Heritability of cough across two generations: the RHINESSA study

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Shareable abstract (@ERSpublications)
This two-generation study finds that chronic cough is a heritable trait independent of asthma, smoking and other confounders. Nonproductive cough in parent associates only with nonproductive cough in offspring and the same applies for productive cough. https://bit.ly/3UpbDmJ

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Abstract

Aim Heritability of cough has not yet been studied. We aimed to evaluate if individuals with cough are more likely to have offspring who develop cough, and if these associations differ by type of cough (productive/nonproductive).

Methods The RHINESSA Generation Study (Respiratory Health In Northern Europe, Spain and Australia) includes 7155 parents (initially aged 30–54) answering detailed questionnaires in 2000 and 2010, and 8176 offspring ⩾20 years answering similar questionnaires in 2012–2019. Chronic cough was categorised as productive or nonproductive (dry) cough. Associations between parental and offspring cough were analysed using mixed-effects logistic regression, adjusting for offspring age, sex, body mass index, smoking history, education level, current asthma, rhinitis, nocturnal gastroesophageal reflux; parent sex and smoking history; centre and family.

Results Among parents with nonproductive cough, 11% of their offspring reported nonproductive cough, compared with 7% of offspring to parents without nonproductive cough, adjusted odds ratio (aOR) 1.59 (95% confidence interval 1.20–2.10). Among parents with productive cough, 14% of their offspring reported productive cough, compared with 11% of offspring to parents without productive cough, aOR 1.34 (1.07–1.67). No associations were found between parent productive cough–offspring nonproductive cough, nor between parent nonproductive cough–offspring productive cough.

Conclusions Parents with chronic cough are more likely to have offspring with chronic cough independent of parental asthma, suggesting cough to be a separate heritable trait. The type of cough is important, as the nonproductive cough in parent associates only with nonproductive cough in offspring, and the same applied for productive cough.

Introduction

Chronic cough is common in the general population, with an estimated prevalence of around 10% [1]. It is often difficult to treat, significantly worsens quality of life and leads to increased sick leave [2, 3]. Chronic cough is currently thought to be caused by upregulation in the cough reflex, called cough hypersensitivity syndrome, even though the exact mechanisms have not been fully established [4, 5].

Recent studies have described upregulated airway sensory nerves in chronic cough [6], and changes in certain proteins in exhaled air particles [7], which supports that biological processes in the airways are important in chronic cough. One study on genetic variants in idiopathic sensory neuropathy found that cough was significantly associated with repeat expansions (RE) in the replication factor C subunit 1(RFC1) gene [8]. Subsequently, in a cohort of highly selected patients with refractory chronic cough, the presence of the RE-RFC1 genetic variant was also found significantly more often than expected, *i.e.* in 25% of all participants (compared with the expected 0.7% as in the general population) [9]. Except for a few studies reporting on self-reported family history of chronic cough, and therefore with a significant risk of recall bias [10–12], there have been no studies on the phenotypic heritability as a primary outcome in chronic cough, or where two generations have been independently evaluated.

The type of cough is likely of importance in this context. Recent studies have found that clinical features of nonproductive cough and productive cough differ significantly, including differences in mortality [3, 13, 14], suggesting that these two types of cough are clinically distinct phenomena.

The primary aim of this study was to evaluate whether chronic cough in parents is associated with chronic cough in their offspring. The secondary aim was to evaluate if the type of cough, *i.e.* nonproductive or productive cough, was of importance for the heritability across the two generations. The hypothesis was that chronic cough is a heritable trait, and we speculate that the type of cough is also a heritable trait.

Methods

This study is a two-generation analysis of chronic cough with data on parents from the Respiratory Health In Northern Europe (RHINE) study and data on their offspring from the Respiratory Health In Northern Europe, Spain and Australia (RHINESSA) study [15]. In short, the RHINE study was conducted on a randomly selected general population sample in 1990, 2000 and 2010 (RHINE I, RHINE II, and RHINE III, respectively), with over 21 000 participants at baseline. The participants answered detailed questionnaires, with identical questions on chronic cough in 2000 and 2010 [16]. The RHINESSA study investigates the offspring of the RHINE study participants, with the baseline study conducted in 2012–2019 including over 10 000 participants [17]. Parents participating in RHINE with at least one offspring ⩾20 years old participating in RHINESSA were included for analysis. Most RHINESSA participants (98%) had only one parent participating in RHINE. As cough in adults and children are somewhat different phenomena [2], and the participants report their cough in recent years (see definition below), the age of 20 years was chosen to properly exclude childhood cough.

Informed written consent was obtained from all participants in each study wave, and both the parent and the offspring studies were approved by the regional ethics committees in all study centres (www.rhinessa.net). The study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [18].

Chronic cough definition

Chronic cough was defined based on the same questions from RHINE and RHINESSA.

First, participants were defined to have cough if they answered affirmatively to the question “Have you in recent years been troubled by a protracted cough?” and/or the question “Do you cough up phlegm or do you have phlegm in your chest that is difficult to cough up, for at least 3 months every year?”. Participants were then further divided into having nonproductive cough if they did not report phlegm, and productive cough if they did report phlegm.

The RHINE parents answered the cough questions at two time points (RHINE II and III in 2000 and 2010). Parents were classified as having any chronic cough on none, one or two occasions (where cough on two occasions was defined as persistent cough in parent). Parents only participating in one survey were classified as having any chronic cough on either none or one occasion. To maintain analytic power, parents with nonproductive and productive cough on one or more occasions were grouped together. Parents could thereby be defined to have both productive and nonproductive cough (the case for 133 participants).

The same definition of chronic cough was used for the RHINESSA offspring, with the exception that data were only available from one time point for all offspring.

Covariates

Data for offspring and parents (from RHINE II, or RHINE III if not available from RHINE II) were obtained on: age, sex, body mass index (BMI), level of education (primary/secondary school/university or higher), smoking status (current, ex- or never-smoker), study centre, current asthma (defined as an asthma attack in the previous 12 months and/or currently using asthma medications), nocturnal gastroesophageal reflux (defined as having heartburn after going to sleep once a week or more) and rhinitis (reporting nasal symptoms without concurrent cold in the last 12 months).

Statistical analysis

Characteristics of parents and offspring were summarised as frequencies and percentages for categorical variables, and as mean±SD or median with interquartile range (IQR) for continuous variables with normal or skewed distribution, respectively. Characteristics are stratified by the presence or absence of any chronic cough in offspring.

A Directed Acyclic Graph (DAGs, www.dagitty.net) was constructed to: 1) visualise the relation between the study variables; 2) identify potential confounders and mediators to include and evaluate in the models; and 3) inform generalised structural equation models which were used for sensitivity analysis. The DAG is presented in figure 1.

The association between chronic cough in parents and chronic cough in offspring was first analysed using unadjusted logistic regression models. Then, we adjusted for confounding factors using a multilevel mixed-effects logistic regression model, adjusting for offspring factors, parent sex and parent smoking status (as identified *a priori* by the DAG), and with random effects for study centre and family ID (as in some cases a single parent had more than one offspring). The analysis was performed for chronic cough in general, as well as by cough types (productive/nonproductive).

The following sensitivity analysis was performed – 1) individuals without asthma: the association between chronic cough in parents and offspring was analysed separately where both parents and offspring were without asthma; 2) never-smokers: the same associations where parents and offspring were never-smokers; 3) influence of sex: the association between chronic cough in offspring and chronic cough in parent was first stratified by both parent and offspring sex, and secondly with an interaction between a) cough from parent and offspring sex, and b) cough from parent and parent sex; and 4) data were finally analysed using a generalised structural equation modelling, based on the same DAG as described above.

All statistical analyses were performed in STATA v16 (Stata Corp, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

Results

In total, the dataset included 7155 parents and 8176 offspring. Offspring with chronic cough were more often female, smokers, had a somewhat lower education level, and more cough-related comorbidities such as asthma, gastroesophageal reflux and rhinitis, compared with offspring without cough (table 1). Age and BMI were however similar. Characteristics of parents to offspring with chronic cough and parents to offspring without cough were similar in most aspects (sex, age, BMI, smoking history, education level). However, parents to offspring with chronic cough had a slightly higher prevalence of asthma, gastroesophageal reflux and rhinitis (table 1).

Association of chronic cough in offspring to persistent cough in parent

As parents had answered two questionnaires with a 10-year interval, the association between more persistent cough in parent to chronic cough in offspring could be analysed. Among parents without cough on both occasions, 18% of their offspring reported cough, while the prevalence of chronic cough in offspring was 21% and 29% among parents with chronic cough on one occasion and both occasions, respectively (p<0.001) (table 2).

When adjusted for confounding factors, the associations between chronic cough in parents to chronic cough in offspring were attenuated, but still significant between chronic cough in parents on both occasions and offspring chronic cough (OR 1.75, 95% CI 1.35–2.26) (table 3).

TABLE 1 Population characteristics

	Offspring without cough	Offspring with chronic cough
Offspring factors		
Participants, n	6665	1511
Female, n (%)	3806 (57.2)	936 (62.0)
Age years, median (IQR)	30.0 (25.0–37.0)	30.0 (24.0–36.0)
BMI kg·m^{-2}, median (IQR)	23.7 (21.5–26.4)	24.0 (21.5–27.1)
Smoking history, n (%)		
Never-smoker	4493 (67.7)	874 (58.2)
Ex-smoker	1366 (20.6)	336 (22.4)
Current smoker	778 (11.7)	291 (19.4)
Education level, n (%)		
Primary	146 (2.2)	61 (4.1)
Secondary	2336 (35.4)	563 (37.8)
University/higher	4117 (62.4)	867 (58.1)
Current asthma, n (%)	437 (6.6)	367 (24.4)
Nocturnal reflux, n (%)	331 (5.0)	167 (11.2)
Rhinitis, n (%)	2770 (41.9)	931 (62.5)
Parent factors		
Participants, n	5801	1354
Mother participated, n (%)	3572 (54.0)	796 (52.9)
Age years, mean±SD	43.7±6.5	43.3±6.6
BMI kg·m^{-2}, median (IQR)	24.3 (22.3–26.7)	24.5 (22.3–26.8)
Smoking history, n (%)		
Never-smoker	2360 (45.2)	516 (42.9)
Ex-smoker	1538 (29.5)	351 (29.2)
Current smoker	1320 (25.3)	337 (28.0)
Education level, n (%)		
Primary	693 (13.2)	154 (12.7)
Secondary	2166 (41.3)	504 (41.7)
University/higher	2388 (45.5)	550 (45.5)
Current asthma, n (%)	681 (11.6)	208 (15.2)
Nocturnal reflux, n (%)	343 (6.6)	111 (9.3)
Rhinitis, n (%)	2229 (40.8)	560 (45.2)

BMI: body mass index.

Association of cough type in offspring to cough type in parent

Nonproductive cough in offspring: Among parents with nonproductive cough, 11% of the offspring had nonproductive cough, compared with a significantly lower prevalence of 7% of offspring to parents without nonproductive cough (figure 2). However, among parents with productive cough, the offspring

TABLE 2 Prevalence of any chronic cough in relation to any chronic cough among parents

	Offspring without cough	Offspring with chronic cough	Odds ratio (95% CI)
All cough types* **			
Participants, n	5801	1354	
No cough in parent (n=6532)	4350 (82)	718 (18)	1.00 (REF)
Chronic cough on one questionnaire (n=1765)	1114 (79)	288 (21)	**1.21 (1.04–1.40)**
Chronic cough on both questionnaires (n=552)	337 (71)	136 (29)	**1.89 (1.53–2.33)**
Nonproductive cough			
Participants, n	6608	560	
Parent without nonproductive cough	5515 (93)	472 (7)	1.00 (REF)
Parent with nonproductive cough	689 (89)	88 (11)	**1.60 (1.26–2.04)**
Productive cough			
Participants, n	6363	805	
Parent without productive cough	5322 (89)	629 (11)	1.00 (REF)
Parent with productive cough	1041 (86)	176 (14)	**1.43 (1.20–1.71)**

Data are reported as n (%). Significant odds ratios are marked in bold. ***: p<0.001 for whole table comparison.

TABLE 3 Associations between chronic cough in parent and chronic cough in offspring, both for all cough and for specific cough types, adjusted for offspring factors (age, sex, body mass index, smoking history, education level, current asthma, rhinitis, nGER), parent sex and parent smoking history, using a mixed-effects logistic regression, with random effects for centre and family

	Offspring with cough, aOR (95% CI)
All cough types[#]	
No cough in parent	1.00 (REF)
Cough on one questionnaire	1.10 (0.91–1.32)
Cough on both questionnaires	**1.75 (1.35–2.26)**
Nonproductive cough[¶]	
Parent without nonproductive cough	1.00 (REF)
Parent with nonproductive cough	**1.59 (1.20–2.10)**
Productive cough[+]	
Parent without productive cough	1.00 (REF)
Parent with productive cough	**1.34 (1.07–1.67)**

Significant odds ratios are marked in bold. nGER; nocturnal gastroesophageal reflux. [#]: n=6086; [¶]: n=6096; [+]: n=6097.

prevalence of nonproductive cough was similar as for parents without productive cough: 8% (non-significant) (figure 2).

Productive cough in offspring: Among parents with productive cough, 14% of the offspring had productive cough, compared with a significantly lower prevalence of 11% of offspring to parents without productive cough (figure 2). However, among parents with nonproductive cough, the offspring prevalence of productive cough was similar as for parents without productive cough: 12% *versus* 11%, respectively (non-significant) (figure 2).

After adjusting for confounding factors, the association between nonproductive cough in parent and nonproductive cough in offspring was relatively unchanged (table 3).

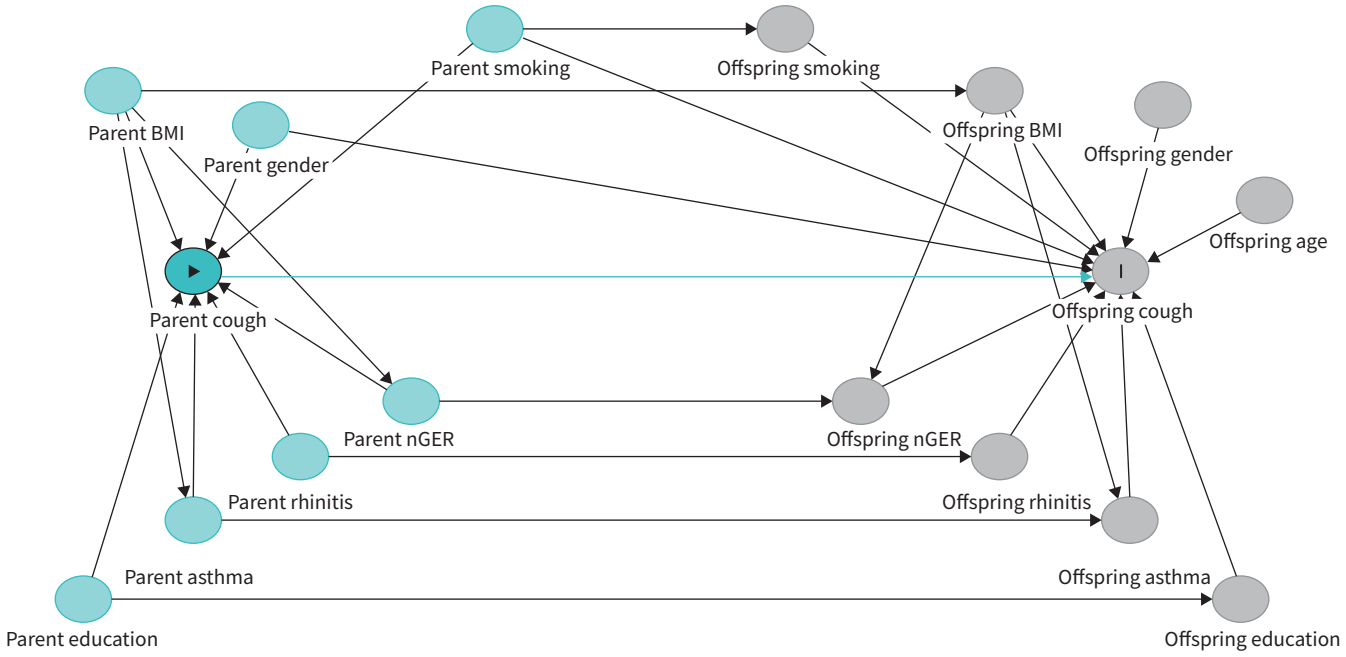

FIGURE 1 Directed acyclic graph for the hypothesised relationship between variables used in the analysis. nGER: nocturnal gastroesophageal reflux; BMI: body mass index.

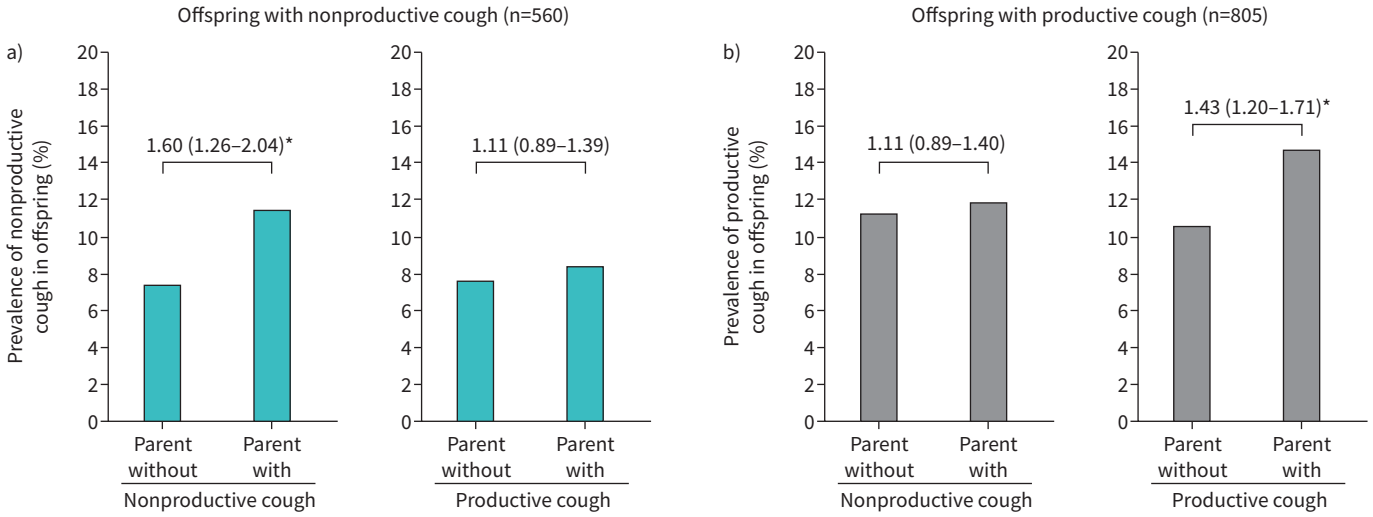

FIGURE 2 Prevalence of a) nonproductive and b) productive cough in offspring, in relation to the presence and type of cough in parents. Comparisons reported as unadjusted odds ratios (95% confidence interval). *: p<0.05.

In adjusted analysis, the association between productive cough in parent and productive cough in offspring was slightly attenuated but still statistically significant (table 3). The sensitivity analysis performed using generalised structural equation modelling resulted in similar effect sizes as in the main analysis (supplementary table S1).

Influence of parent and offspring sex on cough heritability

On stratified analysis, chronic cough in female offspring was associated with chronic cough from both female and male parents (tables 4 and 5). On the other hand, chronic cough in male offspring was not associated with chronic cough from male parents, and there was a weak but non-significant association between chronic cough in male offspring and chronic cough from female parents (tables 4 and 5). This was reflected in an interaction analysis, where there was a significant interaction between offspring sex and chronic cough on both occasions in parent, in relation to chronic cough in offspring (p=0.015). Otherwise, no statistically significant interactions were found for chronic cough in offspring, regarding interactions between chronic cough from parent and offspring sex, or chronic cough from parent and parent sex (p-values for interaction 0.14–0.90, supplementary table S2).

TABLE 4 Female parents (mothers) only and stratified by offspring sex, associations between cough in parent and cough in offspring, both for all cough and for specific cough types, adjusted for offspring factors (age, body mass index, smoking history, education level, current asthma, rhinitis, nGER), parent sex and parent smoking history, using a mixed-effects logistic regression, with random effects for centre and family

	Offspring with cough, aOR (95% CI)	
	Daughter with cough	Son with cough
All cough types[#]		
No cough in mother	1.00 (REF)	1.00 (REF)
Chronic cough on one questionnaire	1.07 (0.76–1.51)	1.35 (0.94–1.94)
Chronic cough on both questionnaires	**2.50 (1.55–4.05)**	1.52 (0.92–2.51)
Nonproductive cough[¶]		
Mother without nonproductive cough	1.00 (REF)	1.00 (REF)
Mother with nonproductive cough	**1.97 (1.27–3.06)**	1.47 (0.87–2.48)
Productive cough[+]		
Mother without productive cough	1.00 (REF)	1.00 (REF)
Mother with productive cough	**1.73 (1.14–1.64)**	0.90 (0.54–1.50)

Significant odds ratios are marked bold. nGER: nocturnal gastroesophageal reflux. [#]: n=3318; [¶]: n=3322; [+]: n=3323.

TABLE 5 Male parents (fathers) only and stratified by offspring sex, associations between cough in parent and cough in offspring, both for all cough and for specific cough types, adjusted for offspring factors (age, sex, body mass index, smoking history, education level, current asthma, rhinitis, nGER), parent sex and parent smoking history, using a mixed-effects logistic regression, with random effects for centre and family

	Offspring with cough, aOR (95% CI)	
	Daughter with cough	Son with cough
All cough types[#]		
No cough in father	1.00 (REF)	1.00 (REF)
Chronic cough on one questionnaire	0.97 (0.68–1.36)	0.96 (0.61–1.52)
Chronic cough on both questionnaires	**2.01 (1.25–3.23)**	0.85 (0.42–1.70)
Nonproductive cough[¶]		
Father without nonproductive cough	1.00 (REF)	1.00 (REF)
Father with nonproductive cough	**1.76 (1.01–3.07)**	0.91 (0.42–1.98)
Productive cough[+]		
Father without productive cough	1.00 (REF)	1.00 (REF)
Father with productive cough	1.38 (0.91–2.09)	1.14 (0.67–1.94)

Significant odds ratios are marked bold. nGER: nocturnal gastroesophageal reflux. [#]: n=2768; [¶]: n=2774; [+]: n=2774.

Subgroup analyses

When restricting the analysis to only never-smoking parents and offspring, the association between nonproductive cough in parent and offspring remained unchanged, but the association for productive cough became non-significant with almost normalised odds ratio (supplementary table S3). When restricting the analyses to parents and offspring without asthma, the associations remained largely unchanged (supplementary table S4).

Discussion

In this study, we found that chronic cough in parents was associated with chronic cough in their adult offspring, independent of confounding factors. The effect was specific for the type of cough, that is, nonproductive cough in parent associated only with nonproductive cough in offspring, and the same pattern was seen for productive cough. For nonproductive cough, no apparent causative factor was identified. Conversely, productive cough seemed to be to a significant degree, driven by smoking.

The heritability of chronic cough has been studied very little. Self-reported heritability among individuals with troublesome chronic cough has been reported to be high [11], but otherwise this study is the first to report on cough heritability. Our findings strongly support that chronic cough can be a heritable trait to some extent, especially when parental cough is persistent. This is consistent with a similar finding in a Korean study, where family history of cough was most pronounced amongst those with long-standing (>4 years) chronic cough [12]. The reason for such heritability is not clear. Essentially, most medical conditions are influenced by genetics and environment. Both genetics and environmental factors are often shared over generations, especially among first generation relatives. Therefore, it is of importance to disentangle to what degree genetics and environment contribute to the heritability, and if any of these factors are potentially modifiable. This could have implications in the development of new treatment modalities. As chronic cough is common and often difficult to treat, with a negative impact on quality of life and with a societal impact from increased sick leave [2, 3], new treatment modalities are of high importance.

In the exploratory analysis stratifying by sex of parents and offspring, the heritability seemed to be stronger for female offspring (daughters), irrespective of parent sex. However, most interaction analyses did not find a significant interaction by sex (except for persistent chronic cough from parent and sex of offspring), hindering strong conclusions on sex differences. Importantly, this pattern is not strictly cohort related, as a previous analysis on sleep-related symptoms in this same cohort found only minimal sex-related differences [19]. One possible reason for this apparent difference between daughters and sons could be a lack of power, as fewer sons had chronic cough, thereby weakening statistical associations. It could also be hypothesised that this reflects sex-related differences in the importance of genetic and environmental factors. Further studies on the heritability of chronic cough should consider sex as a potential modifying factor on the expression of cough heritability.

Regarding nonproductive cough, it is theoretically possible that the heritability of cough is related to genetic variants in proteins implicated in the cough reflex, as exemplified by the recent finding of repeat expansions

in the RFC1 gene among patients with refractory chronic cough [9]. Other theoretically possible genetic variants may be related to respiratory epithelium tight junction proteins, where loss-of-function mutations might increase the likelihood of irritants reaching the airway sensory nerves. A small study on biomarkers in exhaled air particles from individuals with nonproductive cough found a significant difference in one such protein, but larger studies are lacking [7]. Alternatively, genetic variants in nerve receptors responsible for signalling cough may be implicated. However, these hypotheses remain to be tested.

Other possible explanations for the heritability of cough may be related to behavioural aspects, which are known to be heritable to a certain degree [20]. Studies using functional MRI have shown patients with troublesome cough to have a reduced capacity to suppress the cough reflex [5]. Such traits may be in part behaviour related. Another potential explanation is the common exposures that family members may share, such as air pollution [21]. This may apply to both nonproductive and productive cough.

The heritability of productive cough may also have alternative explanations. As we no longer found a significant association between productive cough (in contrast to nonproductive) in parent and offspring if both were nonsmokers, smoking is likely a central mechanism behind the found association. On the other hand, adjustments for smoking status did not markedly change the association between productive cough in parent and offspring, suggesting other factors may also be of importance. For example, a recent study found certain variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene significantly increased the risk for smokers to develop chronic bronchitis [22]. Another potential risk factor is obstructive sleep apnoea, which has been found to be associated with chronic productive cough [13]. The heritability of chronic productive cough is therefore likely multifactorial.

Strengths and weaknesses

The main strengths of this study are the extensive data from similar studies of two generations, based on large well-characterised general population cohorts. Similar questionnaires were sent out to parents, and some years later to their offspring, in separate studies, minimising although not excluding risk for differential recall bias. Further strengths are the unchanged effect sizes obtained using different statistical methods to control for confounding factors. However, this study also had some important weaknesses. First, we only had information from one parent in most cases, which may dilute or confound the associations found. Also, as many of the offspring were young to early middle-aged adults, some of them may have developed cough later in life. This may have diluted the associations found. Second, objective measurements of lung function and cough frequency were not available for this cohort, which might have shed further light on the found associations. Third, the definition of chronic cough did not include a specified time with cough, such as 8 weeks which is the definition of chronic cough. The definition of productive cough, however, asked for at least 3 months with productive cough. As the prevalence of nonproductive and productive cough was close to what has been described in epidemiological studies [1], our definition using "protracted cough" seems to capture a group similar to chronic cough. Lastly, potential confounders such as sleep apnoea and air pollution were not assessed, and the degree of misclassification of comorbidities could not be formally assessed. Also, potential behavioural aspects could not be assessed. However, as the more common confounding factors adjusted for in this analysis did not result in significant changes in effect sizes, we deem the risk of unmeasured confounders to significantly influence the results to be minimal. Also, the strong signal seen for specific cough types and not between cough types (*i.e.* no association between productive cough in parent and nonproductive cough in offspring, and vice versa) further supports a true relationship.

Conclusion

We conclude that among parents with chronic cough, their offspring are more likely to have chronic cough as well, independent of asthma and other confounders, suggesting chronic cough to be a separate heritable trait. The type of cough is important, as the nonproductive cough in parent associated only with nonproductive cough in offspring, and the same applied for productive cough. For nonproductive cough, we did not identify any significant confounding factors, but for productive cough we found smoking in parent and offspring to be a potential driving factor. Further studies are needed to explore the reason for this heritability, including potential genetic variants.

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Ethics statement: This study was approved by the regional ethics committees in all study centres (www.rhinessa.net).

Conflict of interest: Ö.I. Emilsson has participated in advisory boards with MSD Sweden, not related to this manuscript. The other authors have no other competing interests to declare.

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