

Occupational exposure to vapor, gas, dust, or fumes and chronic airflow limitation, COPD, and emphysema: the Swedish CARDioPulmonary BioImage Study (SCAPIS pilot)

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Background: The aim of this study was to estimate the occupational burden of airflow limitation, chronic airflow limitation, COPD, and emphysema.

Materials and methods: Subjects aged 50–64 years (n=1,050) were investigated with forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC). Airflow limitation was defined as FEV₁/FVC <0.7 before bronchodilation. Chronic airflow limitation was defined after bronchodilation either according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as FEV₁/FVC <0.7 or according to the lower limit of normal (LLN) approach as FEV₁/FVC < LLN. COPD was defined as chronic airflow limitation (GOLD) in combination with dyspnea, wheezing, or chronic bronchitis. Emphysema was classified according to findings from computed tomography of the lungs. Occupational exposure was defined as self-reported occupational exposure to vapor, gas, dust, or fumes (VGDF). Odds ratios (OR) were calculated in models adjusted for age, gender, and smoking; population-attributable fractions and 95% CI were also calculated.

Results: There were significant associations between occupational exposure to VGDF and COPD (OR 2.7, 95% CI 1.4–51), airflow limitation (OR 1.8, 95% CI 1.3–2.5), and emphysema (OR 1.8, 95% CI 1.1–3.1). The associations between occupational exposure to VGDF and chronic airflow limitation were weaker, and for the OR, the CIs included unity. The population-attributable fraction for occupational exposure to VGDF was 0.37 (95% CI 0.23–0.47) for COPD and 0.23 (95% CI 0.05–0.35) for emphysema.

Conclusion: The occupational burden of COPD and computed tomography-verified emphysema is substantial.

Keywords: work, occupation, obstructive airways disease, epidemiology, computed tomography

Introduction

The main cause of COPD is tobacco smoking, but exposure to indoor wood smoke among women is an additional important risk factor.¹ Further, a number of studies have shown an association between occupational exposures to dust, fumes, and smoke and COPD, but the risk estimates vary and there is a lack of gender-specific risk assessments.^{2–4}

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD has been defined as the presence of chronic airflow limitation, expressed as the ratio of forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC), based on spirometry after bronchodilation and using <0.7 as the lower limit.⁵ However, in the

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recent GOLD document from 2017, it has been proposed to define COPD as a combination of chronic airflow limitation and certain key symptoms, such as dyspnea, wheezing, or cough with phlegm.⁶ This would be a more clinically relevant definition of COPD. The GOLD definition of chronic airflow limitation has also been challenged since the fixed ratio $FEV_1/FVC < 0.7$ does not take into account age-related changes in lung function.⁷ An alternative proposed approach is to use the lower limit of normal (LLN) after bronchodilation as a cut-off, calculated using the distribution in reference material adjusted for age, gender, and height.

One important component of COPD is emphysema, which is defined anatomically as destruction of lung parenchyma and loss of alveolar walls. This is different from the operational definitions of COPD that are based on spirometric chronic airflow limitation. COPD and emphysema are overlapping conditions, and emphysema exists without airflow limitation; 50% of subjects with COPD do not have emphysema.⁸ With recent developments in imaging techniques, it is now possible to diagnose emphysema using pulmonary computerized tomography (CT), a technique that can be applied to larger populations.⁹

Epidemiological studies use additional modes of defining COPD, such as the presence of airflow limitation based on spirometry without bronchodilation.^{10,11} COPD has also been defined based on affirmative responses to questions on physician-diagnosed COPD or emphysema.^{12,13} Finally, COPD has also been defined from causes of death based on information in death certificates.¹⁴

Hence, in published studies investigating the risk of occupational exposures and COPD, there is a broad range of operational definitions of the disease. Whether this affects the obtained risk estimates has not been assessed.

The main aims of this study were to assess the risk of COPD, airflow limitation, chronic airflow limitation, and emphysema in relation to different occupational exposures, stratified for gender, and to investigate whether different definitions of COPD, airflow limitations, chronic airflow limitation, or emphysema affect the risk estimates for occupational exposure to vapor, gas dust, or fumes (VGDF).

Materials and methods

Study population

The Swedish CARDioPulmonary BioImage Study (SCAPIS) pilot comprised randomly selected subjects aged 50–64 years from the general population of Gothenburg. Subjects were sampled equally from areas with high and low socioeconomic status. Of 2,243 individuals who were invited, 1,111 participated in the clinical investigation.

The methods have previously been described.^{15,16} For the purposes of this analysis, all subjects completed an extensive questionnaire on physician-diagnosed COPD and respiratory symptoms including the modified Medical Research Council (mMRC) scale for assessing dyspnea.¹⁷ The survey included questions on smoking habits, including the number of cigarettes smoked.

All subjects underwent dynamic spirometry including FEV_1 and FVC according to the BOLD protocol, but slow vital capacity was added.¹⁶ All spirometric maneuvers were performed before and 15 min after inhalation of 400 μ g of salbutamol using a nose clamp with the subject in a sitting position.¹⁸ All measurements used an Erich Jaeger Master Screen PFT lung function analyzer (Friedberg, Germany). Predicted values of FEV_1 and FVC were based on recent data from a Swedish population.^{19,20} FEV_1 and FVC are expressed as percent predicted (% predicted).

Imaging

All CT scanning was performed using a Somatom Definition Flash scanner (Siemens Healthcare, Forchheim, West Germany). Care Dose 4D and SAFIRE were used for dose optimization. Detector configuration (mm) 128×0.6, tube voltage (kVP) 120, tube current (mAs) or reference dose for Care Dose 4D 30, rotation time (s) 0.5, pitch 0.9, kernel B31f and I31f medium sharp ASA SAFIRE level 3, slice thickness (mm) 0.6 increment (mm) 0.6. The median effective radiation dose was 2 mSv.

Quality assessment data (adequate inspiration, inclusion of entire lung, motion artifact) and lung parenchymal findings were visually assessed by one of three board certified radiologists, all with more than 20 years of experience in thoracic radiology. The lung parenchymal findings registered were emphysema, bronchial wall thickening, bronchiectasis, consolidation, cysts, ground glass opacity, honeycombing, linear scars and atelectasis, mosaic attenuation and reticular abnormality. If emphysema was present, the type (centrilobular, panlobular paraseptal, bulla[e], or a combination) was reported, as well as grade (none, mild, moderate, or severe) and localization in the upper, middle, and lower part of right and left lung.

To ensure consistent interpretation across radiologists, a consensus meeting was held before the start of the study. All terms for imaging were used in accordance with those of the Fleischner Society.²¹

Definitions

Wheezing was defined as an affirmative answer to “Have you had wheezing or whistling in your chest during the last 12 months?”

Dyspnea was defined as mMRC > grade 1.

Airflow limitation was defined as an FEV₁/FVC ratio <0.7 before bronchodilation.

Chronic airflow limitation (GOLD) was defined as an FEV₁/FVC ratio <0.7 after bronchodilation.

Chronic airflow limitation (LLN) was defined as an FEV₁/FVC ratio after bronchodilation below the LLN.

COPD was defined according to the recent GOLD statement as chronic airflow limitation (GOLD) in combination with dyspnea, wheezing, or chronic bronchitis.⁶

Emphysema was categorized according to CT findings of at least mild emphysema in any zone.

Physician-diagnosed COPD/emphysema was defined as an affirmative answer to: "Have you ever had chronic obstructive pulmonary disease or emphysema diagnosed by a physician?"

Smoking status was categorized as current smoker, former smoker, or never-smoker. Former smokers were defined as those who had smoked for at least 1 year but not during the past year. Pack-years were calculated for all participants with a history of smoking.

Body mass index was defined as measured weight/height² (kg/m²).

Occupational exposure to VGDF was assessed based on affirmative answer to the item "Have you ever been exposed at your workplace to vapor, gas, dust, or fumes?"

Of the 1,111 subjects originally included, 59 were excluded due to incomplete data, resulting in a final population of 1,052 subjects. The subjects with the outcomes of interest were grouped as follows: airflow limitation (before bronchodilation) (212), chronic airflow limitation according to GOLD (105), chronic airflow limitation according to LLN (100), COPD (50), CT-verified emphysema (98), and physician-diagnosed COPD/emphysema (25). These conditions overlapped each other; altogether 305 subjects were categorized as having any form of airflow limitation, COPD, or emphysema.

To obtain a control group, a number of 305 subjects with any form of airflow limitation, COPD, or emphysema was excluded from the total population (n=1,052), resulting in a control population of 747 subjects.

The study was approved by the Regional Committee of Ethics in Umeå, 2010/228-31, and all included subjects gave their written informed consent to participate in the study.

Statistics

All calculations were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Categorical variables were compared using χ^2 -test to identify significant associations.

P-values <0.05 were considered significant. Associations between occupational exposures, smoking habits, and other covariates were tested using multiple logistic regression models, resulting in adjusted prevalence odds ratios (OR), and 95% CI were outlined. Interaction was assessed by performing stratified analyses and by including interaction terms (gender × exposure) in the regression models.

The population-attributable fraction (PAF) was calculated as [(OR – 1)/OR] × P, where P is the prevalence of exposure among the cases. Exposure was defined as an affirmative answer to the item on exposure to VGDF. The estimates of attributable proportions were derived with a 95% CI, adjusted for age and smoking and if relevant also for gender. If PAF values were based on non-significantly increased ORs, then the PAFs were notated within brackets and CIs were not derived.

Results

Table 1 outlines the characteristics of the 1,052 subjects included in the study. Among the control population, exposure to VGDF was reported by 206 subjects (27.6%), and among the 305 subjects with different definitions of the outcome, exposure to VGDF varied from 64.0% among subjects with physician-reported COPD/emphysema to 42.5% among subjects with airway obstruction (Table 1).

There were significant associations between occupational exposure to VGDF and COPD (OR 2.7, 95% CI 1.4–51), airflow limitation (OR 1.8, 95% CI 1.3–2.5) and emphysema (OR 1.8, 95% CI 1.1–3.1) (Table 2). There were also significant associations between exposure to VGDF and physician-diagnosed COPD/emphysema (OR 3.5, 95% CI 1.4–8.6) (Table 2). The ORs for occupational exposures and chronic airflow limitation according to GOLD (1.5, 95% CI 0.95–2.5) or the LLN concept (1.4, 95% CI 0.8–2.2) increased, but the confidence limits included unity. When stratified for gender, the ORs increased for men and reached statistical significance for all outcomes. The interaction terms for gender and occupational exposure were not statistically significant in any model.

Among never-smokers, the risk for COPD was 11.8 (95% CI 2.4–58.7); however, this estimate was based on five exposed subjects. The OR for chronic airflow limitation among never-smokers was lower, 2.9 (95% CI 1.2–7.2). For the other outcomes, the ORs were lower and the CIs included unity (data not presented).

Current smoking was strongly associated not only with emphysema (OR 15.4, 95% CI 5.9–40.2) but also with former smoking (OR 2.8, 95% CI 1.1–7.3) (Table 2). Other

Table 1 Descriptive data regarding occupational exposure to vapor, gas, dust, or fumes (VGDF), smoking, lung function, gender, and body mass index (BMI) in relation, and various definitions of airflow limitation, chronic airflow limitation, COPD, and emphysema

Variables	Different definitions of outcomes						
	Control population N=747	Airflow limitation ^a N=212	Chronic airflow limitation (GOLD) ^b N=105	Chronic airflow limitation (LLN) ^c N=100	COPD ^d N=50	Physician-diagnosed COPD/emphysema ^e N=25	Emphysema ^f N=98
Age, years	56.9 (4.3)	58.1 (4.4)	58.7 (4.2)	58.1 (4.3)	58.9 (4.0)	57.3 (4.4)	58.1 (4.5)
Males	371 (49.7%)	96 (45.3%)	60 (57.1%)	57 (57.0%)	31 (62%)	14 (56%)	55 (56.1%)
BMI, kg/m ²	27.3 (4.3)	27.1 (5.0)	27.2 (5.1)	27.2 (5.4)	27.1 (4.5)	28.4 (6.4)	26.2 (4.4)
Never-smokers	370 (49.5%)	59 (27.8%)	21 (20.0%)	20 (20.0%)	9 (18.0%)	5 (20%)	6 (6.0%)
Former smokers	282 (37.8%)	94 (44.3%)	43 (41.0%)	41 (41.0%)	22 (44.0%)	10 (40%)	34 (34.7%)
Current smokers	95 (12.7%)	59 (27.8%)	41 (39.1%)	39 (39.0%)	19 (38.0%)	10 (40%)	58 (59.2%)
Pack-years	7.4 (12.1)	16.0 (19.3)	21.6 (23.1)	20.6 (2.3)	23.4 (27.1)	23.3 (17.8)	27.8 (28.7)
Occupational exposure to VGDF	206 (27.6%)	90 (42.5%)	46 (43.8%)	42 (42.0%)	29 (58.0%)	16 (64%)	50 (51.0%)
FEV ₁ , % predicted	103.5 (22.2)	90.2 (23.7)	83.1 (22.2)	86.3 (25.0)	80.4 (25.6)	73.8 (19.9)	87.2 (21.7)
FVC, % predicted	100.8 (23.4)	101.7 (25.2)	100.6 (24.4)	104.7 (26.6)	99.8 (26.9)	84.5 (17.7)	94.8 (22.1)
FEV ₁ /FVC, %	80.7 (4.1)	69.3 (7.0)	64.3 (6.0)	64.1 (6.1)	62.4 (7.7)	68.2 (12.4)	71.9 (9.1)

Notes: Categories overlap and are not mutually exclusive. SD is given in parentheses unless otherwise indicated. ^aAirflow limitation was defined as an FEV₁/FVC ratio <0.7 before bronchodilation. ^bChronic airflow limitation (GOLD) was defined as an FEV₁/FVC ratio <0.7 after bronchodilation. ^cChronic airflow limitation (LLN) was defined as an FEV₁/FVC ratio after bronchodilation below the lower limit of the normal. ^dCOPD was defined as chronic airflow limitation (GOLD) in combination with dyspnea, wheezing, or chronic bronchitis. ^ePhysician-diagnosed COPD/emphysema was defined as an affirmative answer to "Have you ever had chronic obstructive pulmonary disease or emphysema diagnosed by a physician?" ^fEmphysema was categorized according to CT findings of at least mild emphysema in any zone.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; CT, computed tomography; LLN, lower limit of normal.

outcomes with airflow limitation were also related to current smoking, but the relationship to former smoking was less marked and without formal statistical significance for any outcomes except emphysema.

The PAFs for occupational exposure to VGDF among subjects with airflow limitation, chronic airflow limitation,

COPD, and emphysema are presented in Table 3. The PAF was 0.37 (95% CI 0.23–0.47) among subjects with COPD and 0.23 (95% CI 0.05–0.35) among subjects with emphysema. Among men, the PAFs for COPD and emphysema were higher: 0.46 (95% CI 0.12–0.60) and 0.34 (95% CI 0.01–0.51), respectively.

Table 2 Associations between occupational exposure to vapor, gas, dust, and fumes (VGDF) and smoking, and various definitions of airflow limitation, chronic airflow limitation, COPD, and emphysema among all subjects and stratified by gender and smoking

Independent variables	Dependent variables (outcomes)					
	Airflow limitation ^a N=212	Chronic airflow limitation (GOLD) ^b N=105	Chronic airflow limitation (LLN) ^c N=100	COPD ^d N=50	Physician-diagnosed COPD/emphysema ^e N=25	Emphysema ^f N=98
All subjects						
Occupational exposure to VGDF	1.8 (1.3–2.5)	1.5 (0.95–2.5)	1.4 (0.8–2.2)	2.7 (1.4–5.1)	3.5 (1.4–8.6)	1.8 (1.1–3.1)
Current smoking	2.1 (1.3–3.6)	3.6 (1.8–7.2)	3.8 (1.9–7.6)	4.0 (1.5–10.4)	2.4 (0.7–8.9)	15.4 (5.9–40.2)
Former smoking	1.3 (0.8–2.0)	1.3 (0.7–2.4)	1.4 (0.7–2.7)	1.4 (0.6–3.5)	0.9 (0.2–3.4)	2.8 (1.1–7.3)
Males						
Occupational exposure to VGDF	2.0 (1.2–3.3)	2.1 (1.1–3.9)	1.9 (1.04–3.6)	2.8 (1.2–6.4)	6.5 (1.4–13.9)	2.0 (1.02–4.1)
Females						
Occupational exposure to VGDF	1.6 (0.97–2.7)	0.9 (0.4–2.2)	0.8 (0.3–1.9)	2.7 (0.9–7.8)	2.0 (0.5–7.9)	1.9 (0.8–4.5)

Notes: Categories overlap and are not mutually exclusive. Odds ratios with 95% CI are from logistic regression models adjusted for age and pack-years. ^aAirflow limitation was defined as an FEV₁/FVC ratio <0.7 before bronchodilation. ^bChronic airflow limitation (GOLD) was defined as an FEV₁/FVC ratio <0.7 after bronchodilation. ^cChronic airflow limitation (LLN) was defined as an FEV₁/FVC ratio after bronchodilation below the lower limit of the normal. ^dCOPD was defined as chronic airflow limitation (GOLD) in combination with dyspnea, wheezing, or chronic bronchitis. ^ePhysician-diagnosed COPD/emphysema was defined as an affirmative answer to "Have you ever had chronic obstructive pulmonary disease or emphysema diagnosed by a physician?" ^fEmphysema was categorized according to CT findings of at least mild emphysema in any zone.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; CT, computed tomography; LLN, lower limit of normal.

Table 3 Occupational burden, expressed as population-attributable fraction (PAF), of airflow limitation, chronic airflow limitation, COPD, physician-diagnosed COPD/emphysema, and emphysema among all subjects and according to gender, with 95% CI

	Airflow limitation ^a	Chronic airflow limitation (GOLD) ^b	Chronic airflow limitation (LLN) ^c	COPD ^d	Physician-diagnosed COPD/emphysema ^e	Emphysema ^f
All	0.19 (95% CI 0.10–0.26)	(0.15)	(0.15)	0.37 (95% CI 0.23–0.47)	0.46 (95% CI 0.12–0.57)	0.23 (95% CI 0.05–0.35)
Males	0.30 (95% CI 0.10–0.42)	0.19 (95% CI 0.10–0.39)	0.19 (95% CI 0.10–0.38)	0.46 (95% CI 0.12–0.60)	0.73 (95% CI 0.34–0.80)	0.34 (95% CI 0.01–0.51)
Females	(0.09)	(0.08)	(0.07)	(0.23)	(0.18)	(0.27)

Notes: PAF values in brackets are calculated from odds ratios without statistical significance. ^aAirflow limitation was defined as an FEV₁/FVC ratio <0.7 before bronchodilation. ^bChronic airflow limitation (GOLD) was defined as an FEV₁/FVC ratio <0.7 after bronchodilation. ^cChronic airflow limitation (LLN) was defined as an FEV₁/FVC ratio after bronchodilation below the lower limit of the normal. ^dCOPD was defined as chronic airflow limitation (GOLD) in combination with dyspnea, wheezing, or chronic bronchitis. ^ePhysician-diagnosed COPD/emphysema was defined as an affirmative answer to “Have you ever had chronic obstructive pulmonary disease or emphysema diagnosed by a physician?” ^fEmphysema was categorized according to CT findings of at least mild emphysema in any zone.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; CT, computed tomography; LLN, lower limit of normal.

Discussion

In the present cross-sectional analysis, we found that the associations with occupational exposure to VGDF were similar regardless of the definition used for airflow limitation and COPD. The most original observation was that CT-defined emphysema was clearly related to occupational exposure to VGDF.

We defined chronic airflow limitation according to both GOLD and LLN approach. The risk estimates were similar, indicating that the actual definition used is not a major concern. However, it must be emphasized that this conclusion is only valid for the narrow age span of 50–64 years, reflecting our study population. Men had higher ORs for chronic airflow limitation than women. Whether this reflects a true difference is unclear. Men may be more heavily exposed to VGDF than women, explaining the higher risk estimates. However, the ORs for occupational exposures and COPD or emphysema did not differ between men (2.8 and 2.0, respectively) and women (2.7 and 1.9, respectively).

Few studies have calculated gender-specific estimates for occupational exposures and COPD. The MESA study found a higher OR for women with airflow limitation and physician-diagnosed COPD than for men.²² One Australian study found that women had a higher risk for COPD and emphysema following exposure to biological dust, but not following exposure to mineral dust or gases and fumes.¹⁰ These studies with their contradictory findings further underscore the need for additional studies, as there is an obvious lack of gender-specific estimates of the occupational burden of COPD or airflow limitation.^{2,3,23}

As the main feature of COPD is irreversible bronchoconstriction, GOLD has recommended that spirometric diagnosis of COPD should be based on post-bronchodilation

spirometric testing, but in the most recent GOLD document, this is emphasized less.^{6,24} The prevalence of airflow limitation will be higher when pre-bronchodilator values are used, and in our study, there was a twofold difference in prevalence. However, the ORs for occupational exposure were quite similar regardless of whether airflow limitation was based on spirometric values before or after bronchodilation. Similar findings for occupational risk estimates were reported in a Norwegian study, supporting our findings.²⁵

In the present study, COPD was defined as presence of chronic airway limitation and current respiratory symptoms. This will probably identify subjects with more severe COPD.²⁶ A definition of COPD that combines spirometric findings with symptoms would probably yield a more specific outcome than a definition just based only on chronic airflow limitation. Narrowing the definition decreased the number of cases from 105 to 50, and the exposure prevalence among cases increased from 43.8% to 58.0%, resulting in a PAF of 0.37 (95% CI 0.23–0.47). Previous reviews have estimated a PAF of ~0.15, but with a wide variation. Interestingly, commonly used operational definitions of COPD in occupational epidemiological studies, chronic airflow limitation, and airway obstruction, yield a PAR of ~0.15 in the present analysis, which is similar to that proposed by a number of reviews.^{2,3,23} That a more specific and clinically relevant operational definition of COPD has a stronger association with occupational exposures should be regarded as supportive of a true relationship.

The outcome “physician-diagnosed COPD/emphysema” yielded a high risk estimate (OR 6.5, 95% CI 1.4–13.9) for VGDF exposure, and the male/female difference in ORs was substantial (6.5 for men and 2.0 for women). These estimates differ from those of other outcomes, which ranged

from 1.9 to 2.8. Physician-diagnosed COPD/emphysema has been shown as a COPD definition with very high specificity, hence higher risks are expected compared with estimates for more sensitive outcomes.¹³ This was, however, not observed in relation to smoking status, where the risk estimate was lower, compared with the estimates for other COPD definitions. These differences can be random or reflect an underlying mechanism. One explanation could be reporting bias, if subjects occupationally exposed to VGDF have an increased tendency to report physician-diagnosed COPD/emphysema. In contrast, smokers may tend to underreport physician-diagnosed COPD/emphysema. Hence, our findings indicate that studies using physician-diagnosed COPD/emphysema as an outcome may overestimate the occupational burden of COPD and underestimate the effect of smoking.

Our results regarding the occupational burden of emphysema are of interest. As expected we found a very high risk in relation to current smoking (OR=15.4, 95% CI 5.9–40.2), which could serve as a positive control. In relation to VGDF exposure, the risk was doubled and the population attributable risk was substantial: 0.23 (95% CI 0.05–0.35).

This study has several limitations. The most obvious is the cross-sectional design that hampers the possibility of performing time-dependent analyses. The occupational exposure assessment was based on questionnaire data, which may be prone to recall bias; subjects with disease may be more prone to report occupational exposure. We found indications of recall bias in relation to physician-diagnosed COPD/emphysema, as discussed earlier. Another weakness is the limited age span, 50–64 years, which precludes generalization to other age groups. Finally, the study sample was small, resulting in low power, especially among women and never-smokers.

Conclusion

Occupational exposure to VGDF is associated with an increased risk of COPD and emphysema. Our findings indicate that the occupational burden of COPD and CT-verified emphysema is substantial.

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Disclosure

The authors report no conflicts of interest in this work.

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