Association of metabolic syndrome with chronic obstructive pulmonary disease in an Indian population

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ABSTRACT

Background and Aims: Chronic obstructive pulmonary disease (COPD) is thought to have increased association with metabolic syndrome (MS) which represents a cluster of factors that increase the risk of cardiovascular diseases and diabetes mellitus. However, the extent of association of COPD with MS and its individual components are still an unsettled issue, and it is likely to vary from population to population. Under the above context, this study was undertaken to investigate the association of MS and its components with COPD. Materials and Methods: With a cross-sectional analytic design, 77 COPD and an equal number of non-COPD (apparently healthy) participants were studied purposively. The two groups were found to be matched by age, sex, and monthly income groups. The data of COPD patients and non-COPD participants were collected from a tertiary level hospital in Kolkata and a locality of Greater Kolkata, respectively. They were interviewed, and the frequencies of MS were assessed using 3 criteria (National Cholesterol Education Program-Third Adult Treatment Panel [NCEP ATP III], modified NCEP ATP III, and International Diabetic Federation [IDF]). Anthropometric measurements were taken, and fasting blood sample was collected to test the fasting blood glucose (FBG), triglyceride (TG), and high-density lipoprotein (HDL) of respondents. Logistic regression was applied to estimate the odds ratio (OR). Results: Among the COPD subjects, 44%, 46%, and 31% had coexisting MS as defined by NCEP ATP III, modified NCEP ATP III, and IDF criteria, respectively. The corresponding percentages in the non-COPD groups were 31%, 38%, and 32%. On multivariate analysis, a significant association of MS (P < 0.015) with COPD was found only when the NCEP ATP III criteria were used. The (mean ± standard deviation) FBG concentration among COPD and non-COPD groups was 130 ± 65 mg/dl and 97 ± 26 mg/dl, which was significantly different (P < 0.001). The difference in systolic blood pressure (SBP) (P < 0.063) and HDL level (P < 0.058) lied just outside the statistical significance among COPD and non-COPD groups. Gender, exercise habit, family history of hypertension, and smoking habits were important confounders for the association of individual MS components. Using NCEP ATP III criteria, female gender (OR = 3.48), COPD groups (OR = 3.05), and family history of hypertension (OR = 3.31) were found as determinants (P < 0.05) of MS. Conclusions: COPD is associated with MS only when the NCEP ATP III is used for the diagnosis of MS. No association can be revealed on using the IDF criteria for MS. Body mass index (BMI), and waist circumference does not seem to be appropriate measures for assessing the presence of MS among COPD patients. Among the components of MS BMI, SBP, FBG, TG, and HDL are significantly associated with COPD.

KEY WORDS: Association, chronic obstructive pulmonary disease, determinants, India, metabolic syndrome

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INTRODUCTION

The metabolic syndrome (MS) represents a cluster of risk factors that increases the risk for developing diabetes mellitus,[1] nonfetal and fatal cardiovascular disease.[2,3] The common risk factors are raised fasting plasma glucose, abdominal obesity, dyslipidemia, and high blood pressure.[4] In 1998, World Health Organization (WHO) proposed a unifying definition for this syndrome and chose to call it the “MS;” previously, it was named as insulin resistance syndrome, syndrome X, Reaven’s syndrome, etc.[5] This syndrome has outspread as epidemic worldwide.[6] Some studies from USA and Australia found 20–25% of the adult population suffering from MS.[7,8] In India, this prevalence is varying with different population. It is reported that the prevalence of MS among adult in Kolkata was 31.4%.[9] Different international expert committees developed varied clinical criteria for the diagnosis of MS. Among them, definition prepared by International Diabetic Federation (IDF), National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III), and WHO were wildly accepted. As a gross, all the Expert Committee agreed that obesity, insulin resistance, dyslipidemia, and hypertension are the important markers of MS.[10] The exact pathogenesis of MS is unknown, but it is predicted that obesity, insulin resistance associated with systemic inflammation are the causative factors.[11]

Chronic obstructive pulmonary disease (COPD) is a major cause of health care burden throughout the world-wide, and the only leading cause of death that is increasing in prevalence.[12] In 1990, COPD ranked the sixth most common cause of death worldwide and were predicted to become the third most common cause of mortality, and the fifth most common cause of chronic disability by 2020.[13] COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary components are characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.[14] COPD is not only a lung disease but also has some systemic effects. With the progression of this disease, systemic inflammation occurred among the COPD patients, and the patients suffered from different symptoms of chronic diseases, for example, dyslipidemia, diabetes mellitus, hypertension, coronary and peripheral artery diseases, anemia, osteoporosis, and rheumatoid arthritis. They are called as the comorbidities of the COPD. The exact pathological way of these systemic inflammations are not known but is believed to be related to enhance systemic inflammation and oxidative stress. These mechanisms may be multifactorial. The smoking, “spilling-over” of the pulmonary inflammatory response into the systemic circulation, activation of inflammatory cells during their transit through an inflamed milieu in the lungs, lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction, steroid intake, and/or abnormal bone marrow response may be potential causes of this systemic inflammation.[15] It is also very common to observe the rise of high-sensitive C-reactive protein among COPD patients. Probably, the increased level of interleukin-6 and tumor necrosis factor-α, soluble receptor I concentrations were the main mechanism for developing insulin resistance among COPD patients.[16] The association between chronic inflammation and increased insulin resistance may be accounted for disruption of insulin receptor signaling by inflammatory mediators.[11] Usually, insulin resistance occurs in combination with obesity, dyslipidemia, and hypertension. These together make up the “MS;” which is a major determinant of cardiovascular morbidity and mortality.[17]

It has been found that very few numbers of studies were conducted on this topic; among them, some studies found a positive association between COPD and MS. In a study with 38 COPD patients, almost 50% of patients with COPD had one or more components of the MS.[18] In a study at Canada, Marquis et al., concluded that among COPD patents, 61%, 63%, 24%, and 82% had abdominal obesity, elevated triglycerides (TGs) level, low high-density lipoprotein (HDL)-c levels, and raised blood pressure level, respectively.[19] Watz et al. conducted a study in Germany, which found that more than 47% COPD patients were affected with MS.[19] A major population in South East Asia region is prone to develop different chronic diseases due to a genetic cause, lifestyle abnormality, and hazard of rapid urbanization. This study is designed to identify the association of COPD and MS and its determinants in an Indian population of India.

MATERIALS AND METHODS

A cross-sectional analytic design study was conducted in the Department of Pulmonary Medicine, National Medical College and Hospital, Kolkata and a part of greater Kolkata. A total of 154 subjects were selected by purposive sampling procedure divided into two equal groups (case/COPD and control/non-COPD) in this study. Patients of COPD were taken as case group, diagnosed and confirmed by spirometry test and hyperinfiltration in chest X-ray and classified by the standard International Classification of Diseases criterion. The controls were selected from a community of Greater Kolkata, who did not have any history of shortness of breath and thus apparently were healthy. The two groups were found to be matched by age, sex, and monthly income groups. Participants with serious health condition, history of cerebral vascular accident, and unwilling to participation were excluded from this study. A questionnaire was prepared in the local languages including Hindi, Bengali, and English with the help of a trained interpreter. Data were collected ensuring the privacy and confidentiality by face-to-face interviews and document’s review. The data related to demographic (age, sex, ethnicity, education level, occupation, household monthly income, and living area) and lifestyles (habit of smoking, alcohol intake, and exercise) were collected using semi-structured questionnaire based on the objectives in simple and understandable language. The
anthropometric measurements (height, weight, and waist circumference) were measured by proper procedure. Aseptically, 5 ml of venous blood (fasting condition) were collected from each participant for measuring fasting blood glucose (FBG), TG, and HDL. Blood pressure was measured twice in the sitting position in the interval of 5 min by mercury sphygmomanometer. Participants were identified as hypertensive according to the IDF criteria if on antihypertensive medications or those who had a systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg.

The MS was diagnosed by three well-accepted guidelines. They are as following NCEP ATP III, Modified NCEP ATP III for south Asian people, and IDF.

The protocol was approved by the Institutional Ethical Committee. All the participants were verbally informed about the name of the researcher, study objectives, procedure, and the risk and benefit involved. This information was sufficiently discussed with participants, and they were allowed to ask any information and clarification. All the participants signed an informed consent, and illiterate people were involved after a witness signature. They were informed about their right to withdraw from the study at any time without showing any cause. The participants were reassured about the confidentiality of data which will be used for research purpose. The questionnaires were kept securely. All the procedures were done by giving respect and dignity to the participants.

After collection of data, it was checked, cleaned, edited, and verified daily to exclude any error and inconsistency. The data has been presented as numbers with a percentage (frequency) or mean with standard deviation (SD) as appropriate. Student’s t-test was performed to compare continuous variables. The significance of the difference between the proportions of qualitative characteristics has been tested using Chi-square test (of independent attributes). The binary logistic regression was applied to estimate the odds ratio (OR) and corresponding 95% confidence interval for the determinate of MS, the value $P < 0.05$ were considered statistically significant. The entire data were analyzed using SPSS version 11.5 5 (SPSS Inc, headquartered in Chicago, IL, USA).

RESULTS

A total of 77 COPD subjects and a same number of non-COPD subjects were studied. Age (years, mean ± SD) of the case and control group were 60 ± 12, 60 ± 10, respectively [Table 1]. Among both groups, male and female were 57 (74%) and 22 (26%), respectively. Among them, 49 (64%) came from urban, 28 (36%) from rural areas in the case group. In control group, 62 (81%) participants were from urban area. The study participants were also divided into three groups according to their education level. 28 subjects (36%) were illiterate, 43 (56%) were Class 1 to Class 10, and 6 (8%) were Class 11 to postgraduate level among COPD patients [Table 1]. In non-COPD participants, 15 (19%) were illiterate, 35 (45%) were Class 1 to Class 10 level, and 27 (35%) were from Class 11 to postgraduate level. The higher proportion of Bengali ethnic respondents were found in both case and control groups accounting 87% and 93.5%, respectively, which was higher than Bihari (13% and 6.5%). In case group, 35 (45%) were unemployed or retired group, 19 (25%) were in blue collar job, 12 (16%) were house worker, and 11 (14%) were involve in other group of work. In control group, 23 (30%) were unemployed or retired group, 13 (17%) were in blue collar job, 15 (19%) were house worker, and 26 (34%) were involve in other group of work. The others group comprised cultivators, white collar job, and self-employed. Among study subjects, the household family income (Rs. mean ± SD) of case and control group was 5544 ± 3227 and 5483 ± 2952, respectively. In both groups, more than 70% respondent’s monthly household income was <Rs. 6000 [Table 1]. Chi-square test in bivariate analysis and estimate for risk showed that education level ($P < 0.001$), occupation ($P < 0.02$), living area ($P < 0.02$), smoking habit ($P < 0.001$), smoking pattern ($P < 0.001$), alcohol intake habit ($P < 0.003$), and exercise habit ($P < 0.001$) were significantly different between cases and control groups [Table 2].

In this study, a total of 34 (44.15%), 36 (46.75%), and 24 (31.16%) COPD subjects met the NCEP ATP III, modified NCEP ATP III, and IDF criteria for MS, respectively [Table 3]. In counterpart, 24 (31.16%), 29 (37.66%), and 25 (32.46%) control subjects met the definition of MS according to the NCEP ATPIII, modified NCEP ATV III, and IDF criteria for MS.
respectively [Table 3]. Applying NCEP ATP III and Modified NCEP ATP III criteria, the MS showed more frequent among COPD group than controls (31.16%, 37.66%). By IDF definition, this study showed opposite results. There MS was more frequently found among controls (32%) than COPD [Figure 1]. This study showed significant association of MS ($P < 0.015$) with COPD only, when the NCEP ATP III criteria were used in multivariate analysis [Table 4]. Other diagnostic criteria could not found the significant association of MS with COPD.

The tendency of a higher level of mean SBP, diastolic blood pressure, FBG, and waist circumference were presented in COPD groups compared to control groups. The mean (± SD) FBG concentration among COPD and non-COPD were 129.53 ± 65.19 mg/dl and 96.95 ± 26.12 mg/dl, which was statistically significant ($P < 0.001$). SBP ($P < 0.063$) and HDL level ($P < 0.058$) were lied just outside the statistical significance among COPD and non-COPD groups. But the mean of TG, body mass index (BMI), and HDL were much high among control group compared to COPD groups in this study [Table 5].

In multivariate analysis, gender, exercise habit, family history of hypertension, and smoking habits were important confounders for the association of COPD with individual MS components. With the help of NCEP ATP III criteria, female gender (OR = 3), COPD groups (OR = 3),

**Table 2: Lifestyle related characteristics of the COPD and non-COPD groups**

| Variables                  | COPD n (%) | Non-COPD n (%) | P   |
|---------------------------|------------|----------------|-----|
| Smoking habit             |            |                |     |
| Current smoker            | 4 (5.19)   | 17 (22.07)     | <0.001 |
| Nonsmoker                 | 21 (27.27) | 45 (58.44)     |     |
| Past smoker               | 52 (67.53) | 15 (19.48)     |     |
| Smoking pattern           |            |                |     |
| Cigarette                 | 7 (12.50)  | 10 (31.25)     | <0.001 |
| Biri                      | 48 (85.71) | 22 (68.75)     |     |
| Gaja                      | 1 (1.78)   | 0 (0.00)       |     |
| Alcohol intake habit      |            |                |     |
| Present alcoholic         | 3 (3.89)   | 3 (3.89)       | 0.002 |
| Never alcoholic           | 54 (70.12) | 70 (91.90)     |     |
| Past alcoholic            | 20 (25.97) | 4 (5.19)       |     |
| Exercise habit            |            |                |     |
| Yes                       | 38 (49.35) | 65 (84.41)     | <0.001 |
| No                        | 39 (50.64) | 12 (15.58)     |     |
| Duration of exercise (min/week) | 125.39±207.71 | 361.30±422.71 |     |
| <150                      | 54 (70.12) | 25 (32.46)     | <0.001 |
| ≥150                      | 23 (29.87) | 52 (67.53)     |     |
| Duration (mean±SD)        |            |                |     |
| Extra salt intake         |            |                |     |
| Yes                       | 34 (44.15) | 28 (36.36)     | 0.341 |
| No                        | 43 (55.84) | 49 (63.63)     |     |

n=Number of participants (77), comparison done by Chi-square test.

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

**Table 3: MS (NCEP ATP III) among COPD and non-COPD subjects**

| Criteria                  | MS COPD n (%) | Non-COPD n (%) | P  |
|---------------------------|---------------|----------------|----|
| NCEP ATP III             |               |                |    |
| Yes                       | 34 (44.15)    | 24 (31.16)     | 0.096 |
| No                        | 43 (55.84)    | 53 (68.83)     |     |
| Modified NCEP ATP III    |               |                |    |
| Yes                       | 36 (46.75)    | 29 (37.66)     | 0.253 |
| No                        | 41 (53.24)    | 48 (62.33)     |     |
| IDF                       |               |                |    |
| Yes                       | 24 (31.16)    | 25 (32.46)     | 0.863 |
| No                        | 53 (68.83)    | 52 (67.53)     |     |

n=Number of participants (77), comparison done by Chi-square test.

COPD: Chronic obstructive pulmonary disease, NCEP ATP III: National Cholesterol Education Program-Third Adult Treatment Panel, IDF: International Diabetic Federation, MS: Metabolic syndrome

**Figure 1:** Frequency of metabolic syndrome among chronic obstructive pulmonary disease and non-chronic obstructive pulmonary disease groups according to different criteria

**Table 4: Determinant of MS of the study according to ATP III, modified ATP III and IDF criteria**

| Variables                  | ATP III | Modified ATP III | IDF  |
|---------------------------|---------|------------------|------|
| Gender                    |         |                  |      |
| Male                      | Reference|                  |      |
| Female                    | 0.018   | 0.29 (0.11-0.81) | 0.011 |
| Group                     |         |                  |      |
| Non-COPD                  | Reference|                  |      |
| COPD                      | 0.015   | 2.80 (1.22-6.44) | 0.072 |
| Smoking habit             |         |                  |      |
| No                        | Reference|                  |      |
| Yes                       | 0.629   | 1.27 (0.47-3.47) | 0.867 |
| Family history of hypertension |         |                  |      |
| No                        | Reference|                  |      |
| Yes                       | 0.001   | 0.23 (0.11-0.53) | 0.001 |
| Constant                  | 0.364   | 0.23 (0.11-0.53) | 0.021 |

NCEP ATP III criteria, modified NCEP ATP III criteria and IDF criteria was taken dependent variables whereas other taken as independent variables. Significant at $P<0.005$ levels. CI: Confidence interval, OR: Odds ratio, MS: Metabolic syndrome, ATP III: Third Adult Treatment Panel, IDF: International Diabetic Federation, COPD: Chronic obstructive pulmonary disease, NCEP ATP III: National Cholesterol Education Program-Third Adult Treatment Panel.
and family history of hypertension (OR = 3) were found determinants ($P < 0.05$) of MS. Modified NCEP ATP III also explored female (OR = 4) and family history of hypertension, (OR = 4) as determinants ($P < 0.05$) of MS [Table 4].

**DISCUSSION**

MS is a family of disorders sharing some common risk factors, and the members of the family are continuously increasing in number. COPD is also a candidate of this membership as major diseases in COPD are thought to be associated with insulin resistance and other basis defects of MS. However, the extent of association of COPD with MS and its individual components are still an unsettled issue, and it is likely to vary from population to population. Both COPD and MS are common in South Asian Indians,[10,21] but the association between the two disorders and their common determinants have not been properly investigated. In this study, these issues have been addressed through a case control design.

The association of MS with any disorder is complicated by the absence of universally agreed criteria for the diagnosis of MS. In this study, we used three different criteria (the NCEP ATP III criteria, the modified NCEP ATP III criteria, and IDF criteria) for the diagnosis of MS. Using the NCEP ATP III criteria, there was a strong trend of higher proportion of MS (44.15%) in COPD as compared to non-COPD (31.16%); however, the difference did not reach statistical significance ($P < 0.096$).

With modified NCEP ATP III criteria, the corresponding trend was relatively weaker (46.75% vs. 37.66%). The proportion of MS in COPD reported in this study were closely similar to that (47%) reported by Marquis et al.,[18] who used modified NCEP ATP III criteria. The proportion in the non-COPD group was also similar to that (31.4%) reported by Das and Ghosh[9] on a Kolkata population. However, this proportion is higher than two other studies conducted in Canada[19] and Germany.[19] As per IDF criteria, the proportion of MS in COPD was even lower (31.16%); however, the proportion in non-COPD cases (32.46%) was almost similar to that found using the NCEP ATP III and modified NCEP ATP III criteria. Watz et al.[19] found a much higher proportion (47.5%) among German COPD subjects.

The differences in the proportion of MS in non-COPD cases can mostly be explained by ethnicity and lifestyle (particularly nutritional). The differences in COPD cases, however, are complicated by the severity of COPD as well as by diverse criteria used to diagnose of MS. Steuten et al.[22] showed that with the advancement of stages of severity of COPD, the prevalence of obesity is decreased and they also showed a higher prevalence of obesity in GOLD stage I and II than stages onward. The prevalence of low body weight was more among GOLD stage IV.

**Table 5: Anthropometric, clinical and biochemical characteristics of the COPD and non-COPD groups**

| Variable                  | COPD          | Non-COPD      | $P$  |
|---------------------------|---------------|---------------|------|
| Waist circumference (cm)  | 87±17         | 86±12         | 0.453|
| BMI (kg/m$^2$)            | 23±6          | 24±4          | 0.135|
| SBP (mm Hg)               | 136±23        | 130±17        | 0.063|
| DBP (mm Hg)               | 83±10         | 81±10         | 0.360|
| TG (mg/dl)                | 130±77        | 97±26         | 0.001|
| HDL (mg/dl)               | 43±9          | 45±5          | 0.058|

**Table 6: Logistic regression on COPD**

| Independent variables | $\beta$ | $P$  | OR  | 95.0% CI for Exponent($\beta$) |
|-----------------------|---------|------|-----|--------------------------------|
| BMI                   | -0.132  | 0.042| 0.877| 0.772 - 0.995                 |
| Waist circumference   | 0.053   | 0.001| 1.034| 1.019 - 1.053                 |
| FG                    | 0.035   | 0.001| 1.036| 1.019 - 1.053                 |
| TG                    | -0.015  | 0.985| 0.977| 0.994 - 1.019                 |
| HDL                   | -0.017  | 0.983| 0.922| 1.047 - 1.053                 |
| SBP                   | 0.012   | 0.001| 1.012| 0.984 - 1.042                 |
| DBP                   | -0.007  | 0.993| 0.936| 1.053 - 1.093                 |
| Total duration        | -0.004  | 0.996| 0.994| 0.994 - 0.999                 |
| Smoking habit no      | -1.260  | 0.001| 0.259| 0.134 - 0.499                 |
| Smoking habit yes     | 1.620   | 0.001| 5.524| 2.761 - 11.203               |
| Constant              | 0.783   | 0.001| 2.152| 1.354 - 3.401                 |

Although on univariate analysis only a trend of association of COPD with MS was found. Using NCEP ATP III criteria, the association became clearly evident ($P < 0.010$) when effects of other confounding variables were adjusted in a logistic regression model. Similar analysis showed a strong tendency of association between MS and COPD ($P < 0.070$) using the modified NCEP ATP III criteria. There was, however, no association between COPD and MS using the IDF criteria. The data indicate that association between COPD and MS is highly dependent on the definition used for the diagnosis of the syndrome. Association between MS and COPD has been shown by Marquis et al.[18] using the NCEP ATP III criteria at Canada.

Another objective of the study was to explore the association of individual components of MS with COPD. From the comparison of the mean [Table 6], only FBG was significantly higher in COPD ($P < 0.001$). The SBP was also higher and HDL lower in COPD as compared to non-COPD; however, the difference lied just outside the statistical significance. The association with individual components was further explored using the multiple regression models. The data showed a significant positive association with SBP.
TG, and FBG. A significant association was also seen with BMI\(^2\) which supports the notion that body weight is rather reduced in longstanding COPD. The negative association is also seen with total duration of exercise per week which may again reflect an effect rather than cause in COPD cases. Only a few reports are available on the association of COPD with individual components of MS. Marquis \textit{et al.}\(^{18}\) showed SBP \((P < 0.05)\), HDL \((P < 0.05)\), and low-density lipoprotein \((P < 0.001)\) are statistically significant with COPD. Current study showed FBG is also associated with COPD. The probable reason of difference was corticosteroid drug medication. Almost 95% COPD patients of recent study medicated with corticosteroids drugs at least last 7 days of data collection and in the study of Marquis,\(^{18}\) any COPD patient were not in corticosteroids drugs management in last 3 months. Corticosteroids can induce hyperglycemia among COPD patients. In a meta-analysis of studies in patients with stable COPD, patients taking oral corticosteroids were 7.7 times more likely to have an adverse event such as glucose intolerance and mild hypertension than placebo.\(^{23}\) It was doubtful but probable, it was the main cause of alteration of this finding.

The last objective of the study was to explore the determinants of association between MS and COPD as well as between the individual components of MS and COPD. This was best explored by multivariate analysis. Female gender and family history of hypertension were associated with MS by using the NCEP ATP III criteria and the modified NCEP ATP III criteria, but there was no such association as per IDF criteria. On analysis of individual components; total duration of exercise/week had a negative association with COPD, which may be either cause or effect. The data also show that smoking habit is associated with COPD \((P < 0.001)\).

**CONCLUSIONS**

COPD is associated with MS only when the NCEP ATP III is used for the diagnosis of MS in this population. No association can be revealed on using the IDF criteria for MS. Through the frequency is very alarming, COPD subjects have lower body weight and adiposity, thus anthropometric markers of these physiological entities (such as BMI and waist circumference) are not appropriate measure for assessing the presence of MS in this condition. Among the components of MS BMI, SBP, FBG, TG, and HDL are significantly associated with COPD. Genders, exercise habit, family history of hypertension, and smoking habits are important confounders for the association of COPD with individual components of MS.

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**Conflicts of interest**

There are no conflicts of interest.

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