Association between health literacy and multimorbidity: a nationwide, cross-sectional study of a Japanese population

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ABSTRACT

Objectives To examine the relationship between health literacy and multimorbidity.

Design Nationwide cross-sectional study.

Setting Community settings across Japan.

Participants Community-dwelling participants aged 20 years or older were selected based on a quota sampling method that adjusted for age, sex and residential area. In total, 3678 participants from the Health Diary Study, with a mean age of 52.3 years (SD, 18.2 years; 1943 (52.8%) female participants), were included.

Primary outcome measure Multimorbidity, the primary outcome measure, was defined as the presence of two or more chronic diseases.

Results Of the 3678 participants, 824 (22.4%) had multimorbidity. The mean functional health literacy (FHL) and communicative and critical health literacy (CCHL) scores were 3.2 (SD, 0.7) and 3.6 (SD, 0.9), respectively. In the univariable analysis, both scores were associated with multimorbidity (p<0.001). However, in the multivariable modified Poisson regression analysis, only the FHL score was significantly associated with multimorbidity (per 1-point increase, 0.91; 95% CI 0.84 to 0.99).

Conclusions After adjusting for confounding variables, FHL, not CCHL, was significantly related to the presence of multimorbidity. Further longitudinal studies are required to examine the causal relationship between health literacy and multimorbidity.

INTRODUCTION

Multimorbidity is a condition where an individual has multiple chronic diseases. Patients with multimorbidity require substantial medical resources and have a low quality of life, an 8.8 times higher prevalence of polypharmacy, and 1.73 times higher mortality rates. Managing these patients and exploring the mechanisms leading to multimorbidity are global issues, and understanding the susceptibility to multimorbidity is essential for healthcare providers for early detection. The prevalence of multimorbidity increases with ageing, as the number of patients with multimorbidity increases 1.78 times per 10-year increase in age. The prevalence of multimorbidity is 62.8% among individuals aged ≥65 years in Japan. The prevalence of multimorbidity is also related to sex, mental health problems, socioeconomic status and other factors.

There is a possibility that health literacy is associated with multimorbidity. Health literacy is defined as ‘the degree to which individuals have the capacity to obtain, process and understand basic health information and needed services to make appropriate health decisions.’ It has been proposed that the components of health literacy are functional health literacy (FHL), including basic skills, and communicative and critical health literacy (CCHL), including application skills. Health literacy is associated with health outcomes such as all-cause mortality and cardiovascular death among elderly individuals, as well as the demand for healthcare services. The direct association between health literacy and non-communicable diseases is unclear. Geboers et al reported the association of health literacy with poor self-management abilities among older adults; therefore, low health literacy might be a risk factor for the development of

Strengths and limitations of this study

The sample size was large, with participants enrolled from a national, representative population of Japan.

Due to the limitation of the cross-sectional design, we could not confirm a causal relationship between multimorbidity and functional health literacy.

The self-reported data about chronic diseases might not have fully captured the diseases of the participants; therefore, there were risks of misclassification.

Data were obtained using quota sampling, and not all elements of quota sampling are representative of the general population; therefore, there could have been selection bias.
non-communicable diseases and their eventual accumulation (ie, multimorbidity).

Previous studies have assessed the association between health literacy and multimorbidity; however, this relationship remains controversial. A previous study reported no significant relationship between health literacy and multimorbidity; however, another reported that some health literacy scores are related to multimorbidity. A major controversial issue regarding the association between health literacy and multimorbidity is that only one domain of health literacy has been measured in the previous studies. However, the concept of health literacy is more elaborate. Therefore, considering that different domains may have different associations with health literacy, the results of each study may be inconsistent. To determine the actual association, multimorbidity should be investigated using the two domains of health literacy, with a large sample size. The results of such a study could lead to additional cohort studies that investigate further causality.

This study aimed to investigate the association of two domains of health literacy, FHL and CCHL, with multimorbidity using a cross-sectional survey based on a large sample of Japanese participants.

METHODS

Study design and participants

We performed a cross-sectional study of a dataset from the Health Diary Study. These data were obtained from a nationwide study of community-dwelling residents across Japan that was performed in October 2013.

Samples were extracted from survey respondents (79 749 individuals; 37 643 men and 42 106 women) and provided by a commercial survey company (JMA, Tokyo, Japan). Among the 19 633 individuals who agreed to participate in the Health Diary Study, 5 000 were selected based on a quota sampling method that adjusted for age, sex and residential area (figure 1, online supplemental material 1). Written informed consent was obtained by postal mail. A health diary to manually record the required information, questionnaire, and gift voucher (approximately US$30 per person) were sent to each participant. Participants received weekly reminders through telephone calls, and 4 548 participants eventually completed the survey. From this set of participants, we extracted data from citizens ≥20 years of age and excluded data that did not include the literacy score.

Measurements

Multimorbidity

In this study, participants were asked to indicate their conditions out of 65 chronic diseases, including malignancy, stroke, chronic obstructive pulmonary disease, diabetes, hypertension, psychiatric disease, heart disease, asthma, thyroid disease, anaemia, obesity, liver disease, kidney disease, hyperuricaemia and dyslipidaemia (online supplemental material 2). Then, we narrowed the list to 15 clinically important chronic diseases. We defined
multimorbidity as the presence of two or more chronic diseases.21

Health literacy
The health literacy score was measured using the FHL domain of the Functional, Communicative and Critical Health Literacy scale22 and CCHL scale, which have been validated previously.23–24 We made a slight modification to the lead sentence in FHL to make it applicable to the general public, with permission from Ishikawa, the author of this scale (online supplemental material 3).22–24 We calculated the FHL and CCHL scores by adding five item scores and dividing the sum by the number of items in the scale. The FHL domain contains five items, wherein lower scores (1, never; 4, often) indicate higher health literacy. However, the CCHL scale contains five items, and higher scores (1, strongly disagree; 5, strongly agree) indicate higher health literacy. Therefore, the scores were reversed for FHL such that higher scores indicated higher health literacy. For the FHL questions assessing reading and understanding skills, higher scores indicate higher health literacy. The CCHL questions assessed critical analysis skills.

Other data
We also collected data on other variables that could be correlated with multimorbidity, such as age, sex, household income during 1 year (<JPY4.0 million (=US$36 000), JPY4.0–9.9 million or ≥JPY10.0 million; the average income was JPY4.14 million),25 education, weight, height, smoking habits (never, ≤20 pack-years, >20–40 pack-years or >40 pack-years), monthly alcohol consumption (light: <10 drinks; moderate: 10–40 drinks; heavy: >40 drinks; 1 drink=10g alcohol), and marital status. These data were obtained from a self-administered questionnaire using categorical items and distributive columns (weight, height and smoking habits). We selected age, sex, income and education as covariates for the analysis. Those covariates were clinically important confounders and were previously reported as such in the relationships between health literacy and health outcomes.26–27

Statistical analyses
We mainly reported data as frequencies and percentages in the descriptive analyses. In the univariable analysis, we applied Student’s t-test, Pearson’s χ² test and the Mann-Whitney U test to compare the backgrounds of individuals with and without multimorbidity. We also applied the χ² test for trend to determine the trend of the prevalence of chronic diseases. We used a multivariable modified Poisson regression model with robust error variance; age, sex, education and income level were set as confounding factors that could be correlated with multimorbidity in the analysis. The other items were intermediate factors. We developed three models for multivariable analyses. Using model 1, we performed a single regression analysis of the crude risk ratio. Using model 2, we adjusted only for sex and age. Using model 3, we adjusted for age, sex, income and education. Because there were missing data for a few variables (0%–2.1%), cases with missing covariates were removed. Sensitivity analysis of chronic diseases was performed using negative binomial regression to determine whether there was an association between health literacy and the number of diseases. All analyses were two-tailed and performed using STATA V.16 (STATA). Statistical significance was set at p<0.05.

Patient and public involvement
No patients were involved in the design, conduct, reporting or dissemination of this study.

RESULTS
Table 1 shows the characteristics of the participants. In total, 3678 individuals with a mean age of 53.3 years (SD, 18.2 years; 1943 (52.8%) female participants) were included. The overall prevalence of multimorbidity was 22.4% (n=824). The rates of multimorbidity based on age groups were 7.4% (age 20–39 years), 19.8% (age 40–59 years), 34.5% (age 60–79 years) and 43.3% (age 80 years or older). The mean FHL and CCHL scores were 3.2 (SD, 0.7) and 3.6 (SD, 0.9), respectively. The median FHL and CCHL scores were significantly higher for participants without multimorbidity according to the Mann-Whitney U test (p<0.001). Individuals with multimorbidity were older, had a lower household income, were considered heavy smokers and had fewer years of education than those without multimorbidity.

The prevalence rates of chronic diseases are shown in table 2. Hypertension and obesity had relatively high prevalence rates (>15%), whereas chronic obstructive pulmonary disease, thyroid disease, liver disease and kidney disease had relatively low prevalence rates (<2.5%). The prevalence rates of most chronic diseases, except obesity, psychiatric disease and thyroid disease, consistently increased with age.

Table 3 shows the results of the modified Poisson regression analysis of the relationship between FHL and multimorbidity. The FHL score was significantly negatively associated with multimorbidity (per 1-point increase, 0.91; 95% CI 0.84 to 0.99). Sex and age were also significantly associated with the prevalence of multimorbidity. Moreover, the prevalence of multimorbidity became higher with age (p<0.001). After adjustment, educational background and household income were not associated with multimorbidity.

Table 4 shows the results of the Poisson regression analysis of the relationship between the CCHL score and multimorbidity. In the univariable model (model 1) and the age-adjusted and sex-adjusted model (model 2), relationships between CCHL and multimorbidity were observed. However, such significant relationships were not observed after adjustments for education and household income (model 3).
## Table 1: Patient characteristics

|                        | Total n=3678 | Multimorbidity n=824 | No multimorbidity n=2854 |
|------------------------|--------------|-----------------------|--------------------------|
| **Age, mean (SD), years** |              |                       |                          |
| 20–39                  | 52.3 (18.2)  | 62.7 (15.8)           | 49.3 (17.8)              |
| 40–59                  | 1079 (29.3) | 80 (7.4)              | 999 (92.6)              |
| 60–79                  | 1200 (32.6) | 251 (19.8)            | 949 (80.3)              |
| ≥80                    | 1129 (30.7) | 453 (35.4)            | 676 (65.5)              |
| **Data missing**       | 0            | 0                     | 0                        |
| **Sex, female, n (%)** |              |                       |                          |
| 20–39                  | 1943 (52.8) | 413 (50.1)            | 1530 (53.6)             |
| 40–59                  | 0            | 0                     | 0                        |
| 60–79                  | 22.4 (3.5)  | 24.5 (4.1)            | 21.7 (3.1)              |
| **BMI, mean (SD)**     |              |                       |                          |
| <JPY4.0 (=US$36 000)   | 1067 (29.1) | 290 (35.3)            | 777 (27.3)              |
| JPY4.0–JPY9.9          | 2204 (60.1) | 463 (56.3)            | 1741 (61.2)             |
| ≥JPY10.0              | 396 (10.8)  | 69 (8.4)              | 327 (11.5)              |
| **Data missing**       | 5            | 0                     | 5                        |
| **Alcohol*, n (%)**    |              |                       |                          |
| Non-drinker            | 1735 (47.2) | 429 (51.8)            | 1306 (45.9)             |
| Light                  | 1486 (40.4) | 310 (37.7)            | 1176 (41.2)             |
| Moderate               | 409 (11.1)  | 82 (10.2)             | 327 (11.4)              |
| Heavy                  | 48 (1.3)    | 3 (0.36)              | 45 (1.6)                |
| **Data missing**       | 0            | 0                     | 0                        |
| **Smoking, n (%)**     |              |                       |                          |
| Never                  | 2395 (65.1) | 468 (56.8)            | 1927 (67.5)             |
| ≤20 pack-years         | 789 (21.5)  | 171 (20.8)            | 618 (21.7)              |
| >20–40 pack-years      | 307 (8.4)   | 108 (13.1)            | 199 (7.0)               |
| >40 pack-years         | 187 (5.1)   | 77 (9.3)              | 110 (3.9)               |
| **Data missing**       | 0            | 0                     | 0                        |
| **Marital status, n (%)** |            |                       |                          |
| Married                | 2457 (67.9) | 601 (73.6)            | 1856 (66.2)             |
| Single                 | 806 (22.3)  | 71 (8.7)              | 735 (26.2)              |
| Widowed                | 249 (6.9)   | 115 (14.1)            | 134 (4.8)               |
| Divorced               | 109 (3.0)   | 30 (3.7)              | 79 (2.8)                |
| **Data missing**       | 57           | 7                     | 50                       |
| **Years of education** |              |                       |                          |
| ≤9                     | 272 (7.6)   | 99 (12.2)             | 173 (6.2)               |
| 10–12                  | 1271 (35.3) | 327 (40.4)            | 944 (33.8)              |
| >12                    | 2058 (57.2) | 383 (47.3)            | 1675 (60.0)             |
| **Data missing**       | 77           | 15                    | 62                       |
| **FHL score, median (IQR)** |      | 3.4 (2.8–3.8)        | 3.2 (2.6–3.6)            |
| **CCHL score, median (IQR)** |     | 3.8 (3.2–4.2)        | 3.8 (3.0–4.0)            |
Sensitivity analysis indicated that higher FHL scores were negatively associated with the number of chronic diseases (prevalence ratio, 0.89; 95% CI 0.84 to 0.94); however, higher CCHL scores did not show this association (prevalence ratio, 0.96; 95% CI 0.92 to 1.01) (online supplemental materials 4 and 5).

**DISCUSSION**

To the best of our knowledge, this is one of the few studies that investigated the data of a large population to examine the associations of two concepts of health literacy (FHL and CCHL) with multimorbidity. In this study, FHL, which comprises basic health literacy, was related to the prevalence of multimorbidity after adjusting for potential confounding factors; this result was consistent across multiple models. However, there was no significant relationship between CCHL, which comprises advanced health literacy and the prevalence of multimorbidity. The results were consistent and a similar trend was observed after a series of sensitivity analyses when using the number of diseases as the outcome.

We found that FHL was related to the prevalence of multimorbidity. In contrast, a previous clinic-based study by Hudon et al showed no significant relationship between basic health literacy and multimorbidity; however, their study limited the target population to those who visited the clinic, which could have resulted in selection bias. The participants of our study were...

### Table 2 Prevalence of chronic diseases

| Total population N=3678 | **Age, years** |  
|-------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                         | n* (%)         | 20–39 (n=1079) | 40–59 (n=1200) | 60–79 (n=1129) | ≥80 (n=270) | P value† |
| Obese                  | (19.2)         | (15.7)         | (23.3)         | (19.5)         | (14.1)         | 0.537 |
| Hypertension           | (7.5)          | (1.1)          | (11.3)         | (32.5)         | (47.0)         | <0.001 |
| Dyslipidaemia          | (7.2)          | (1.4)          | (6.8)          | (12.8)         | (8.2)          | <0.001 |
| Heart disease          | (6.5)          | (1.5)          | (4.0)          | (10.5)         | (20.7)         | <0.001 |
| Anaemia                | (6.1)          | (5.5)          | (9.0)          | (4.2)          | (3.7)          | 0.0388 |
| Malignancy             | (5.0)          | (2.0)          | (4.1)          | (9.4)          | (12.2)         | <0.001 |
| Asthma                 | (5.7)          | (7.0)          | (6.5)          | (4.1)          | (4.1)          | <0.01 |
| Diabetes               | (5.7)          | (0.8)          | (3.3)          | (11.6)         | (11.1)         | <0.001 |
| Psychiatric disease    | (3.5)          | (3.9)          | (4.3)          | (2.4)          | (3.3)          | 0.0889 |
| Hyperuricaemia         | (3.0)          | (0.5)          | (3.8)          | (4.9)          | (1.5)          | <0.001 |
| Stroke                 | (2.7)          | (0.4)          | (0.5)          | (5.2)          | (15.2)         | <0.001 |
| Thyroid disease        | (2.2)          | (1.3)          | (2.8)          | (2.6)          | (1.5)          | 0.278 |
| Liver disease          | (1.2)          | (0.6)          | (1.1)          | (1.7)          | (2.2)          | <0.01 |
| Kidney disease         | (0.7)          | (0.3)          | (0.4)          | (1.0)          | (3.0)          | <0.001 |
| COPD                   | (0.5)          | (0)            | (0.25)         | (1.2)          | (1.1)          | <0.001 |

*Number of participants with the disease.
†P value by χ² test for trend.

COPD, chronic obstructive pulmonary disease.
enrolled from the general population; therefore, we could include individuals who had no access to the medical system because of low health literacy but had multiple diseases, and our results were likely to reflect a more accurate description of the relationship between health literacy and multimorbidity.

### Table 3 Modified Poisson regression analyses of relationships between functional health literacy and multimorbidity

|                        | Model 1                      | Model 2                      | Model 3                      |
|------------------------|-----------------------------|-----------------------------|-----------------------------|
|                        | Crude risk ratio (95% CI)    | Adjusted risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
| FHL score              | 0.71 (0.66 to 0.76)          | 0.90 (0.83 to 0.97)          | 0.91 (0.84 to 0.99)          |
|                        | 0.001                        | 0.009                        | 0.037                        |
| Covariates             |                             |                             |                             |
| Sex, female            | –                            | 0.83 (0.74 to 0.94)          | 0.83 (0.74 to 0.93)          |
| Age, years             | 20–39 – – – – Reference      | 40–59 – – – – 2.59 (2.04 to 3.30) | 4.45 (3.54 to 5.60)          |
|                        |                             |                             |                             |
|                        | 40–59 – – – – 2.59 (2.04 to 3.30) | 4.45 (3.54 to 5.60)          |                             |
|                        |                             |                             |                             |
|                        | 60–79 – – – – 4.45 (3.54 to 5.60) | 5.38 (4.13 to 7.03)          |                             |
| Years of education     | ≤9 years – – – – Reference   | ≥80 – – – – 5.38 (4.13 to 7.03) |                             |
|                        |                             |                             |                             |
|                        | 10–12 years – – – –          |                             |                             |
|                        | >12 years – – – –            |                             |                             |
| Household income, in million JPY | <JPY4.0 (=US$36 000) – – – – Reference | JPY4.0–JPY9.9 – – – – 0.95 (0.84 to 1.08) |                             |
|                        | ≥JPY10.0 – – – –             |                             |                             |

US$1, JPY110.
FHL, functional health literacy.;

### Table 4 Modified Poisson regression analyses of relationships between communicative and critical health literacy and multimorbidity

|                        | Model 1                      | Model 2                      | Model 3                      |
|------------------------|-----------------------------|-----------------------------|-----------------------------|
|                        | Crude risk ratio (95% CI)    | Adjusted risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
| CCHL score             | 0.84 (0.78 to 0.89)          | 0.94 (0.88 to 0.995)         | 0.95 (0.89 to 1.02)         |
|                        | <0.001                       | 0.035                       | 0.134                       |
| Covariates             |                             |                             |                             |
| Sex, female            | –                            | 0.84 (0.75 to 0.94)          | 0.83 (0.74 to 0.93)          |
| Age, years             | 20–39 – – – – Reference      |                             |                             |
|                        |                             |                             |                             |
|                        | 40–59 – – – – 2.68 (2.11 to 3.40) |                             |                             |
|                        |                             |                             |                             |
|                        | 60–79 – – – – 4.62 (3.68 to 5.79) |                             |                             |
|                        |                             |                             |                             |
|                        | ≥80 – – – – 5.63 (4.34 to 7.29) |                             |                             |
| Years of education     | ≤9 years – – – – Reference   |                             |                             |
|                        |                             |                             |                             |
|                        | 10–12 years – – – –          |                             |                             |
|                        | >12 years – – – –            |                             |                             |
| Household income, in million JPY | <JPY4.0 (=US$36 000) – – – – Reference | JPY4.0–JPY9.9 – – – – 0.95 (0.84 to 1.08) |                             |
|                        | ≥JPY10.0 – – – –             |                             |                             |

US$1, JPY110.
CCHL, communicative and critical health literacy.;
In our study, there was no significant relationship between CCHL and the prevalence of multimorbidity. However, a previous study by Aaby et al using the Health Literacy Questionnaire showed significant relationships between the low prevalence of multimorbidity and two health literacy items, ‘actively managing my health’ and ‘social support for health,’ which appear to be specific aspects of CCHL concepts. We surveyed the relationship between a generic concept of CCHL and multimorbidity, even though CCHL includes a diverse range of specific concepts such as the ability to judge the reliability of information. The possibility that only specific aspects of CCHL concepts, not the generic CCHL concept, may be associated with multimorbidity should be further explored in the future.

The mechanism of the association between FHL and multimorbidity may be inferred from several studies that examined the relationship between health literacy and health outcomes such as chronic disease. Many chronic diseases require decades of self-management as a part of health behaviour to prevent further illness. Although the association between health literacy and health behaviours is still controversial, a systematic review by Mackey et al found an association between health literacy and disease-related knowledge, self-efficacy and beliefs regarding many diseases. These three domains are thought to be necessary during the initial stage of self-management. According to the causal pathways modelled by Paasche-Orlow and Wolf, these domains are intermediate between health literacy and health outcomes. Therefore, we think it is possible that low health literacy increases the risk of further illness for individuals with chronic diseases, which may progress to multimorbidity through poor self-management. As Nutbeam indicated, FHL can be considered a basic skill that leads to improved knowledge of disease risks and health services. It helps individuals to understand the importance of receiving vaccinations and undergoing health examinations that could prevent diseases such as cervical and liver cancers. Moreover, it is associated with the ability to gather information about when to visit the hospital. However, the most common health literacy indicator used in those studies was the FHL score or comprehensive health literacy score; CCHL was not measured independently. It is quite possible that the more advanced health literacy, CCHL, is associated with the development of multimorbidity; this requires confirmation in future investigations. Additionally, it is possible that CCHL has less of an impact on multimorbidity due to differences in the disease patterns that compose multimorbidity, such as multimorbidity patterns including diseases that are less dependent on the ability to actively collect health information.

This study suggests that community health promotion may be useful for Japanese residents who do not have adequate FHL. We found that FHL was associated with multimorbidity in Japanese population, where the literacy rate is considered to be 100%. This indicates that there is still potential for improving health literacy in similarly developed countries. Regional health promotion activities for residents who have insufficient FHL may be effective even in developed countries. Our study indicated an association of multimorbidity with FHL but, unexpectedly, not with CCHL, even though these two types of literacy are not independent. Considering that CCHL comprises more advanced literacy skills compared with FHL, CCHL should be associated with the occurrence of multimorbidity because it increases self-confidence in the collection of adequate information regarding health and participation in social networking. Therefore, further evidence is required to investigate the relationship between multimorbidity and specific elements of CCHL.

Our study had several limitations. Although it was a population-based study, among 80 000 individuals, approximately 20 000 candidates agreed to participate, which may have comprised individuals with relatively greater health concerns; a few might have been excluded because of their inability to respond to the questionnaire due to serious physical illnesses or dementia. Our data showed that more than 50% graduated from university, which is higher than the average rate in Japan. It has been reported that education is strongly associated with health literacy; therefore, the health literacy of our participants may have been higher than that of the general population. Nonetheless, within the highly literate population, there was a relationship between FHL and multimorbidity. This suggests that the relationship between FHL and multimorbidity may be even stronger in the general population. This was a cross-sectional study; hence, we could not suggest a causal relationship between FHL and multimorbidity. It cannot be ruled out that the presence of multimorbidity as a health outcome may have had a contrasting causal effect of increasing health literacy through regular healthcare visits and instructions from healthcare workers. This would underestimate the relationship between health literacy and multimorbidity in this study. The FHL and CCHL scores were determined using different scales. The CCHL scale was validated for the general public, while the FHL scale was validated for diabetes patients. However, the same questions were used in the 14-item health literacy scale for the general population, which was developed and validated later. Therefore, we are not concerned about the content validity of the questionnaire administered to the general population. The FHL score was skewed and many participants had complete scores, which could have had a ceiling effect. As another limitation, the data were collected in 2013; therefore, the current situation could have changed. In addition, all measurements were based on the self-reported questionnaire; therefore, there were risks of misclassification. Finally, our data were obtained using quota sampling, not random sampling. Not all elements of quota sampling are representative of the general population; therefore, there could have been selection bias.

In conclusion, the findings of our study show that FHL, but not CCHL, was significantly related to multimorbidity. Therefore, increasing FHL might be related to
decreased multimorbidity. Further longitudinal studies are required to examine the causal relationship between health literacy and multimorbidity.

Contributors ST, TA, SO, OT, TK and MM were involved in study design and data interpretation. ST, TA, SO and MM were involved in the data analysis. All authors critically revised the report, commented on drafts of the manuscript and approved the final report. ST is the guarantor of the work and accepts full responsibility for the presented content.

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