs 20.0) and breathlessness (17.0 vs 5.0)	Reduced FEV ₁ and FVC	--	

United Arab Emirates	Al-Neaimi (2001) (42) Cross-sectional	E=67 C=134	--	--	Increased prolonged cough (30 vs 9.7), phlegm (25.4 vs 5), wheezing (7.5 vs 3.0), dyspnoea (20.9 vs 4.5) and bronchitis (13.4 vs 3.7)	Reduced FEV ₁ , FVC and FEV ₁ /FVC ratio	--
Malaysia	Noor (2000) (43) Cross-sectional	E=62 C=70	Total dust: 10.2	--	Increased cough (25.0 vs 5.7), phlegm (15.3 vs 4.3) and chest tightness (19.4 vs 5.7)	Reduced FEV ₁ and FEV ₁ /FVC ratio, no difference in FVC	--
Taiwan	Yang (1996) (44) Cross-sectional	E=412 C=179	Respirable dust: 3.58(4.9) (range: 1.3-8.1)	--	Increased cough (19.4 vs 12.1), phlegm (17.6 vs 13.0), wheezing (8.7 vs 6.2) and dyspnoea (8.7 vs 7.2), except chronic bronchitis (12.0 vs 10.8)	Reduced FEV ₁ and FVC No difference in FEV ₁ /FVC ratio	--
EUROPE							
Denmark	Mølgaard (2013) (34) Prospective follow-up	E=5633	--	--	--	--	Increased% (SHR; 134)
8 European countries	Nordby (2011) (21) Cross-sectional	E=3636 C=629	--	Thoracic dust: 0.83 (4.6)	Production workers and cleaners, respectively, coughing (20.0 vs 16.0, and 19.0 vs 16), wheezing and dyspnoea (6.2 vs 3.7, and 2.5 vs 3.7), coughing wheezing and dyspnoea (4.6 vs 1.7, and 1.3 vs 1.7), and chronic bronchitis (4.1 vs 1.4, and 3.8 vs 1.4).	Reduced FVC Dose-response relationship between thoracic dust exposure and FEV ₁ reduction	Increased % among foremen (12.0 vs 4.0) Similar % among production workers and cleaners (4.4 vs 4.0, and 5.2 vs 4.0)
Norway	Fell (2003) (5) Retrospective follow-up	E=119 C=50	Total dust: 7.4(13) (range: 0.3-53.7) Respirable dust:0.9(0.6) (range:0.0-2.3)	--	No difference in chronic cough (18.0 vs 21.0), cough or phlegm for >3 weeks (36.0 vs 34.0), attacks of dyspnoea (14.0 vs 13.0), occasional wheezing (54.0 vs 46.0) and symptoms during work (43.0 vs 27.0)	No difference in FEV ₁ , FVC and FEV ₁ /FVC ratio.	Similar % (14.3 vs 14.0)
Denmark	Vestbo (1990)(45) Retrospective follow-up	E=546 C=857	Median total dust: 3.3 (range: 2.0-7.8) Median respirable dust:1.5 (range: 1.0-2.2)	--	No difference in phlegm production (26.0 vs 19.0), breathlessness (19.0 vs 16.0) and chronic bronchitis (11.0 vs 9.0)	No difference in FEV ₁	Similar % (HR; 4.9 vs 3.9) ^s
Italy	Siracusa (1988) (29) Prospective follow-up	E=68 C=0	Total dust in 1978: 7.4(1.0) (range:1.4-56.0) Total dust in 1783: 5.3(0.8) (range: 0.5-147)	--	--	Reduced FEV ₁ and FVC No difference in FEV ₁ /FVC ratio	--
Yugoslavia	Saric (1976) (28) Prospective follow-up	E=160 C=80	--	--	--	Reduced FEV ₁ , FVC and FEV ₁ /FVC ratio	--

AM (SD) =arithmetic mean (standard deviation); GM (GSD) =geometric mean (geometric standard deviation); E=exposed, C=controls; SHR= Standardized hospitalization ratio; HR=hospitalization rate; \$=Trend towards increase hospitalization rate due to COPD among cement workers with less than or equal to 30 years of employment compared to controls.

1.9 Proposed mechanisms of adverse effects of dust exposure

The mechanism of the adverse respiratory effects of dust exposure in cement factories remains unknown. Proposed mechanisms include irritation of the mucus membrane due to high cement alkalinity and stimulation of inflammatory processes (4, 22, 46, 47). However, studies on inflammation have reported conflicting results (22, 46, 48). Two studies among cement production workers reported elevations of neutrophils and blood inflammatory markers compared to un-exposed controls, suggesting a possible inflammatory process (22, 46). A recent experimental study involving human lung cells reported a decreased concentration of a pro-inflammatory cytokine, IL-8, when laryngeal cells and lung cells were exposed to cement (48). The suggested mechanisms of reduction in IL-8 include absorption of IL-8 on the surface of cement particles and impaired release from basal cells in the presence of cement particles. In that study, no inhibition of production of IL-8 was reported.

A “gold standard” for detection of airway inflammation is histological examination of the tissues affected (49). However, this method is invasive, time consuming, costly and/or requires complex procedures and a skilled workforce to make the diagnosis. Recent advances in diagnostic methods have provided non-invasive methods for detection of airway inflammatory processes (50). The methods include examination of exhaled breath condensates, induced sputum examination and FE_{NO} measurement (50). However, the exhaled breath condensate and induced sputum examination are either semi-invasive or require skilled personnel and laboratory analysis. Therefore, histological examinations, exhaled breath condensates and induced sputum may not be feasible for examinations at workplace, particularly in areas with limited resources.

1.10 Background information on fractional exhaled nitric oxide

Gustafsson and colleagues first described NO in the exhaled breath of humans and animals in 1991 (51). This gas is commonly found in air as a pollutant from cigarette smoke and fuel combustion (52, 53). NO plays important roles in various physiological and pathological processes in the human body, but high concentrations of NO can damage body tissues (54). Production of NO in humans is controlled by three iso-enzymes of NOS by oxidation of L-arginine to L-citrulline. Constitutive neuronal NOS is responsible for neurotransmission while constitutive endothelial NOS controls smooth muscle relaxation and is mainly found in the endothelium of blood vessels and in the airways. Inducible NOS is produced in response to inflammatory stimuli. In pulmonary cells, the production of inducible NOS increases in the presence of pro-inflammatory cytokines such as interferon gamma (IF-gamma), tumour necrosis factor alpha (TNF-alpha) and Interleukin 1 beta (IL-1 β) during airway inflammation (54).

1.11 Fractional exhaled nitric oxide and airway inflammation

The fraction of nitric oxide detectable in the exhaled breath is referred to as fractional exhaled nitric oxide (FE_{NO}). Exposure to occupational agents such as mineral dust, organic dust and chemical agents may result in occupational-related airway inflammatory diseases (52), like occupational asthma.

FE_{NO} measurement has been performed mostly in clinical settings where high FE_{NO} concentrations have been reported among patients with asthma and eosinophilic inflammation (49). At workplaces, previous studies have reported high FE_{NO} concentrations among workers exposed to inorganic dust (55-57), organic dust and

endotoxins (58, 59), and among workers exposed to chemical agents such as persulfate salts (60), ozone (61) and organic solvents (62) compared to un-exposed controls. However, these FE_{NO} changes are within the normal values based on the criteria for clinical interpretation of FE_{NO} (53) (Table 2). This may suggest that sub-clinical inflammatory processes occur (55) among workers following exposure to various agents at workplaces.

FE_{NO} measurement has the advantage that it is a non-invasive method to detect eosinophilic airway inflammation, and it is quick and easy to perform (49, 63). However, this method is confounded by many factors such measurement techniques, age, atopy, height, smoking, upper respiratory infections and use of medications such as corticosteroids (49). Also, biological variations of FE_{NO} are not well known although it is recommended to consider the effect of the period of the day during FE_{NO} examinations (53).

In the cement industry, there is limited evidence whether the mechanism of inflammations related to dust exposure is associated with changes in FE_{NO} . Only one study has examined FE_{NO} as a non-invasive marker of eosinophilic airway inflammation among cement workers (22). Although a reduction of FE_{NO} was reported among cement workers there was no clear association between dust exposure and FE_{NO} (22).

Table 2-Studies on fractional exhaled nitric oxide (ppb) as marker of airway inflammation among workers exposed to inorganic dust

Author (year)	Industry, Country	Dust exposure	N	F _{ENO} main findings			Median (range)	Comments on FE _{NO} among exposed	Clinical significance
				AM(SD)	GM(SD)				
Sauni (2011)(64)	Construction, Finland	Silica	E= 94 C=35	E=20.0 C=20.1	--	--	No difference in FE _{NO} No correlation with exposure	Normal	
Fell (2011)(22)	Cement, Norway	Dust	E= 95 C=0	--	a) 14.0(0-96) b) 14.0(0-98) c) 12.0(0-82)		Cross-shift decrease in FE _{NO} No correlation with exposure No association between cross-shift decrease in FE _{NO} and cross-shift decrease in FEV ₁ or PEF	Normal	
Carlsten (2007)(65)	Construction, USA	Silica	E= 11 C=21	E=12.9 C=17.1	--	--	No difference in FE _{NO} No association between FE _{NO} and exposure	Normal	
Sjåheim (2004)(65)	Aluminium pot room, Norway		E= 8 C=10	--	E=18.1 C=6.1		Increased FE _{NO}		
Lund (2000)(56)	Aluminium pot room, Norway	Dust and Fluorides	E=186 C=40	--	E=9.3(6.2-15.6) C= 5.7(4.6-8.4)		Increased FE _{NO} No correlation between FE _{NO} and exposure	Normal	
Ulvestad (2001)(57)	Construction, Norway	Dust and NO ₂	E=29 C=26	E=8.4(1.1) C=5.6(1.1)	--	--	Increased FE _{NO} Higher among workers with chest tightness and wheezing than among workers without these symptoms (9.6 vs 6.3)	Normal	

AM(SD)=arithmetic mean(standard deviation), GM(GSD)=geometric mean (geometric standard deviation), E=exposed, C=controls; a, b and c=FE_{NO} at 0 h, 24h and 32h, respectively.

2. Rationale and objectives of the study

2.1 Rationale of the study

A large number of workers are employed in the cement industry, both globally and in Tanzania, but there is a lack of knowledge concerning the effects of improvement of dust control measures on respiratory health in cement factories. Several cross-sectional studies have reported associations between occupational dust exposure and high prevalence of chronic respiratory symptoms, reduced lung function and COPD among cement workers. There are only few follow-up studies on dust exposure and chronic respiratory health effects among cement workers. The existing follow-up studies are either very old, hospital based population studies or they originate from developed countries in Europe, except one from Ethiopia. The Ethiopian study reported very high dust exposure levels, and there were no dust control measures taken during follow-up.

In the present Tanzanian cement factory, previously reported dust exposure levels were high, and measures to reduce dust exposure levels were subsequently taken. To our knowledge, there are no follow-up studies in factories that have improved dust control measures. Documentation of the present dust exposure and the possible associated chronic adverse respiratory health effects in this factory is important. The underlying mechanisms of adverse respiratory health effects associated with dust exposure among cement workers are unknown. Previous studies investigating airway inflammation have reported conflicting results. A study that attempted to examine airway inflammation, using FE_{NO} as a non-invasive marker of inflammation, reported a cross-shift reduction in FE_{NO} . Therefore, a more detailed understanding of possible associations between dust exposure and FE_{NO} is needed. This is important, if there is

a relationship, since FE_{NO} might be used as a biomarker for surveillance among cement workers.

2.2 General objective

The general objective of this study was to explore associations between total dust exposure and respiratory health problems among Tanzanian cement workers in a factory with improved dust control measures, and to explore possible associations between personal total dust exposure and FE_{NO} , as a possible marker of (eosinophilic) inflammation.

2.3 Specific objectives

- 2.3.1. To examine total dust exposure levels, prevalence of chronic respiratory symptoms, lung function and COPD among Tanzanian cement workers in a factory with improved dust control measures (Papers I & II).
- 2.3.2. To explore possible associations between dust exposure and FE_{NO} , used as a marker of eosinophilic airway inflammation, among Tanzanian cement workers (Papers III & IV).

3. Materials and methods

3.1 Study setting

This study was carried out among cement workers at the TPCC factory in Dar es Salaam, Tanzania, between June and August in 2010 and 2011, respectively. We also used a previous study conducted among production workers in the same cement factory in 2002 (18, 27, 37) for comparison purposes. The factory was constructed in 1959 and started production in 1965. It is located in the northern area of the city, 25 km from the city centre. The TPCC is the largest producer of cement in Tanzania, and it is operated by one of the world's largest cement group, the Heidelberg Cement Group. The factory produced 0.5 million tons of cement in 2002. In 2010 and 2011, TPCC produced about 1.1 million tons of cement in each year. Cement production in this factory is expected to rise due to completion of a clinker production line which is capable of producing 0.3 million tpa (8). A control group was obtained from maintenance and administrative workers in the cement factory in 2002, whereas the controls in 2010–11 were obtained from mineral water factory, which is located in Mikocheni Industrial Area, north of Dar es Salaam city centre.

3.2 The cement factory workplace conditions and occupational groups

The main sections in the cement production line are the crusher, crane, raw mill, kiln, cement mill and packing. In 2002, these sections were reported to have poor working conditions that lead to high dust exposure levels among the cement production workers (18). Measures to reduce the dust exposure levels in this factory were taken as part of recommendations from previous studies in 2002 (Figure 2).

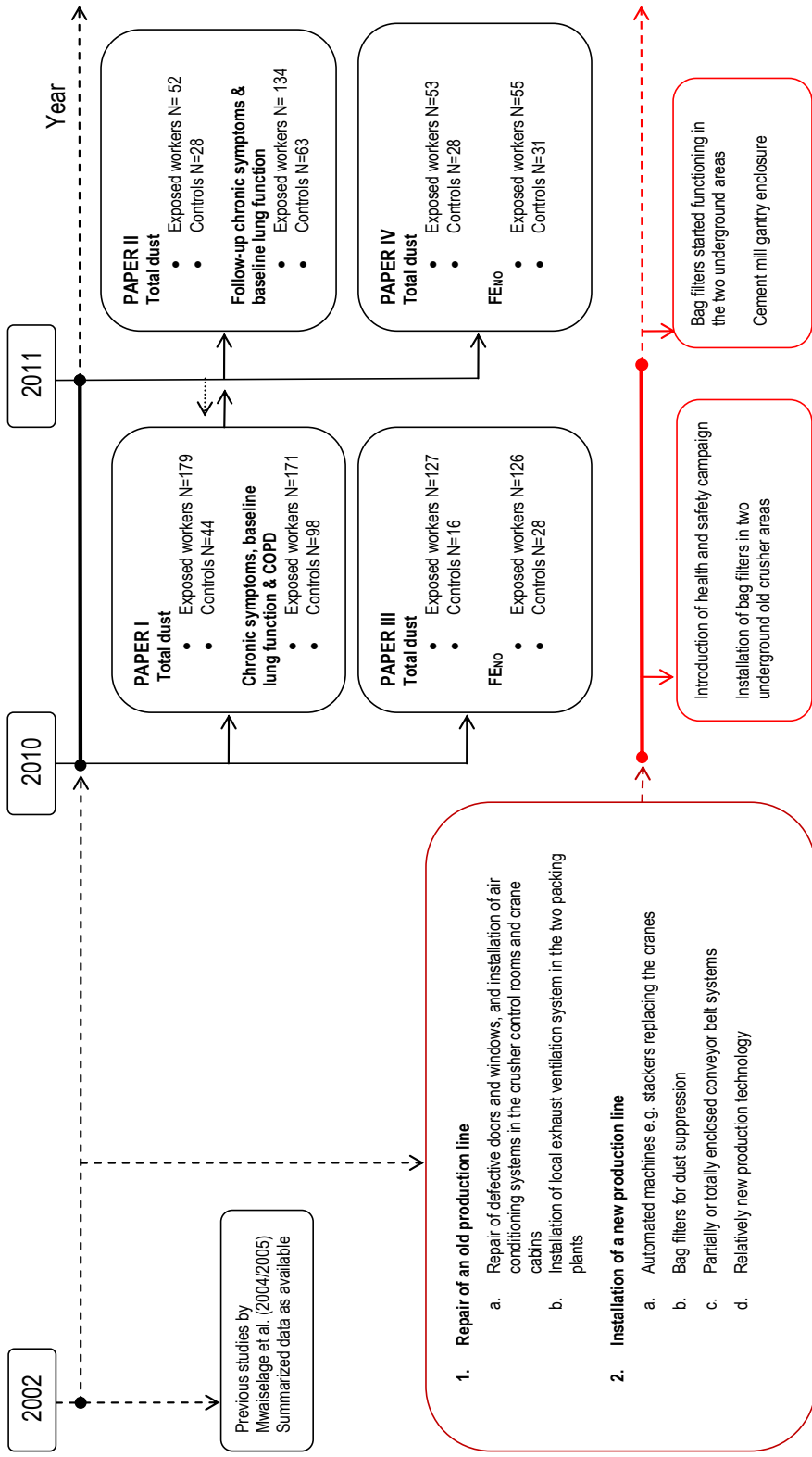


Figure 2: A timeline indicating workplace improvements (red lines) and periods of studies (black lines) performed in a Tanzanian cement factory

In addition, a new supplementary production line with a relatively new dust control system and production technology was established and became operational in the beginning of 2010 (Figure 2).

The main occupational groups studied in each section of the production line were operators, attendants, millers, packers, loaders, loaded truck coverers and foremen. The attendants were present in all sections and they are responsible for manual cleaning of piled materials along the production line, and ensuring smooth running of machines. The current workplace conditions and the occupational groups in each section are described as follows:

3.2.1 Crusher

The raw materials from the quarry were fed into the old and new crushers using dumper trucks and wheel loaders (old crushers). The old crusher control rooms had air conditioning systems which were functioning in both 2010 and 2011, but not in 2002. Bag filters for dust suppression systems were installed in the two old underground areas and became functional in 2011 (Figure 3). The conveyor belts in the old crusher were not enclosed (Figure 4), and the workers performed manual removal of clogged bulky raw materials in the crusher.

In the new production line, the underground crusher area had a functioning bag filter dust suppression system, the conveyor belts were partially enclosed, and the crusher had larger openings on both ends. The new crusher had a “hammer breaker” for breaking down clogged bulky raw materials into smaller pieces. The hammer breaker had an air conditioned operation cabin. The crusher operators were responsible for

machine operations, performing periodic checks of the machines and counting trips of raw materials delivered by dumper trucks from the quarry.



Figure 3: Bag filter dust suppression system in the old crusher (Photo by Tungu)



Figure 4: A crusher attendant observing flow of raw materials on the old crusher conveyor belt (Photo by Tungu)

3.2.2 Crane

The crane cabins in the old production line were air conditioned, and defective glass windows and doors of the old crane cabins observed in the previous study were repaired (Figure 5).



Figure 5: A crane operator entering the overhead crane cabin in the old production line (Photo by Tungu)

In the new production line, the cranes were replaced by automated machines (stackers) which fed raw materials onto the conveyor belts. The stackers had air conditioned operating rooms in case manual operation was needed (Figure 6). The crane operators are responsible for filling the raw mill and the cement mill hoppers.



Figure 6: An automated machine (stacker) in the new production line had replaced the crane for feeding raw materials onto the conveyor belt (Photo by Tungu)

3.2.3 Raw mill and kiln

Both the old and new raw mills were indoors and had bag filters for dust suppression (Figure 7). The kilns were located outdoors, and the kiln operators stayed in local control rooms or in a central control room. The central control room had computerized systems for monitoring the production process. The millers and kiln operators make periodic visits in the production line.

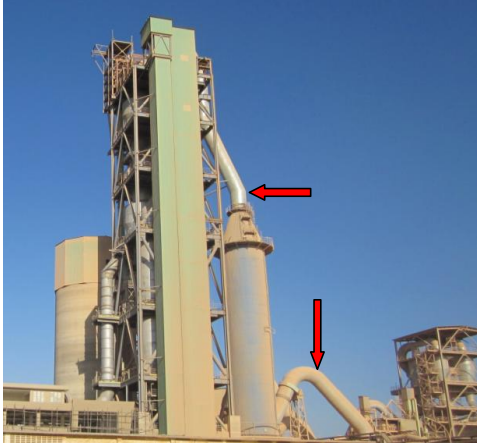


Figure 7: A bag filter dust suppression system (Red arrows) in the new raw mill area (Photo by Tungu)



Figure 8: An enclosed conveyor belt system in the cement mill (Red arrow) (Photo by Tungu)



Figure 9: A cement mill attendant observing transport of materials from the crane into the mill hoppers in the gantry (Photo by Tungu)

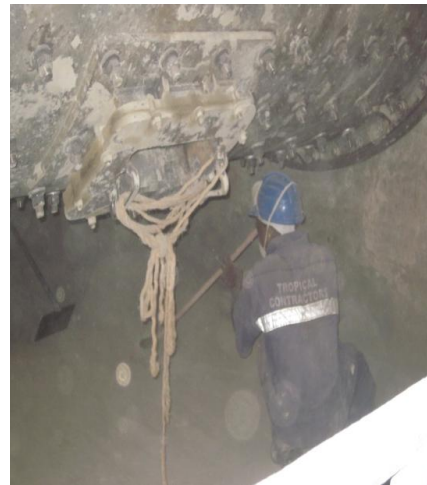


Figure 10: An attendant cleaning spilt materials under the cement mill (Photo by Tungu)

3.2.4 Cement mill

The old cement mill had an electrostatic precipitator for dust suppression but the conveyor belts were not enclosed, giving a rise to much dust, whereas the new cement mill had bag filters and enclosed conveyor belts (Figure 8). Both cement mills use the same gantry for clinker storage. The gantry is located in the old production

line and was not enclosed (Figure 9). Attendants in the gantry observe whether materials are properly put in the mill hoppers, remove clogged materials in the hoppers and remove split materials in the mill areas (Figure 9 and 10). The millers operate the milling machine from local control rooms or the central control room. The millers make periodic visits to the production line.

3.2.5 Packing plant

There were two packing plants in both the old and the new production lines. One of the old packing plants was located in a room with one large glass window on one side and an open end on the other side. The other plant was placed in a closed room with small openings. However, both plants had a local exhaust ventilation system installed close to the rotary packing machines.

In the new packing plant, the two packing machines were located in the same room. The room was partially closed, with large openings on both ends. The two packing plants in the new production line had bag filter dust suppression system. The conveyor belts were not enclosed in the two production lines. The packers are responsible for operating the rotary packing machines, and ensuring the smooth running of cement bags on the conveyor belts (Figure 11). The loaders are responsible for loading cement filled bags into trucks (Figure 12).



Figure 11: Packers in operating the rotary packing machine (Photo by Tungu)



Figure 12: Loaders putting cement bags into a truck (Photo by Tungu)

3.3 Study design

We conducted three cross-sectional studies (Paper I, III and IV) and one follow-up study from 2010–11 (Paper II) among exposed workers and controls (Figure 2). In Paper I, total dust exposure reported previously in 2002 was compared with total dust exposure assessed in both 2010 and 2011, combined together. Similarly, chronic respiratory symptoms, lung function and COPD in 2002 were compared with analogous data obtained in 2010. Due to lack of a data set from 2002, comparisons between 2002 and 2010–11 were feasible for summarized data only (66). In Paper II, we conducted a one-year follow-up on chronic respiratory symptoms. Possible associations between total dust exposure and FE_{NO} were examined using one cross-sectional study (Paper III) and a cross-shift study (Paper IV) among exposed workers and controls (Figure 2).

3.4 Study participants

In 2002, the total number of workers in the cement factory was 300. All production workers and controls from maintenance and administration participated in the study in 2002 (n: 120 and 107, respectively) (Paper I). In 2010, there were 495 cement factory workers, with 411 workers in the production section. A total of 210 out of 411 production workers were randomly selected and invited to participate in the study (exposed group). The control group was obtained from the production section in a mineral water factory in 2010. In the mineral water factory, there were 679 workers, with 349 workers in the production section. Of these, 105 production workers were randomly selected and invited to participate in the study.

In 2010–11, personnel lists and day shift lists were used for daily selection of 5 to 6 participants among exposed workers and controls. Among the invited exposed workers and controls in 2010, the response rates were 82.4% and 93.3% (n: 171 and 98, respectively). In both 2002 and 2010, participants were assessed for chronic respiratory symptoms and lung function.

In paper II, participants who were previously examined in 2010 were re-invited for follow-up assessment of chronic respiratory symptoms in 2011. A total of 134 exposed workers and 63 controls participated in 2011 (Figure 2). The exposed workers and controls who participated in baseline examinations but not during follow-up were regarded as dropouts (n: 37 and 35, respectively).

In Paper III, all participating exposed workers and controls were examined for FE_{NO} in 2010. However, 44 exposed workers and 2 controls were excluded either due to smoking, missing data, history of childhood asthma, performing vacuum cleaning or

being a supervisor. Therefore, the final analysis of FE_{NO} consisted of 127 exposed workers and 28 controls in 2010 (Figure 2).

In Paper IV, a total of 103 out of 134 exposed workers and 41 out of 63 controls were eligible for FE_{NO} examinations in 2011. Of these, 60 exposed workers and 31 controls were randomly selected and invited to participate in cross-shift FE_{NO} examinations. Five exposed workers did not participate in the study while all the invited controls participated, thus leaving 55 and 31 exposed workers and controls, respectively (Figure 2).

3.5 Statistical power estimation

Sample size estimation for chronic respiratory symptoms and lung function in 2010 was based on the previous study among cement workers in 2002 (27). The prevalence of chronic cough among cement workers and controls was 28.5% and 12.1%, respectively. To achieve 90% power to detect a difference in chronic cough between the two groups at significance level of 0.05, a total of 210 exposed workers and 105 controls were needed.

The sample size for FE_{NO} in Paper III was based on a pilot study among Tanzanian coffee factory workers (67). The mean FE_{NO} concentration among the coffee factory workers and controls were 28 ppb and 14 ppb, with a SD of 15 in each group. At a significance level of 0.05 and 95% statistical power, we needed 30 participants in each group.

3.6 Ethical clearance

Ethical approval of the study was given by the respective ethical committees in Norway and Tanzania, both in 2002 and 2010–11. The management teams in both factories gave permission to conduct the study. Each participating worker gave written informed consent. No information about study participants was at any point made available to the employers.

3.7 Questionnaire

A modified BMRC questionnaire was used in both 2002 and 2010–11. Translation of the questionnaire was done from English to Swahili and back to English. The questionnaire was self-administered in 2002, while interviews were conducted by same investigator among exposed workers and controls in 2010–11.

The questionnaire assessed chronic respiratory symptoms (Papers I–II), socio-demographic data, and occupational history, past chest illnesses, use of RPE and smoking habits (Papers I–IV). In Paper I, the symptoms assessed were chronic cough, chronic sputum production, dyspnoea, work-related shortness of breath, wheezing and chronic bronchitis. In Paper II, the prevalence of cough, cough with sputum production, dyspnoea, work-related shortness of breath, and wheezing were defined as the proportion of participants having at least one of the symptoms in each of these symptom categories. For smoking habits, participants were asked whether they had ever-smoked cigarettes (yes/no), were currently smoking cigarettes (yes/no), and whether they had stopped smoking cigarettes more than or less than 1 year ago. Pack years of smoking were calculated as the number of cigarettes per year divided by 20.

3.8 Spirometry

In both 2002 and 2010, lung function tests were performed in accordance with ATS/ERS criteria for acceptability and reproducibility of spirometry (68).

However, different spirometers were used and the tests were performed at different time periods: a Vitalograph spirometer, 10:00 am – 12:30 pm in 2002; and a digital Spirare spirometer (SPS 310), 12:00 pm – 16:00 pm in 2010. The lung function indices tested in our study include FVC, FEV₁, FVC %, FEV1% and the FEV1/FVC ratio.

Maximum values for FVC and FEV₁ were statically analysed in both periods.

Predicted values for FVC and FEV₁ were derived from predictive equations developed for Tanzanian males in both periods (69). Participants with an FEV₁/FVC ratio <0.70 were regarded as having COPD in accordance with the 2001 GOLD criteria (33).

Due to logistical constraints and the assumption that changes in lung function at the presently examined dust levels were unlikely to occur after one year, only baseline lung function was performed in 2010, but not in 2011(Papers I and II).

3.9 Fractional exhaled nitric oxide measurement

Measurement of FE_{NO} was performed using a NIOX MINO machine both in 2010 and 2011 (Papers III and IV). The FE_{NO} measurements were conducted in accordance with ATS/ERS criteria (49). One exception is that only one measurement was performed every time FE_{NO} was examined due to the high reproducibility of the NIOX MINO device (70, 71). Participants were advised not to eat or drink beverages

within 1 hour prior the FE_{NO} measurements (49). The measurements were conducted in a room located at the Health and Safety Department and a company dispensary in the cement factory and mineral water factory, respectively. Ambient nitric oxide was recorded daily in both 2010 and 2011.

The eligibility criteria for FE_{NO} examination were non-smoking, not using corticosteroids, not having childhood asthma or current asthma, history of heart diseases or COPD. An additional criterion required participants to be off-work for at least two days before FE_{NO} examinations (Paper IV). In Paper III, the measurements were conducted from 14:00 pm to 16:00 pm daily in both exposed workers and controls. In Paper IV, pre- and post-shift FE_{NO} measurements were conducted for three consecutive days among the exposed workers and for two consecutive days among controls. The cross-shift change in FE_{NO} was obtained as post-shift FE_{NO} minus pre-shift FE_{NO} (Paper IV).

3.10 Exposure assessment

Total dust sampling was conducted in both 2002 and 2010–11. In 2002, 79 and 41 dust samples were collected among exposed workers and controls, respectively (Table 3). In 2010–11, 179 and 44 dust samples were collected among exposed workers and controls, respectively. In Paper I, summarized data for the dust samples obtained in 2002 were compared with those collected in 2010–11. In a one-year follow-up (Paper II), a total of 126 and 16 total dust samples in 2010, and 53 and 28 total dust samples in 2011 were collected among exposed workers and controls, respectively (Table 3). Total dust samples collected in 2010 and 2011 were used in Papers III and IV, respectively.

In Paper III, the number of dust samples was based on the suggestion by Rappaport and Kupper of 10–20 measurements from an observational group of 5 to 10 randomly selected individuals (17). With 5 sections in the exposed group, at least 50–100 samples were needed, but 126 samples were collected from 102 participants. In Paper IV, 53 individuals were randomly selected and each individual had a single measurement for total dust sampling.

Total dust samples were collected on pre-weighed 37 mm cellulose acetate filters, with a pore size of 0.8 μm , placed in closed-faced three-piece Millipore cassettes both in 2002 and 2010–11. The cassette was connected to an SKC pump (Sidekick Casella; SKC Limited, Blandford Forum, U.K.), calibrated at a flow rate of 2.0 l/min. The dust samples were analysed using the same gravimetric technique, with the exception that the analyses were performed in different laboratories in 2002 and 2010–11, the X-lab AS laboratory in Norway and the Eurofins product testing laboratory in Denmark, respectively. However, the X-lab AS was purchased by Eurofins, and afterwards all analytic activity was performed in Denmark. The mean sampling time in 2002, 2010 and 2011 was 436 (387–463), 373 (145–432) and 371 (221–463), respectively.

3.11 Statistical analyses

SPPSS versions 16 (Paper III) and 19 (Paper I, II and IV) were used in statistical analyses. Various statistical methods were used for comparisons between the study groups (Table 4). Summary statistics such as total number and percentages for categorical variables, and AM, GM, SD, GSD, and ranges for continuous variables were used.

Table 3: Methods used in statistical analyses

Statistical method	Paper			
	I	II	III	IV
X ² - test / Fisher's exact test	✓	✓	✓	✓
X ² - test with Breslow-Day test	-	✓	-	-
Pearson's correlation test	-	-	-	✓
ANOVA	-	-	✓	✓
Independent t - test	✓	✓	✓	✓
Paired t- test	-	-	-	✓
Two sample t - test	✓	✓	-	-
Multiple linear regression	✓	✓	✓	✓
Multiple logistic regression	✓	✓	✓	✓
Linear mixed effects model	-	-	✓	✓
Wilcoxon signed ranks test / Man-Whitney U test	-	✓	-	-

Categorical variables were compared between groups using X²-test, Fisher's exact test, Breslow-Day test of homogeneity and multiple logistic regression analyses, whereas, independent t-test, two sample t-test paired t-test, ANOVA, multiple linear regression and linear mixed effects models were used for continuous variables (Table 3). Wilcoxon signed ranks test and Mann-Whitney U test were used for comparing changes in respiratory symptoms and the symptom score from 2010 to 2011 (Paper II).

The distributions of total dust exposure levels and FENO levels were skewed, which were log_e-transformed to achieve a normal distribution before analyses.

The linear mixed effects model was used to compare total dust exposure levels between groups and between *a priori* and *a posteriori* grouping schemes (Paper III).

The mixed effects model was also used to compare pre- and post-shift FE_{NO} measurements and the FENO change between groups using group, personal identity number as random effects, while group, day of examination and height were used as random factors (Paper IV). Pearson's correlation test was used to determine the association between total dust exposure and cross-shift FE_{NO} change (Paper IV).

4. Summary of results

4.1 Paper I

This cross-sectional study compared total dust exposure (2010–11), prevalence of chronic respiratory symptoms, lung function and COPD among exposed workers compared to controls in 2010. In addition, results from previous studies in 2002, before improvement of dust control measures, were compared with the results in 2010–11.

The overall GM for total dust exposure among exposed workers was lower in 2010–11 compared to 2002 (5.8 mg/m³ vs. 10.6 mg/m³). Significantly lower dust exposure levels in 2010–11 compared to 2002 were observed among workers in the crusher, crane and the packing (GM: 7.0 mg/m³ vs. 13.5 mg/m³, 2.8 mg/m³ vs. 38.6 mg/m³, and 8.2 mg/m³ vs. 21.3 mg/m³). The proportion of total dust exposure exceeding the TLV of 10 mg/m³ for PNOS in 2002 and 2010–11 were 58% vs. 31%, respectively. In 2010–11, the loaders and crusher attendants were highly exposed to dust (GM: 19.8 mg/m³ and 12.5 mg/m³, respectively).

In 2002, the exposed workers had higher symptom prevalence and reduced lung function compared to controls, whereas there were no significant differences in these parameters between exposed workers and controls in 2010. The prevalence of chronic cough, chronic sputum production, chronic bronchitis and COPD among exposed workers was lower in 2010 compared to 2002 (26% vs. 8%, 34% vs. 5%, 20% vs. 3%, and 23% vs. 2%, respectively). The exposed workers in 2010 had higher FEV₁, FEV₁% and FVC% than the exposed workers in 2002.

4.2 Paper II

This one-year follow-up study from 2010 to 2011 assessed changes in respiratory symptoms among cement workers in a factory with improved dust control measures that had started a dust control program and among controls. In addition, baseline respiratory symptoms and FEV₁/FVC ratio were compared between followed up workers and those lost to follow-up (dropouts). At baseline in 2010, the response rate among exposed workers and controls were 82.4% and 93.3%, respectively. The proportion of dropouts was lower among exposed workers compared to controls (22% vs. 35%, $p < 0.05$). The GM for total dust exposure did not differ significantly in 2011 compared to 2010, except in the cement mill where the dust exposure was higher in 2011 than 2010 (GM: 11 mg/m³ vs. 5.2 mg/m³). The exposed workers had somewhat higher symptom prevalence and overall symptoms score at baseline (2010) compared to controls, but the differences were not significant. There was a significantly lower prevalence of cough, cough with sputum, dyspnoea and wheezing in 2011 compared to 2010 among the exposed workers, but not among controls. The dropouts had higher symptom prevalence, but this association was significantly modified by smoking.

4.3 Paper III

This paper explored possible associations between total dust exposure and FE_{NO}, using FE_{NO} as a marker of airway eosinophilic inflammation among cement production workers and controls from a mineral water factory. In addition, differences in FE_{NO} concentration between the two stages of cement production were examined. All participants were non-smoking males, without history of childhood and/or current asthma, COPD and they did not use corticosteroids. The exposed workers and controls had similar age, weight, education level and duration of employment. However, the cement workers were shorter than controls (164 cm vs. 168 cm, p=0007).

The concentrations of FE_{NO} did not differ significantly between exposed workers and controls (GM: 16 ppb for each group). The FE_{NO} concentration between the exposed workers with high total dust exposure (GM \geq 5 mg/m³) (n=63) and low total dust exposure (GM < 5 mg/m³) (n=64) did not differ significantly (GM; 17 ppb vs. 16 ppb). Likewise, there was no difference in FE_{NO} concentration between the workers in stage I (n=65) and stage II (n=62) of cement production (GM: 17 ppb vs. 16 ppb). The GM for total dust exposure was higher among the exposed workers compared to controls (5.0 m vs. 0.6 mg/m³, respectively).

4.4 Paper IV

This study assessed pre- and post-shift changes in FE_{NO} for three consecutive days among exposed workers and for two consecutive days among controls. All participants were non-smoking males, off work for at least two days before FE_{NO} examination, without history of childhood or current asthma, without history of chronic obstructive pulmonary disease, and they were not on any medications for chest treatment. Exposed workers and controls had similar baseline characteristics, except for height and education level.

We observed a statistically significant cross-shift decrease in FE_{NO} on each of the three days of examination among exposed workers, but not for the two days among controls. However, there was no significant difference in the cross-shift decrease in FE_{NO} when comparing the exposed workers and controls (mixed effects model, $\beta = -0.26$, 95% CI: -5.4 to 0.2). Among the exposed, the cross-shift decrease in FE_{NO} did not differ significantly between workers in the first and second stages of cement production (mixed effects models, $\beta = -0.26$, CI: -0.53 to 0.24 and $\beta = 1.67$, CI -2.46 to 5.80, respectively). Furthermore, the cross-shift decrease in FE_{NO} was not associated with individually measured total dust exposure levels ($r = -0.175$, 95% CI: -0.36, 0.04).

The GM for total dust exposure among exposed workers and controls was 8.3 mg/m³ and 0.28 mg/m³, respectively.

5. Main discussion

5.1 Occupational dust exposure among cement workers

We found an overall reduction in personal total dust exposure levels among cement production workers in 2010–11 compared to the dust levels reported in the same cement factory in 2002, before improvements in dust control measures were performed. The GM for total dust exposure among cement production workers in 2002 and 2010–11 was 10.6 mg/m^3 and 5.8 mg/m^3 and, respectively.

The dust exposure levels in 2010 were lower than in 2011 (5.0 mg/m^3 vs. 7.4 mg/m^3), which was explained by the latter having higher dust exposure levels in the cement mill than in the former. The higher dust exposure in the cement mill in 2011 was probably due to more dust samples taken among highly exposed cement mill attendants (GM= 14.3 mg/m^3) compared to low exposed millers (0.7 mg/m^3).

Similarly, a consistent reduction in dust exposure levels for the job groups in the different sections of the cement factory was also observed in 2010–11 compared to 2002, indicating a clear reduction in the dust exposure levels. The reduction in personal total dust exposure in the current study is probably due to the improvement in the dust control measures in the cement factory. Nevertheless, there was still a considerable proportion (25–43%) of the dust exposure levels exceeding the TLV value of 10 mg/m^3 for PNOS (20). The high dust exposure levels could be due to manual cleaning and removal of piled cement material among attendants and/or cleaners (5, 6) and insufficient air ventilation during manual handling of cement bags among the loaders.

To our knowledge, this is the first study to report on dust exposure levels after improvement of dust control measures in a cement factory. However, a cross-sectional study from the United Arab Emirates (UAE) mentioned a possible introduction of new safety measures in the cement factories in that country, such as modification of dust filters and enclosure of transport systems (41). It was not clear whether any of the control measures were implemented in the particular factory where that study was performed. The UAE study reported relatively higher dust exposure levels among cement workers than in our study (total dust, GM: 8.9 mg/m³) (Table 1).

In studies from Africa and Asia where no improvements of dust control measures were reported, the total dust exposure levels were higher than in our study, for instance in Ethiopia (total dust, GM: 439 mg/m³) (6), Iran (inhalable dust, AM: 53 mg/m³) (32) and Malaysia (total dust, AM: 10.2 mg/m³) (25) (Table 1). The present dust levels were, however, higher than those reported in Europe and America, for instance in Norway (inhalable dust, GM: 2.3 mg/m³) (22), USA (total dust, GM: 2.9 mg/m³) (23) (Table 1), and in Germany (inhalable dust, GM: 3.0 mg/m³) (24). The low dust exposure levels in the European and American studies are probably due to better dust control measures.

5.2 Chronic respiratory symptoms

We observed a considerably lower prevalence of chronic cough, chronic sputum production and chronic bronchitis among exposed workers in 2010 compared to 2002. A one-year follow-up of chronic respiratory symptoms revealed a significant reduction in symptom prevalence among exposed workers, but not among controls. In Tanzania, the findings of higher symptom prevalence, and lower lung function among the exposed workers in 2002 were related to higher dust exposure levels, whereas the exposed workers and controls did not differ in such respiratory symptoms in 2010. The findings in 2010 may partly be explained by reduced dust exposure levels observed after improvement of the dust controls measures in the factory after the 2002 study. In the one-year follow-up from 2010 to 2011, reductions in respiratory symptoms among exposed workers, but not among controls could be related to an increase in awareness and attitude towards the use of personal protection among cement workers as a result of the health and safety campaign. Although a similar proportion of the exposed workers reported to use RPE in 2010 and 2011, it is likely that better health and safety training of the cement workers has led to more proper use of RPE in 2011.

Symptom prevalence might vary with time (72), and a possibility of an “undetected epidemic” of respiratory infections among exposed workers at baseline could explain the higher prevalence of symptoms in 2010 compared to 2011. These might cause lower symptom prevalence at follow-up compared to baseline. However, the epidemic of respiratory infections seems to be unlikely due to similar geographical locations of the exposed workers and controls, which should have affected the two groups equally.

Comparisons of symptom prevalence between studies may be complicated by methodological differences (35) such as definitions of symptom prevalence and background information and knowledge among study participants. At low dust exposure levels, previous studies have reported similar symptom prevalence between exposed workers and controls (5, 23, 45) (Table 1), consistent with our findings from 2010–11. For instance, the prevalence of chronic cough and attacks of dyspnoea in Norway (18% vs. 21%, and 14% vs. 14.2%, respectively) (5), sputum production and breathlessness in Denmark (26% vs. 19.4%) (45), and chronic bronchitis (with exacerbations or with obstruction) in the USA (6% vs. 3% or 4% vs. 3%, respectively) (23). Other respiratory symptoms in those studies had higher prevalence than in the present study. This could be explained by higher age and prevalence of smoking and also due to longer duration of exposure to dust among the cement workers (5, 23, 45). For instance, in a study involving 8 European countries, significantly increased odds ratios among cement workers compared to administrative controls was found for cough among foremen (1.9), and cough, wheezing and dyspnoea combined together among production workers (2.7) (21). The mean thoracic dust exposure level in that study was 0.85 mg/m^3 , which was probably lower than in our study. However, the participants in that study were older (40 years), and it is likely that they had a longer duration of employment compared to our study participants.

The decrease in symptom prevalence among the exposed workers during the follow up from 2010 to 2011 is similar to a study among Norwegian smelters. However, this decrease was possibly due to a healthy worker effect among the smelters and no improvements were described (73). Our findings differ from a one-year follow-up

among Ethiopian cement worker where a significantly increased symptom prevalence among the cement workers was associated with excessive dust exposure, but in that study only 21% of the exposed workers used RPE (35), and no other specific control measures were implemented.

Our finding of a lack of significant difference in symptom prevalence between exposed workers and controls at baseline in 2010 is contrary to several cross-sectional studies among cement workers such as in Iran (32), UAE (9, 42), Malaysia (25) and Taiwan (74) (Table 1). The dust levels were higher in those studies than in our study.

We found a tendency of higher symptom prevalence among dropouts compared to the followed up workers. This observation is consistent with a previous study among cement workers in Ethiopia (35) and in a study among aluminium smelters in Norway (75). However, the association between higher symptom prevalence and dropout in our study was due to effect measure modification by smoking. A healthy worker effect has been reported as a possible reason for dropping out from follow-up studies (75, 76). In our follow-up study from 2010 to 2011, it was not clear whether the healthy worker effect played a role as there were heterogeneous reasons for dropping out and these reasons were not fully examined.

5.3 Lung function impairment

There were significant reductions in lung function indices among exposed workers compared to controls before improvement of dust control measures in 2002, whereas we did not observe such differences in 2010. A comparison of lung function indices among the exposed workers revealed significantly higher FEV₁, and percentage predicted values for FEV₁ and FVC in 2010 than 2002. This difference could not be explained by differences in height and duration of employment among the exposed workers between the two periods. However, lower height among the exposed workers in 2010 might instead have underestimated the difference in lung function, whereas shorter duration of employment in 2010 compared to 2011 might have overestimated the difference. Multiple explanations could account for the observation of higher lung function in addition to reduced dust exposure levels in 2010, including an increased personal protection against dust exposure, and a possibility that workers who had dust-related impaired lung function in 2002 might have quit their jobs.

Several previous studies have reported similar lung function indices between cement workers exposed to low dust levels compared to controls, consistent with the findings in our study (5, 23, 45) (Table 1). A follow-up of lung function also could have been preferable at the present dust levels. However, it is not likely that a significant change in lung function could be detected given the current dust exposure levels and only one year of follow-up. The one-year follow-up in Ethiopia reported a reduced lung function but the dust exposure levels were extremely high (35). The reduction in lung function among cement workers in several cross-sectional studies is probably associated with high dust exposure levels (25, 31, 32, 35), and older age and/or a possible longer duration of employment than in our study (21, 40) (Table 1).

In our follow-up study of respiratory symptoms from 2010 to 2011, dropouts and followed-up workers had similar FEV₁/FVC ratio. There are few such studies among cement workers (29, 35). Our finding is consistent with a study among Ethiopian cement workers (35) and among Turkish cotton mill workers (77). However, this finding is contrary to studies which followed up the workers for longer periods, and reported a reduction in lung function among dropouts compared to followed-up workers (29, 75).

5.4 Chronic obstructive pulmonary disease

There was a significantly higher prevalence of COPD among exposed workers compared to controls in 2002. However, the prevalence of COPD among exposed workers and controls was similar in 2010. The higher prevalence of COPD among exposed workers in 2002, but not in 2010 may be accounted for by a reduction in dust exposure levels, but also a healthy workers effect might have contributed. All workers with COPD in 2010 had worked less than 8 years in the cement factory, indicating a possibility that workers with such a problem had already left their jobs due to ill-health or that they had changed work positions in the factory. However, the observation of similar COPD prevalence between the exposed workers and controls in 2010 is consistent with studies among low dust-exposed workers (5, 21, 45). Nevertheless, the COPD prevalence was relatively higher in some studies than in our study, possibly related to aging, long-term exposure and a high prevalence of smoking (5, 45). A recent follow-up study found an increased risk of lower airway disease among cement workers (34). However, that study used hospital data, did not

have data on dust exposure levels and smoking, hence, it is difficult to interpret the study findings.

5.5 Fractional exhaled nitric oxide

We found no significant difference in FE_{NO} between exposed workers and controls, between cement workers with high and low total dust exposure, and between cement workers in stage I and II. These findings suggest that eosinophilic inflammation is an unlikely pathogenic mechanism for cement-related adverse respiratory health effects. However, there was a consistent and a significant cross-shift decrease in FE_{NO} among exposed workers, which was not related to individually measured total dust exposure. The lack of significant difference in FE_{NO} between exposed workers and controls is consistent with a cross-sectional study among cement mason apprentices in the USA (65), among construction workers in Finland (64) and in population studies in Sweden (78), UK (79) and New Zealand (80). In the USA, Carlsten et al. (2007) (65) did not find a significant difference in FE_{NO} when comparing cement mason apprentices and a control group of electrician apprentices (Table 2). Likewise, Sauni et al (2011) (64), found no significant difference in FE_{NO} among construction workers compared to controls in Finland. However, a significantly higher level of alveolar nitric oxide was reported among former Finnish construction workers who were heavily exposed to silica for a mean duration of 31 years. The increase in alveolar nitric oxide suggested an early inflammatory phase of silicosis (64). In the present study, the FE_{NO} levels were similar when compared between workers in stage I and II, although there was a tendency of an increased proportion of FE_{NO} above 50 ppb among workers in stage I compared to stage II. The tendency could be due to

exposure to crystalline silica present in the dust generated from the raw materials in stage I (5-7). However, the amount of free silica present in the dust from cement factories is small (5-7), and the duration of exposure in the present study is relatively short.

The lack of significant difference in FE_{NO} is in contrast with studies showing an increase in FE_{NO} among workers exposed to a complex mixture of dust and gases in aluminium pot rooms (55, 56), organic dust and endotoxin (58, 59) and among workers exposed to chemical agents such as ozone (61) and organic solvents (62) (Table 2), but these types of exposure are completely different from our study.

The cross-shift decrease in FE_{NO} among exposed workers is consistent with a cross-shift study among cement workers in Norway when baseline FE_{NO} was compared with FE_{NO} measured 32 hours later (22) (Table 2). The cross-shift decrease in FE_{NO} was not associated with total dust exposure, which is similar to the observation reported in Norway (22). However, the cross-shift decrease in the current study seems not to be due to diurnal variation in FE_{NO} since previous studies have either reported higher values in the afternoon than in the morning (81, 82) or a lack of diurnal variation of FE_{NO} (79, 83).

The reason for the consistent cross-shift decrease in FE_{NO} observed for three consecutive days among exposed workers is unknown. One possibility is that this decrease might be related to a decrease in a pro-inflammatory cytokine (IL-8) which has been reported when laryngeal mucosa cells and carcinoma cells of the lung were exposed to cement-related particles in vitro (48), and also in a study among low-dust exposed Norwegian cement workers (22). The decrease in IL-8 might consequently lead to a decrease in FE_{NO} secondary to impairment of IL-8 activated neutrophils

mobilization, as IL-8 activated neutrophils augment trans-membrane migration of eosinophils (84). However, the association between IL-8 and FE_{NO} decrease remains as a speculation and we did not measure IL-8 in the present study. Also, it might be considered that the cross-shift decrease in FE_{NO} among cement workers could be due to mechanical changes in the airways due to acute effects of dust exposure (7, 15, 22, 26). However, a previous study among cement workers did not find any association between FE_{NO} decrease and a decrease in either FEV₁ or mid-expiratory flow rate (FEF_{25-75%}) across the shift (22). In addition, our study mean FE_{NO} values (pre- and post-shift) were within the normal range on the basis of clinical interpretation of FE_{NO}, which suggests an unlikelihood of eosinophilic inflammation when FE_{NO} levels is below 25 ppb (53). Therefore, both pathological and clinical significances of the observed FE_{NO} decrease among cement workers need further evaluation.

6. Methodological discussion

6.1 Study design and setting

This thesis consists of two cross-sectional studies (Papers III and IV), one ordinary follow-up study (Paper II) and in another study where we used summarized data (66) from 2002 and compared with data from 2010–11 (Paper I), since a follow-up of workers examined from 2002 was not possible due to the lack of data set. The choice of the present cement factory enabled us to study possible effects of improvement in dust control measures. In Paper I, total dust exposure levels and health outcomes were examined at two different points in time (2002 vs. 2010–11). Due to the lack of individual data, no adjustments for potential confounders were made (66) when comparing analogous groups in the two time periods. Nevertheless, adjustments for potential confounders were made when comparing between exposed workers and controls in each of the two time periods.

A major limitation of the cross-sectional studies is that both exposure and outcome are examined at the same time. Therefore, no conclusive remarks can be drawn on causal-outcome associations between dust exposure and adverse respiratory health effects in such studies (85). However, the causal-outcome relationship between dust exposure and adverse health effects has been reported in previous studies (29, 35). To investigate any causal-outcome association between reduction in respiratory symptoms and improvement of dust control measures, we conducted a follow-up in the cement factory from 2002 to 2010 and from 2010 to 2011.

The follow-up on respiratory symptoms showed a significant reduction in symptom prevalence among exposed workers, but not among controls.

A follow-up on lung function in 2011 might have been of interest. We did not carry out the lung follow-up since we presumed that changes in lung function were unlikely to occur at the presently measured total dust levels and there were logistical constraints in the factories.

To determine possible associations between dust exposure and FE_{NO} , we conducted two cross-sectional studies (Papers III and IV). Whereas no significant difference in FE_{NO} was observed between exposed workers and controls in Paper III, a short follow-up on FE_{NO} (pre- and post-shift) (Paper IV) revealed a significant reduction in FE_{NO} among the exposed workers, but not among the controls.

6.2 Validity

An observation (result) is regarded to be valid if it accurately represents the features of a phenomenon under investigation (85-87). A result can either be internally or externally valid.

6.2.1 Internal validity

This term refers to the extent to which the results of a study are valid for the study group (86, 87). Internal validity can be achieved by minimizing alternative explanations such as bias, confounding and/or effect modification as briefly described below. Another alternative explanation is the role of chance, which may occur due to a random variation from sample to sample (85). For brevity, the role of chance is not discussed in details in this section.

6.2.1.1 Loss to follow-up and non-participation bias

A bias is a systematic error which results in an incorrect estimate of the association between exposure and outcome (86). For instance, loss to follow-up (dropouts) may be a major source of bias in follow-up studies and it may raise serious doubts in the

validity of the study results if the proportion of dropouts ranges from 30% to 40% (85). Non-participation bias occurs when those who do not participate in the study differ from those participating in various aspects, such as background information, exposure and/or disease status, motivation and attitudes towards health (85). In our follow-up study (Paper II), high participation rates were achieved at baseline both among exposed workers and controls (82.4% vs 93.3%). At the end of the follow-up, the proportion of dropouts was lower among exposed workers compared to controls (22% vs 35%). In addition, the dropouts and followed-up workers did not differ significantly in the baseline characteristics and health outcomes, which indicate that the reduction in symptom prevalence among exposed workers is unlikely to be explained by non-participation or loss to follow-up. However, only a small number of participants who were examined in 2002 were also examined in 2010, which might have influenced our results.

6.2.1.2 Selection bias

Selection bias occurs when non-comparable criteria are used to recruit study participants (85). This causes a systematic difference in characteristics between those who are participating in a study and those who are not (87). A common selection bias in occupational epidemiology is a “healthy worker effect”. This effect is characterised by a relatively healthier working group compared to the general population in terms of morbidity and mortality (85, 88). This effect may be a result of hiring relatively healthy individuals (healthy hire effect), or when workers quit jobs due to work-related ill-health (healthy worker survivor effect) or when there are changes in life associated with employment (85, 88, 89). The healthy worker effect can cause an underestimation of true associations between exposure and outcome when the

general population is used as control group (85). The higher lung function indices and lower prevalence of COPD among the exposed workers in 2010 compared to 2002 probably indicate a relatively healthy workforce in the cement factory in 2010 compared to 2002. In 2010, we used mineral water factory workers as controls, as we presumed that they were healthy since they undergo pre-entry and periodic medical examinations (90). Therefore, comparison of the exposed workers and the healthy controls might have minimized the healthy worker effect in our study.

A selection bias might have occurred among participants in FE_{NO} examination in 2010–11, since we restricted these examinations to males, non-smoking production workers only. However, examination of only non-smoking males was necessary as smokers have been reported to have lower FE_{NO} levels compared to their smoking counterparts (91).

6.2.1.3 Information bias

Information bias occurs whenever non-comparable information is obtained or a misclassification of information occurs between the study groups (85, 87).

Information bias can either be differential or non-differential, and may be a result of both the investigator (s) (observer bias) and the study participants (response bias) (87). A differential misclassification may either underestimate or over-estimate an association between exposure and outcome, whereas a non-differential misclassification may bias the association towards the null hypothesis.

A recall bias for instance might have occurred among the dust exposed workers by tending to report more respiratory symptoms than among the un-exposed controls, thus overestimating the association between dust exposure and adverse health outcomes (92). On the contrary, under-reporting of the symptoms or smoking habits

among the study participants might have occurred due to social desirability (92, 93) or job insecurity, thus biasing our results towards no difference. In our study in 2010–11, the interviewer was aware of the exposure status and the interventions performed to reduce dust exposure levels in the factory, which might have influenced our results. To minimize the interviewer bias, we used a structured interview with standardized questions among both exposed workers and controls. Also, we reduced response bias by conducting the interviews in a separate room, with one participant at a time, and by ensuring confidentiality such that no information about any participant was given to the leaders of the factories. Translation of the questionnaire from English to Swahili may have influenced our results.

6.2.1.4 Ecological fallacy

An “ecological fallacy” or bias occurs when conclusions at an individual level are drawn based on group data (ecological data), because possible associations between exposure and outcome at the group level may not necessarily represent associations that may exist at the individual level (66, 87). The ecological analysis is, however, important in hypothesis generation, comparison of populations with widely differing characteristics, identification of problems of public health importance and evaluation of effects of group based interventions (66, 87, 94). The ecological bias may be minimized by comparing as homogeneous groups as possible (66). In our study, the ecological bias might have occurred when comparing total dust exposure and health outcomes between 2002 and 2010–11. Nevertheless, the exposed workers in both examination periods had similar age, education levels and smoking habits, except for height and duration of employment, which were higher in 2002 compared to 2010–11. It is less likely that the difference of 2 years in the duration of employment

between 2002 and 2010 should fully account for the finding of higher FEV₁ by 370 mls among the exposed workers in 2010 compared to 2002. In addition, the similar predicted values for lung function specifically for Tanzanian males (69) accounted for the difference in height between the two periods. Thus, the effect of ecological bias in our study may be minimal.

6.2.1.5 Confounding and effect modification

Confounding simply means “mixing of effects” or the distortion of associations between an exposure and an outcome due to presence of a third variable, a confounder (85, 87). For confounding to occur, the confounder must be a risk factor for a given outcome, must be associated with both the exposure and the outcome, but the association with the outcome is not a true association, and the confounder should not be an intermediate step in the causal pathway between the exposure and outcome. Confounding can be controlled by randomization, matching and restriction during the designing phase of a study, while stratification and multivariate analyses can be used during data analysis (85, 87). In order to minimize confounding in 2010–11, information on potential confounders such as age, education level, smoking habits, weight, height, duration of employment and previous chest illnesses were gathered and adjusted for during multivariate regression and mixed effects model analyses. In addition, we restricted our study to male production workers in both factories, and FE_{NO} was examined among non-smokers only. Therefore, it is less likely that the reduction in symptom prevalence among exposed workers and the findings on FE_{NO} can be due to the factors mentioned above.

Possible effects of exposures outside workplaces on the health outcomes, atopy infections, and dietary differences are unknown in our study (residual confounding).

Atopy has been associated with high levels of FE_{NO} (78, 91), but we did not perform skin prick test or determine serum immunoglobulin E levels as blood samples were not taken, and possible dietary differences were not assessed. However, both exposed workers and controls resided in the same geographical area, hence effects of these factors on our results should be minimal.

Unlike confounding, effect modification is a biological phenomenon that occurs when the association between exposure and outcome varies based on strata of a third variable, an effect modifier (85). In effect modification, the association between exposure and outcome is described during analysis (instead of controlling) and results of the association are presented depending on the strata of the effect modifier (85). In our study, effect modification of symptom prevalence by smoking among dropouts compared to followed-up workers was observed. The tendency of more symptoms among dropouts was less among exposed workers compared to controls, but still after one year, there was a significant reduction in symptoms prevalence among exposed workers, but not among the controls.

6.2.2 External validity

External validity or generalisability refers to the extent to which study findings apply to those not involved in the study (85, 87). Our findings can be generalized to the study population in the cement factory. Whether the present finding can be generalised to other cement factories in Tanzania, Africa or other developing countries remains questionable. There are no similar studies on improvement that have been reported from those areas. However, the reduction in dust exposure levels

observed in 2010–11 compared to 2002 can be generalised to old cement factories which had had similar improvements in dust control measures.

Our findings on the prevalence of chronic respiratory symptoms, lung function and COPD are comparable to studies that have been performed in Europe and America (5, 23, 45). Therefore, the findings on these parameters might be generalised among cement workers with similar duration of employment who are exposed to similar or lower levels of total dust exposure.

The findings on the lack of associations between total dust exposure and FE_{NO} , and the cross-shift in FE_{NO} among exposed workers are consistent with a previous study among cement production workers (22). Therefore, our findings on FE_{NO} can be generalised to non-smoking cement workers exposed to similar or lower levels of total dust exposure.

6.3 Exposure assessment

The three-piece closed-faced Millipore cassettes were used for total dust sampling in 2002 and 2010–11. These sampling heads have the advantage that they protect the dust filters from damage due to vigorous activities during sampling, but they have a disadvantage that they underestimate the amount of dust compared to the inhalable convention (95, 96). Another possibility could have been to use the IOM sampler which is commonly used for dust sampling (95). This sampler collects inhalable particles close to the inhalable convention. However, the IOM sampler has a wide and open inlet (15mm) that may allow mechanical damage of the dust filters during sampling (14), therefore, we chose the Millipore cassettes.

Thoracic samplers collect dust particles which are deposited in the tracheobronchial region, an area presumed to be relevant for pathophysiology of dust-related airway obstruction (13, 21). Currently, there are no limit values for the thoracic fraction; hence, it is difficult to interpret or compare the study results. The use of total dust measurements in the present study was chosen since it allowed comparisons with previously measured total dust levels in the same cement factory and with the TLV of 10 mg/m^3 for PNOS (20).

Some dust samples were detected to have loose dust on the walls of sampling cassettes ($n=16$), and they were marked as overloaded in the laboratory in 2010–11. Nevertheless, both the loose dust and the dust attached on the filters were analysed, which may introduce uncertainties in the analysis of these dust samples. To minimize the uncertainty due to overloading, the sampling time could have been reduced (35). Since the mean sampling time was approximately 6 hours we presumed that the dust exposure levels obtained in our study were representative of the exposure in an 8 hour shift.

Another uncertainty might be due to transportation of dust samples from Tanzania for analysis in the Eurofins laboratory in Denmark. This might cause weight changes for the dust filters due to perturbation and differences in climatic conditions. However, blank filters were used for correction and the climatic conditions were controlled in the laboratory during gravimetric analysis.

One limitation in comparisons of dust levels is the issue of inter-laboratory differences between 2002 and 2010–11. However, similar sampling and analytical techniques were used in both periods. Therefore, we presumed that any effects due to

inter-laboratory differences on the reduction of total dust levels observed in 2010–11 compared to 2002 were negligible.

The total dust exposure levels among cement workers could have been compared between the old and new production lines. This comparison was not done due to the fact that the cement workers in analogous sections moved freely between the two production lines. Nevertheless, stationary sampling could have been performed for comparison purposes, but this type of sampling is beyond the scope of the thesis.

The *a posteriori* grouping scheme of total dust exposure as high or low dust exposure indicated a higher contrast in exposure compared to the *a priori* grouping of stage I and II. This indicates that a misclassification of exposure was reduced in the *a posteriori* grouping scheme compared to the *a priori* grouping scheme (17, 18).

Total dust exposure level in the cement mill in 2010–11 seemed to depend on the number of dust samples among highly exposed attendants. However, inclusion of more attendants compared to the low exposed millers in 2010–11 might have resulted in reduced uncertainties for exposure estimates among the attendants. In addition, the crane operators may be exposed to dusts particles from both stage I and II, because of feeding materials into the raw mill and the cement mill hoppers, respectively. Hence, misclassification of exposure cannot be totally excluded in our study. The misclassification might have underestimated the association between total dust exposure and FE_{NO} when comparing FE_{NO} between the two stages.

6.4 Questionnaire

Chronic respiratory symptoms were assessed using a validated BMRC questionnaire in both 2002 and 2010–11 (97). This questionnaire was translated from English to Swahili and back to English using standard translation procedures, in both periods. The questionnaire was self-administered in 2002, whereas interviews based on the questionnaire were conducted for each study participant in 2010–11. Thus, we cannot totally exclude bias due to mode of administration, which may underestimate or overestimate our results (85, 98, 99).

Interviews may be preferred to self-administered questionnaires in the case of an investigation of non-serious conditions that do not require hospitalization (99), and the interviews remove the possibility of a non-targeted person responding to the questionnaire (100). We used standardized BMRC questions in both 2002 and 2010–11, which probably minimized bias between the two periods, and one interviewer conducted the interviews among exposed workers and controls in 2010 and 2011.

6.5 Spirometry

Lung function tests in both 2002 and 2010–11 were performed based on the ATS/ERS criteria for acceptability and reproducibility of spirometry (68), and similar equations for prediction of lung function indices were used in both periods (69).

FEV₁, FVC, and the FEV₁/FVC ratio are the commonly used lung function indices which were also used in our study. The spirometric tests were taken at different time points in 2002 (10:00 am to 12:30 pm) and 2010 (12:00 pm to 16:00 pm). Thus, the lung function indices among the exposed workers in 2010 might have been underestimated due to diurnal variations in the lung function and acute effects of dust

exposure (15, 22, 26, 101). In addition, the differences in spirometers and personnel performing the lung function tests between the two periods may have impacted the results (102, 103). We do not know how or whether these differences may have affected our results. However, we presumed that any inter-device differences had minimal impact on our results due to similarities in acceptability and repeatability criteria (68) in both periods. Also, we eliminated inter-personnel differences in 2010 by having only one personnel who performed the spirometric tests among both the exposed workers and controls.

The 2001 GOLD criteria recommend using the $FEV_1/FVC < 0.7$ ratio and post-bronchodilator $FEV_1 < 80\%$ of the predicted value for confirmatory diagnosis of COPD, in line with the 2004 ATS/ERS criteria (33, 104). The fixed ratio criterion ($FEV_1/FVC < 0.7$) can either underestimate (in the younger adult population, 30 – 50 years) or overestimate the prevalence of COPD (in the older adult population, 70 years or above) (105, 106). Another possibility could have been to use the recently proposed ATS/ERS criteria for diagnosis of COPD which account for age-related obstruction by using the lower limit of the normal for $FEV_1/FVC < 0.7$ and FEV_1 (107). These criteria give a relatively lower prevalence of COPD compared to the $FEV_1/FVC < 0.7$ ratio alone (105, 106). In our study, post-bronchial dilatation tests were not feasible and the study participants were relatively young. Therefore, a possible underestimation of the prevalence of COPD in our study cannot be excluded.

6.6 Measurement of fractional exhaled nitric oxide

Measurements of FE_{NO} were performed using a single flow rate NIOX MINO device pre-calibrated by the manufacturer; hence no further calibrations were required in the

field (70). All measurements were performed in accordance with the ATS/ERS criteria for online measurement of FE_{NO} (49). One exception of using the NIOX MINO device was that a single test for each participant each time FE_{NO} was examined, as only one test has been considered sufficient due to its high reproducibility (70, 71). Since total dust is likely to be deposited along the whole respiratory tract, we presumed that FE_{NO} could be a relevant non-invasive marker for the dust-related inflammatory process among cement workers.

Another method could have been to use a multiple flow technique (49, 64, 108). This technique can identify whether exhaled nitric oxide is produced from the proximal (bronchial nitric oxide) or distal region (alveolar nitric oxide) of the lung (108, 109). In this technique, the exhaled nitric oxide is examined at different flow rates such as 50 ml/s, 100 ml/s and 200 ml/s, and the fractions of alveolar and bronchial nitric oxide are calculated. High levels of alveolar nitric oxide suggest an inflammatory process in the alveoli (64). However, there are no comparable studies which have used this technique among dust-exposed cement workers, thus its application in this particular group is currently unknown.

7. Study conclusions

7.1. There was a reduction in personal total dust exposure, prevalence of chronic respiratory symptoms and COPD among Tanzanian cement production workers, after improvement of dust control measures, from 2002 to 2010. The lung function indices among cement production workers were higher in 2010 compared to 2002.

In a one-year follow-up from 2010 to 2011, there was a significant reduction in the prevalence of chronic respiratory symptom among Tanzanian cement production workers compared to controls.

There was no significant difference in baseline lung function indices between the cement workers and controls in 2010.

7.2. There was no difference in fractional exhaled nitric oxide between Tanzanian cement production workers and controls. However, we observed a consistent and significant cross-shift decrease in fractional exhaled nitric oxide among the Tanzanian cement production workers, but not among the controls. The reason for this decrease is unknown.

8. Future perspectives and recommendations

8.1 Research

The following studies are suggested in the future:

1. Long term follow-up of chronic respiratory symptoms and lung function among cement workers.
2. Qualitative assessment of dust control measures in the cement factory such as assessment of general and local ventilation systems, knowledge, attitude and practise towards personal protection among cement workers.
3. Multi-centre /multi-national comparison of effects of different methods and technology for dust control.
4. Laboratory studies should be performed to identify the reason for cross-shift decrease in fractional exhaled nitric oxide.
5. Using other non-invasive biomarkers of airway inflammation such as pH changes in the exhaled breath, alveolar nitric oxide and induced sputum examinations to elucidate the underlying mechanisms of dust-related respiratory disorders among cement production workers.

8.2 Policy and practice

8.2.1. Specifically for the cement factory

1. More targeted engineering dust control measures should be taken to reduce dust exposure, specifically for workers exposed to dust levels above the threshold limit value of 10 mg/m^3 .
2. Short-term rotations for workers in different sections will reduce long-term adverse respiratory health effects associated with high dust exposure, and the

workers should be provided with more information on adverse respiratory health effects related to dust exposure.

3. The cement factory workers who are still exposed to high dust levels such as the attendants and loaders should be provided with efficient personal respiratory protective equipment.
4. Periodic risk assessment and regular medical examinations should be performed for early identification of workers at high risk of developing chronic respiratory diseases in the cement factory.

8.2.2. The cement industry

A multi-sector approach including co-operations between the cement factories and regulatory authorities, health professionals and/or researchers should be adopted to reduce the burden of dust-related chronic respiratory diseases among cement workers, in Tanzania and worldwide.

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