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## EXTENDED REPORT

## Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case–control study

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## ABSTRACT

**Objectives** Lung exposures including cigarette smoking and silica exposure are associated with the risk of rheumatoid arthritis (RA). We investigated the association between textile dust exposure and the risk of RA in the Malaysian population, with a focus on women who rarely smoke.

**Methods** Data from the Malaysian Epidemiological Investigation of Rheumatoid Arthritis population-based case–control study involving 910 female early RA cases and 910 female age-matched controls were analysed. Self-reported information on ever/never occupationally exposed to textile dust was used to estimate the risk of developing anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative RA. Interaction between textile dust and the human leucocyte antigen DR  $\beta$ -1 (HLA-DRB1) shared epitope (SE) was evaluated by calculating the attributable proportion due to interaction (AP), with 95% CI.

**Results** Occupational exposure to textile dust was significantly associated with an increased risk of developing RA in the Malaysian female population (OR 2.8, 95% CI 1.6 to 5.2). The association between occupational exposure to textile dust and risk of RA was uniformly observed for the ACPA-positive RA (OR 2.5, 95% CI 1.3 to 4.8) and ACPA-negative RA (OR 3.5, 95% CI 1.7 to 7.0) subsets, respectively. We observed a significant interaction between exposure to occupational textile dust and HLA-DRB1 SE alleles regarding the risk of ACPA-positive RA (OR for double exposed: 39.1, 95% CI 5.1 to 297.5; AP: 0.8, 95% CI 0.5 to 1.2).

**Conclusions** This is the first study demonstrating that textile dust exposure is associated with an increased risk for RA. In addition, a gene–environment interaction between HLA-DRB1 SE and textile dust exposure provides a high risk for ACPA-positive RA.

## INTRODUCTION

Rheumatoid arthritis (RA) is a multifactorial disease that involves the interaction between environmental and genetic factors.<sup>1–7</sup> Smoking is one of the most established risk factors for disease development,<sup>7–11</sup> and a profound interaction between smoking and human leucocyte antigen DR  $\beta$ -1 (HLA-DRB1) shared epitope (SE) alleles regarding the risk of anti-citrullinated peptide antibody (ACPA)-positive RA has been reported in several studies.<sup>1 2 7 8 12–16</sup> There is growing support for the hypothesis that

this gene–environment interaction may induce changes in the lung tissues, where immunity against citrullinated antigens may be triggered in individuals with certain genotypes.<sup>1 7 17–19</sup>

Silica is another lung exposure that has been associated with the risk of ACPA-positive,<sup>20 21</sup> indicating that exposure to other noxious agents than smoke in the lung may provide a risk for RA. Exposure to textile dust has been shown to impair the lung functions of workers<sup>22–25</sup> and increase the risk of respiratory diseases,<sup>22 26 27</sup> but whether it is involved in RA development remains to be elucidated. The investigation of genetic and environmental risk factors for RA in Malaysia (Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA))<sup>2 21 28–32</sup> offers an opportunity to investigate the association between textile dust and RA risk.

In the present study, we specifically investigated whether occupational exposure to textile dust, which is common in Malaysia, may increase the risk of RA overall as well as the subsets of RA defined by ACPA status. We additionally explored the interaction between textile dust exposure and the HLA SE alleles in relation to the RA subsets.

## MATERIALS AND METHODS

## Study base

This study is based on the MyEIRA case–control study, a sister study to the Swedish EIRA study involving early RA cases.<sup>20</sup> The study design of MyEIRA has been described in details elsewhere.<sup>28 32</sup> Briefly, study subjects aged between 18 and 70 years were recruited between 2005 and 2009 from a defined geographical area in Peninsular Malaysia. In this report, data from 910 female RA cases and 910 female controls were analysed. Male subjects were excluded as textile dust exposure among men was very scarce (two exposed cases among 155 male RA and one exposed control out of 150 male controls). Moreover, the smoking frequency was high among the men (46% and 28% in male RA cases and male controls, respectively) but was very low among the women (1% among cases and 0.4% among controls, respectively).<sup>2</sup>

## Case identification and selection of controls

Patients with early RA were identified from nine rheumatology clinics throughout Peninsular

Malaysia. All RA cases were diagnosed by rheumatologists and fulfilled the 1987 American College of Rheumatology (ACR) criteria.<sup>33</sup> One control per RA case was randomly selected from the general population and matched on the age, sex and residential area. For the RA cases, the disease onset was defined at the time of having first symptoms giving suspicion of RA. The year in which these symptoms occurred was defined as the index year and the same index year was used for the corresponding control.

### Data collection and blood sampling

Both RA cases and controls underwent a face-to-face interview by trained personnel to obtain information on lifestyle and environmental exposures using an identical questionnaire. The questionnaire comprised a wide range of questions on socio-economic background, lifestyle, life events, working history, working conditions and exposures to chemicals or substances at work, including questions on textile and silica dust. Of the 1166 identified early RA cases, 1076 (92%) completed the questionnaire. Of these 1076 RA cases, 85.6% (n=921) were females. Eleven of the female RA cases, however, did not have matched controls and were excluded from analysis. For the control subjects, a total of 1069 population-based controls participated by answering the questionnaire, and 86.0% (n=919) were females. Nine of the females did not match any of the RA cases and thus were excluded from data analysis. Finally, data from 910 female RA cases and 910 age-matched and residential area-matched female controls were analysed in this study. Sera and DNA samples were obtained from all the participants for laboratory investigations.

### HLA-DRB1 genotyping and autoantibodies measurements

The methods for determining the HLA-DRB1 alleles have previously been reported.<sup>28</sup> In brief, the four-digit HLA-DRB1 genotyping was performed by using the LABType HD Class II DRB1 sequence specific oligonucleotide assay (One Lambda, California, USA) with the Luminex Multi-Analyte Profiling System (xMAP, Luminex Corporation, Texas, USA). The HLA-DRB1 SE alleles were defined as the presence of DRB1\*01:01, DRB1\*01:02, DRB1\*01:07, DRB1\*04:01, DRB1\*04:04, DRB1\*04:05, DRB1\*04:08, DRB1\*04:10, DRB1\*10:01 and DRB1\*10:03. Individuals with one or two SE alleles are categorised as SE-positive. ACPA status was assessed by using an anti-cyclic citrullinated peptide (anti-CCP) second-generation ELISA kits (Immunoscan RA, Malmö, Sweden). Samples with results >25 AU/mL were defined as positive.<sup>28 31</sup>

### Assessment of exposures

Participants were asked whether they had ever been exposed to textile dust at work. Individuals were classified as occupationally exposed to textile dust if they reported exposure before or during the index year. Individuals with missing information (53 female RA cases and 35 female controls) were excluded from the analysis (table 1).

### Potential confounding factors

Age and residential area were design variables and adjusted for in the analysis. We considered smoking as a potential confounder, but there were only two female patients with RA who were ever smokers and none in the control group. In addition, formal educational level (categorised as no formal education, primary education, secondary education or college/university) and ethnicity (categorised as Malay, Chinese, Indian and others) were adjusted for in all analyses, but these factors only marginally

**Table 1** Characteristics of female rheumatoid arthritis (RA) cases and female controls in the Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA) study

	Female RA cases (n=910)	Female controls (n=910)
Mean age (SD)	47.5 (11.4)	47.4 (11.3)
Ethnicity		
Malay	381 (41.9)	591 (65.0)
Chinese	182 (20.0)	105 (11.5)
Indian	307 (33.7)	159 (17.5)
Others	40 (4.4)	55 (6.0)
Educational level		
No formal education	41 (4.5)	64 (7.0)
Primary education	202 (22.2)	222 (24.4)
Secondary education	479 (52.6)	444 (48.8)
College/university	184 (20.2)	177 (19.5)
Missing information	4 (0.4)	3 (0.3)
ACPA		
Positive	575 (63.2)	18 (2.0)
Negative	325 (36.8)	892 (98.0)
HLA-DRB1 SE alleles		
Positive	360 (39.6)	147 (16.0)
Negative	549 (60.3)	763 (84.0)
Missing information	1 (0.1)	0
Smoking habits		
Never smoker	870 (95.6)	884 (97.2)
Ever smoker	9 (1.0)	4 (0.4)
Missing information	31 (3.4)	22 (2.4)
Textile dust exposure		
Occupational exposed	41 (4.5)	15 (1.7)
Unexposed	622 (68.4)	647 (71.1)
Missing information	53 (5.8)	35 (3.8)

ACPA, anti-citrullinated peptides antibody; HLA-DRB1 SE, human leucocyte antigen DR  $\beta$ -1 chain shared epitope.

changed the results and were therefore not retained in the final analysis.

### Statistical analysis

In the present study, only data on occupational exposure before and during the index year have been analysed. Subjects who had ever been exposed to occupational textile dust were compared with those unexposed regarding risk of developing RA, ACPA-positive RA and ACPA-negative RA. The ORs with 95% CIs were calculated by means of unconditional logistic regression. Possible interaction between textile dust exposure and HLA-DRB1 SE alleles was evaluated as departure from additivity by calculating the attributable proportion due to interaction (AP), with 95% CI.<sup>44</sup> Analyses were conducted using Stata V12.0.

## RESULTS

### Characteristics of the MyEIRA subjects

In this report, we analysed a total of 910 female RA cases and 910 female population-based controls. The median duration of time from disease onset to enrolment in the study was 1 year, with an IQR of 2 years. The distribution of ethnic groups (Malay, Chinese, Indian and other subethnicities) is presented in table 1. The proportion of ACPA positivity and HLA-DRB1 SE

alleles carriage among the female patients with RA were 63.2% and 39.6%, respectively. Occupational exposure to textile dust was reported by 4.5% of the female patients with RA (n=41, whereof Malay=14, Chinese=11, Indian=13 and other=3) and by 1.7% of the women in the control group (n=15, whereof Malay=6, Chinese=5, Indian=3 and other=1).

### Textile dust and the risk of developing ACPA-positive and ACPA-negative RA

Those exposed to occupational textile dust had an increased risk of developing RA compared with unexposed individuals (OR 2.8, 95% CI 1.6 to 5.2). Furthermore, our findings demonstrated that occupational exposure to textile dust was significantly associated with increased risk for both ACPA-positive RA (OR 2.5, 95% CI 1.3 to 4.8) and ACPA-negative RA (OR 3.5, 95% CI 1.7 to 7.0) (table 2).

### Interaction between occupational textile dust exposures and HLA-DRB1 SE alleles

An increased risk of ACPA-positive RA was seen among carriers of HLA-DRB1 SE alleles who were exposed to occupational textile dust compared with non-carriers of SE alleles not exposed to textile dust (OR 39.1, 95% CI 5.1 to 297.5) (table 3 and figure 1). We observed a significant interaction between HLA-DRB1 SE alleles and occupational exposure to textile dust with regard to risk of ACPA-positive RA (AP=0.8, 95% CI 0.5 to 1.2). The combination of occupational exposure to textile dust and HLA-DRB1 SE alleles was also associated with an increased risk of ACPA-negative RA (OR 9.3, 95% CI 1.0 to 89.4), but no statistical significant interaction was observed (AP=0.6, 95% CI -0.4 to 1.6) (table 3).

## DISCUSSION

We observed that occupational exposure to textile dust was associated with an increased risk of ACPA-positive and ACPA-negative RA among Malaysian women. Additionally, a statistically significant interaction between occupational textile dust exposure and presence of HLA-DRB1 SE alleles was seen concerning risk to develop ACPA-positive RA.

We note that the association between textile dust exposure and risk for RA differs from what has previously been observed for smoking and silica as textile dust exposure is associated with

**Table 3** Risk of developing rheumatoid arthritis (RA) in women with different combinations of occupational textile dust exposure and shared epitope (SE) genes compared with women who reported no exposure to textile dust and carrying no SE genes, Malaysian Epidemiological Investigation of Rheumatoid Arthritis study\*

	No SE		Any SE	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
<i>Occupational exposure to textile dust</i>				
RA overall				
Unexposed	376/545	Referent	244/102	3.4 (2.7 to 4.3)
Ever exposed	24/14	2.5 (1.3 to 4.9)	17/1	25.1 (3.3 to 189.5)
				AP: 0.8 (0.4 to 1.2)**
ACPA-positive RA				
Unexposed	201/545	Referent	198/102	5.1 (4.0 to 6.6)
Ever exposed	9/14	1.8 (0.8 to 4.2)	14/1	39.1 (5.1 to 297.5)
				AP: 0.8 (0.5 to 1.2)**
ACPA-negative RA				
Unexposed	175/545	Referent	46/102	1.5 (1.1 to 2.0)
Ever exposed	15/14	3.3 (1.6 to 6.9)	3/1	9.3 (1.0 to 89.4)
				AP: 0.6 (-0.4 to 1.6)

\*All estimates adjusted for age group, geographical area, educational levels and ethnicity.

\*\*p<0.0001.

ACPA, anti-citrullinated protein antibody; AP, attributable proportion due to interaction; Ca/Co, case/control.

risk for both ACPA-positive and ACPA-negative disease, whereas smoking and silica provide risk for only ACPA-positive disease.<sup>2 8 20 21</sup> We do not have any mechanistic hypothesis for this difference and can only speculate that textile dust exposure may have a more general effect on immune activation, also in ACPA-negative disease than is the case for cigarette smoke and silica dust exposure. Whether there is an interaction between textile dust and smoking with regard to risk of developing ACPA-positive RA, as is the case for silica,<sup>20 34</sup> could not be studied in the present investigation since virtually all women never had smoked.

The properties of textile dust content differ depending on the fabric, the manufacturing and processing of the material. For instance, the source of the dust may originate from both natural (eg, wool, cotton) and synthetic (eg, polyester, nylon) materials.<sup>35</sup> Also, a wide range of chemicals might be used to attain desirable properties of the fabric, like synthetic dyes, flame retardants, mineral lubricants and water repellents (International Agency for Research on Cancer). The association between textile dust and risk of RA might involve several potential disease mechanisms since the differing physicochemical properties of airborne dust affect where it deposits in the respiratory tract.<sup>36</sup>

We further propose that natural or synthetic fibres in textile dust might explain an association between textile dust exposure and risk of RA. Due to their unique shape, fibres have been shown to penetrate deep into the lung, where they initiate an inflammatory response.<sup>37</sup> However, many textiles contain natural organic fibres and the health effects from natural organic fibres are not as strongly linked to lung disease as inorganic fibres.<sup>38</sup>

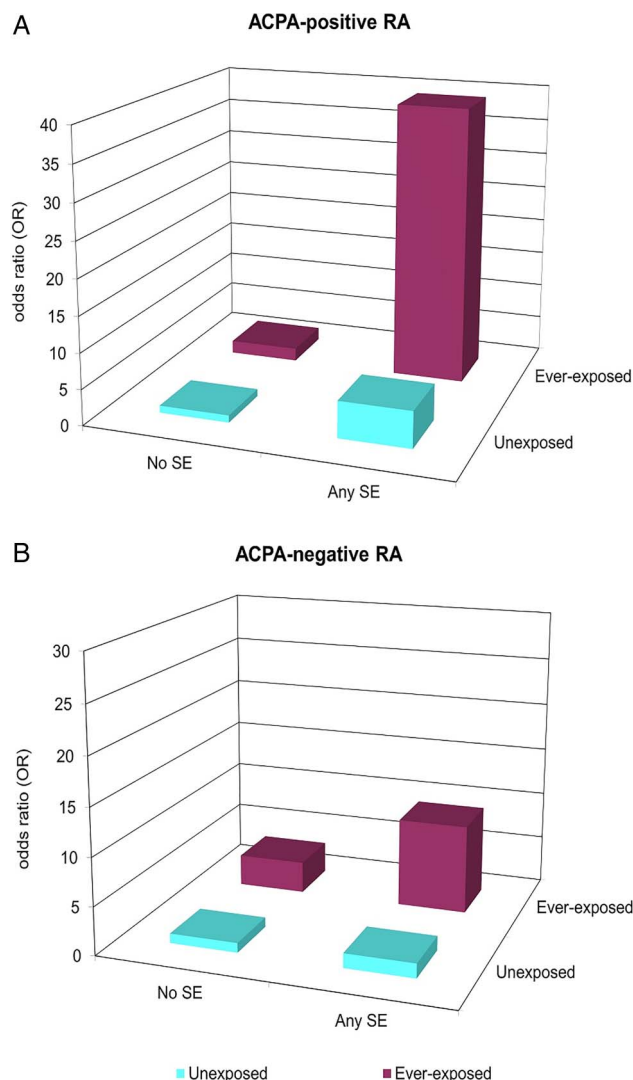
Based on the reasoning above, the participants in MyEIRA may, therefore, have encountered both known and so far to us unknown agents associated with RA either through the textile dust itself or through other confounding hazardous exposures in their work environment during the manufacturing and processing of the textile (like mineral dusts or other chemical dusts).

**Table 2** ORs with 95% CIs of developing rheumatoid arthritis (RA) overall, anti-citrullinated protein antibody (ACPA)-positive RA and ACPA-negative RA, among women with occupational exposure to textile dust compared with women unexposed to textile dust in the Malaysian Epidemiological Investigation of Rheumatoid Arthritis study

	Cases/controls	OR (95% CI)*
<i>Occupational exposure to textile dust</i>		
RA overall		
Unexposed	622/647	Referent
Ever exposed	41/15	2.8 (1.6 to 5.2)
ACPA-positive RA		
Unexposed	399/647	Referent
Ever exposed	23/15	2.5 (1.3 to 4.8)
ACPA-negative RA		
Unexposed	223/647	Referent
Ever exposed	18/15	3.5 (1.7 to 7.0)

\*Adjusted for age group, geographical area, educational levels and ethnicity.





**Figure 1** ORs of developing (A) anti-citrullinated protein antibody (ACPA)-positive and (B) ACPA-negative rheumatoid arthritis (RA) for different combinations of occupational exposure to textile dust and shared epitope (SE) alleles compared with those never exposed to textile dust and having no SE alleles.

Asbestos is another potential airborne exposure among textile workers.<sup>39 40</sup>

Another potential mechanism behind the demonstrated association between exposure to textile dust and risk for RA is bacterial agents that can be found in textile dust, especially endotoxin, which is a bacterial agent produced by all Gram-negative bacteria and is believed to cause respiratory diseases in textile workers by generating an inflammatory response in the lungs.<sup>24 27 41 42</sup> The present study design does not, however, allow us to further address this possibility.

A very interesting finding was the observation of a similar interaction between occupational exposure to textile dust and HLA-DRB1 SE in relation to ACPA-positive disease as has been seen for cigarette smoking and HLA-DRB1 SE.<sup>2 7</sup> Here, we may speculate that similar events, that is, exposure to textile dust or smoking, may contribute to the production of citrullinated peptides, which, in the context of certain HLA alleles, may contribute to activation of anti-citrulline immunity in lungs.<sup>17 18</sup> Our statistical analysis did not identify this SE-textile interaction in ACPA-negative RA. This is in line with the lack of association

between ACPA-negative RA and HLA-DRB1 SE in Malaysian RA.<sup>28</sup> However, the power of this analysis was limited.

Our study has several advantages. The MyEIRA study is a population-based case-control study including incident cases. It contains information on both environmental and genetic risk factors. The response rate was high (94.2% among cases, 96.2% among controls), which limits the risk of selection bias. Also, we recruited cases with short disease duration in an attempt to overcome differential misclassification of exposure, that is, that cases would recall their previous exposures differently from the controls. RA cases were selected by rheumatologists based upon their medical records, and the median duration of disease among the cases was 1 year with an IQR of 2 years. Thus, the inclusion of early RA cases gives an advantage that the patients are less likely to have had time to change their occupation due to RA manifestations, which possibly may influence the quality of the reported information on occupational exposures. However, we do not believe that recalling occupational exposures was difficult neither among cases nor among controls, and therefore, differential misclassification of textile dust exposure most probably is marginal and the possible non-differential misclassification that may have occurred would tend to bias our estimates towards the null value.

The study used the 1987 ACR criteria for the diagnosis of RA<sup>16</sup> as the investigation started before the new 2010 European League Against Rheumatism/ACR criteria were introduced. The frequency of ACPA-positive RA was 63%, which is well in line with data from other similar cohorts, including the Swedish EIRA study.<sup>43</sup> A potential disadvantage is that some cases of RA in the selected areas may not have been included, thus generating a potential selection bias. Provided the design of this study, we consider such missing inclusion to be due mainly to administrative reasons, such as high burden of work and change of personnel (that are not informed about the study) and most probably not related to textile dust exposure. We thus believe that bias due to misclassification of disease does not constitute a major bias in this study.

We did not collect data on potentially harmful chemical hazards present in the textile industry, such as other organic dusts or organic solvents. Moreover, we do not know how many of the female textile workers conducted their work from home. Working with textiles in a home environment or an industrial environment might affect the likelihood of being exposed to chemicals that possibly may act as confounders. Passive smoking is theoretically another exposure that may have confounded the estimated association between textile dust and RA. There is, however, no reason to believe that women exposed to textile dust are more exposed to passive smoking than women that are not exposed.

The genetic heterogeneity in our multiethnic study population for MyEIRA study is a concern. In order to reduce this problem, we performed stratified analyses by ethnicity and could demonstrate that all the ethnic groups showed similar trends towards the risk of developing RA, although the limited power did not permit separate formal analysis in each ethnic group.

## CONCLUSION

We observed an association between occupational textile dust and risk of developing RA. The high risk of developing ACPA-positive RA among HLA-DRB1 SE-positive individuals exposed to textile dust, and the significant gene-environment interaction between HLA-DRB1 SE and textile dust supports the hypothesis that various lung exposures may play an important role in the aetiology of RA. The increased risk also in

ACPA-negative RA where there is no link to HLA-DRB1 SE indicates, however, that also other mechanisms may be involved, which have to be further investigated. From a public health perspective, our results imply that efforts should be considered to reduce the incidence of RA by reducing occupational exposure to textile dust.

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**Contributors** CLT had full access to all data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. CLT, NAM and AI were responsible for the statistical analysis, interpreting the results and drafting the paper. CLT, NAM, LP, LA, LK, SM and CB conceived the study and participated in the design of the study and manuscript editing. CLT and LP performed serological and molecular genetics assay. CLT and LP take responsibility for the acquisition of the experimental data, analysis and interpretation of data. SM is the principal investigator of MyEIRA, LA and LK are the principal investigators of EIRA. All authors were involved in revising the paper critically for important intellectual content, and all authors approved the final version to be published.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** The MyEIRA study was approved by the Medical Research and Ethics Committee of the Ministry of Health in Malaysia (KKM/JEPP/02 Jld.1 (86); (14)dlm.KKM/NIHSEC/08/0804/ MRG-2005-12).

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## Textile dust is a risk factor for the development of rheumatoid arthritis



Exposure to textile dust is associated with an increased risk of developing rheumatoid arthritis. In addition, a gene–environment interaction is also seen.

### INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints and sometimes their internal organs. Rheumatoid arthritis may develop for a number of reasons, and there may be a link between environmental and genetic factors. Cigarette smoking and inhaling certain chemicals such as silica have both been shown to increase a person's risk of developing rheumatoid arthritis. It is thought that the chemicals and irritants in smoke and dust particles might cause changes in the lungs. These changes trigger an autoimmune response – leading to inflammation and the development of rheumatoid arthritis.

### WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see whether breathing in airborne dust generated in the manufacture of textiles might cause workers to develop rheumatoid arthritis.

### WHO WAS STUDIED?

The study looked at 910 Malaysian women diagnosed with early stage rheumatoid arthritis. They also looked at 910 women of a similar age who lived in the same geographical area but who did not have rheumatoid arthritis. The study participants were mostly non-smokers in both groups.

### HOW WAS THE STUDY CONDUCTED?

This was an observational study. This means that the groups of people in the studies had no medical intervention, but simply had information about their medical history and lifestyle collected in a database, which allowed researchers to investigate certain links or risks. The authors collected information in a face-to-face interview. The women were asked if they had ever worked in the textile industry, and whether they had been exposed to textile dust during their leisure time. Blood samples were taken to test for antibodies (called ACPA) and the presence of certain genetic variants that might predispose people to developing rheumatoid arthritis.

### WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The authors found that people exposed to occupational textile dust were almost three-times more likely to develop rheumatoid arthritis compared with people who were not exposed. They also found a link between occupational textile dust exposure and the presence of genetic variants associated with risk of developing ACPA-positive rheumatoid arthritis.

### ARE THESE FINDINGS NEW?

This is the first study of its kind showing that textile dust exposure is associated with an increased risk of developing rheumatoid arthritis, and that there is a gene–environment interaction between certain genetic variants and textile dust exposure that provides a high risk for developing ACPA-positive rheumatoid arthritis.

### WHAT ARE THE LIMITATIONS OF THE STUDY?

This was an observational study, and so it is not possible to draw conclusions about the cause and effect for the risks of developing rheumatoid arthritis, and it is not possible to exclude the involvement of other exposures. Additionally, the study participants may have encountered other agents associated with rheumatoid arthritis through other hazardous exposures to mineral or chemical dusts in their working environment.

### WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors have previously investigated the link between smoking and exposure to silica in the development of rheumatoid arthritis, mainly in men. In this new study they found a similar pattern of risk for developing rheumatoid arthritis among women exposed to textile dust. Taken together, these findings support the idea that lung exposure to various agents may play an important role in the development of rheumatoid arthritis. The investigation of more environmental exposures as well as biological and clinical parameters is currently underway.

## WHAT DOES THIS MEAN FOR ME?

These results show how important it is to take precautions to reduce exposure to textile dust. If you work in the manufacture or processing of textiles, you should try to limit how much dust you breathe in by wearing protective clothing and masks. Even if you already have rheumatoid arthritis, limiting your ongoing exposure may possibly help to slow disease progression or worsening.

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