Polypharmacy and saliva volumes in the northeast of Germany – The Study of Health in Pomerania

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Abstract

Objectives: Associations between saliva volumes or salivary flow rates and potentially xerogenic medication are rarely evaluated in cohorts with a wide age range. This cross-sectional cohort study investigated possible relationships between the regular consumption of potentially xerogenic medication and stimulated saliva volumes.

Methods: Data from the German Studies of Health in Pomerania (SHIP-2 and SHIP-Trend-0) were pooled. Potentially xerogenic medications were identified using the Workshop on Oral Medicine VI criteria. Stimulated saliva was sampled using Salivette®, and saliva volumes expressed as μL/min were determined. Applying linear mixed models with adjustment for time point of saliva collection, associations of (a) age and sex with regularly consumed medication, (b) age and sex with saliva volumes, and (c) the number of regularly consumed xerogenic medications with saliva volumes were evaluated.

Results: Six thousand seven hundred and fifty-three participants aged 20-83 years (mean 53.4 ± 14.9) were included. The average number of medications did not differ markedly between females (2.21 ± 2.46) and males (2.24 ± 2.83). Males took more potentially xerogenic medication (1.0 ± 1.3) than did females (0.9 ± 1.3). Also, males took more potentially xerogenic cardiovascular medications than did females (0.9 ± 1.2 versus 0.7 ± 1.1), while females were prescribed a higher number of potentially xerogenic medications affecting the nervous system (0.2 ± 0.5 versus 0.1 ± 0.4). The average stimulated saliva volume was 967.0 ± 433.3 μL/min. Regularly consumed and potentially xerogenic medications were associated with lower saliva volumes. Older age correlated not only with a higher number of total medications and a higher number of xerogenic medications affecting either the cardiovascular (in males) or the nervous system (in females), but also with lower saliva volumes.

Conclusions: Ageing was associated with polypharmacy, especially with the intake of potentially xerogenic medication, and lower average saliva volumes. With regard to complications of dry mouth, anamnesis of medication consumption is of high importance.
1 | INTRODUCTION

Salivary flow substantially differs between and within individuals. Besides the individual's degree of hydration, other important factors affecting salivary flow include olfactory stimuli, body position and/or chewing. Unstimulated salivary flow of ≤0.1 mL/min and/or stimulated salivary flow of ≤0.5 up to 0.7 mL/min is defined as hyposalivation. Among older people, its prevalence ranges from 15% to 23%; among hospitalized older people, its prevalence ranges from 17% to 50%. Hyposalivation is often associated with xerostomia (subjective feeling of dry mouth). Thus, xerostomia well predicts hyposalivation. This widespread symptom significantly reduces an individual's quality of life, with a prevalence of 5.5 to 39% in the general population, and up to 72% in older persons living in residential care homes but only 10% among adults in their early 30s. The main reasons for hyposalivation and xerostomia among older people are the increasing number of systemic diseases (e.g., diabetes mellitus and renal insufficiency) and the resulting medication intake, herein referred to as xerogenic medications.

Potentially xerogenic medication seems to be one of the most common causes of xerostomia, predominantly diuretics, psychotherapeutics and cardiovascular medications, but also analgesics and antihistamines. Xerogenic medications seem to either reduce salivary flow rates or alter individual thresholds for perceived dry mouth. However, a meta-analysis has shown that whole salivary flow rates were significantly lower in older than in younger participants, independent of medication. Additionally, a systematic review reported that at the first level of the Anatomical Therapeutic Chemical (ATC) Classification System, anatomical groups of the alimentary, cardiovascular, nervous and respiratory system might affect salivary gland function and induce xerostomia. In this context, polypharmacy (5-9 medications) and hyperpolypharmacy (>10 medications) become increasingly important. Among several small population-based studies (<1000 participants), Smidt et al. investigated the relationship between self-reported and ATC-classified medication and salivary flow in 668 older adults, suggesting that stimulated and unstimulated salivary flow might be associated with specific diseases and a higher number of medications.

Recently, a consensus paper by The World Workshop on Oral Medicine VI Guide to “Medications Inducing Salivary Gland Dysfunction, Xerostomia, and Subjective Sialorrhea” demanded further human studies to improve understanding of medication-induced salivary gland dysfunction and the underlying pathophysiology. As the population-based Study of Health in Pomerania (SHIP) database provided this opportunity, the aim of this study was to determine the prevalence of regularly consumed miscellaneous medications and potentially xerogenic medications (polypharmacy) and their associations with low saliva flow.

2 | MATERIALS AND METHODS

2.1 | Study design

Analyses are based on data from two independent cohorts of the Studies of Health in Pomerania SHIP and SHIP-Trend. Both were positively evaluated by the ethics committee of the University of Greifswald (SHIP: issued on July 31st 1995; SHIP-Trend: BB 39/08; June 19th 2008). All participants were informed about the study protocol and signed the informed consent and the privacy statement. Reporting was done in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Pooling resulted in 6069 participants for analyses (see Figure S1).

A detailed description of the study design can be found in the Appendix S1.

2.2 | Covariates and medical history

A computer-based questionnaire was used to collect information on age, sex and participant’s medical history in face-to-face interviews conducted by specially trained interviewers. Prescription and nonprescription medications taken within the 7 days prior to the interview were recorded, including homeopathic substances and dietary supplements by asking: “During the last 7 days: have you taken any medications such as tablets, drops, suppositories, or have you had any injection?” and every compound was recorded. Participants had to bring the packages or an intake plan from a physician of all medications for identification by linking the German central pharmacists number with the German drug databases and the code of the ATC Classification System. Data on the administration interval (regularly consumed/as required) were gathered for each medication.

After matching with the World Workshop on Oral Medicine VI Guide to “Medications Inducing Salivary Gland Dysfunction, Xerostomia, and Subjective Sialorrhea”, only groups with higher/moderate levels of evidence on mainly potentially xerogenic effects were identified. We defined numbers of (a) regularly consumed medication (all medications), (b) regularly consumed potentially xerogenic medications (A03, C02, C03, C07, C08, C09, N02, N05, N06, N07 and R06), (c) regularly consumed potentially xerogenic medications affecting the alimentary tract and metabolism (A03), (d) regularly consumed potentially xerogenic medications affecting the cardiovascular system (C02, C03, C07, C08 and C09), (e) regularly consumed potentially xerogenic medications affecting the nervous system (N02, N05, N06 and N07) and (f) regularly consumed potentially xerogenic medications affecting the respiratory system (R06).
2.3 | Saliva sampling and determination of saliva volume

Stimulated saliva per minute was sampled in a sitting position between 7.30 AM and 5 PM with a commercially available kit (Salivette®; Sarstedt) according to the manufacturer’s instructions.

2.4 | Statistical analysis

Continuous data were summarized as means and standard deviations (SD). For categorical variables, numbers and percentages were presented. Mann-Whitney U tests were applied to detect differences in numbers of medications or stimulated saliva volumes between two groups.

Mixed linear models (including a random intercept for study, as indicated by Likelihood ratio tests) were evaluated to estimate the effects of age, sex or the number of medications (included as fixed effects) on stimulated saliva volume (dependent variable), adjusting for the time point of saliva collection (included as fixed effect) using complete case data. The adjustment was necessary because time points of saliva collection varied markedly (between 7.30 AM and 5 PM), and saliva volume is dependent on the time of day. Effect estimates (B), 95% confidence intervals (CI) and P values were presented. Also, P values for linear trends across categories of the independent variables of interest were determined.

P < .05 was considered statistically significant. All analyses were carried out using Stata/SE 16.1 (Stata Corporation) and R 4.0.2 (www.r-project.org).

3 | RESULTS

Participant’s characteristics are provided in Table 1. The average age of the participants was 53.8 years, just under half (48%) were male, and 65% and 45% regularly took medication or potentially xerogenic medications, respectively. Stimulated saliva volume was on average 968.4 μL/min (SD 432.5).

Table 2 presents proportions of participants taking at least one potentially xerogenic medication classified according to ATC main therapeutic groups. Highest prevalences were observed among medications of the main therapeutic group C (cardiovascular system); beta-blocking agents and agents acting on the renin-angiotensin system were found in 26.0% and 30.1% of participants, respectively. Only 0.4% of participants used functional gastrointestinal disorder medications (A03).

Figure 1 shows proportions of participants taking at least one miscellaneous medication or potentially xerogenic medication stratified by age and, at the top of each graph, the mean number of medications among those taking at least one medication. Prevalences of medications, potentially xerogenic medications and potentially xerogenic medications affecting the cardiovascular system (C) were markedly greater in older age groups. This pattern was also found for medications affecting the nervous system (N), albeit much less pronounced. For instance, among 20- to 29-year-old participants, 40.4% took at least one with an average of 1.4 medications. In contrast, among 70- to 79-year-old participants, 90.5% took at least one medication with an average of 5.0 medications; out of these, 2.9 medications belonged to miscellaneous ATC codes, 1.8 medications were potentially xerogenic affecting the cardiovascular system, and 0.2 medications were potentially xerogenic affecting the nervous system (Figure S2).

Data on mean numbers of medications or potentially xerogenic medications by sex are summarized in Table S1. Average numbers of all medications, potentially xerogenic medications and potentially xerogenic cardiovascular medications were significantly higher in males than in females, whereas females were prescribed a higher number of potentially xerogenic medications impacting the nervous system than were males.

Mean stimulated saliva volumes by age and sex are shown in Table 3. Unadjusted mean stimulated saliva volumes varied widely

| TABLE 1 | Characteristic of participants of the pooled sample (SHIP-2 and SHIP-Trend-0) |
|----------|-------------------------------------------------------------------|
|          | Analyses involving medication data only | Analyses involving salivary flow data |
| Number of participants | 6753 | 6069 |
| Age [years] | 53.8 ± 15.1 | 53.4 ± 14.9 |
|            | 54 (42; 66) | 54 (42; 65) |
| Sex        | | |
| Female     | 3510 (52.0) | 3119 (51.4) |
| Male       | 3243 (48.0) | 2950 (48.6) |
| Regularly consumed medication [yes] | 4382 (64.9) | 3909 (64.4) |
| Number of regularly consumed medications | 2.2 ± 2.6 | 2.2 ± 2.6 |
|            | 1 (0; 3) | 1 (0; 3) |
| Regularly consumed potentially xerogenic medication* [yes] | 3036 (45.0) | 2663 (43.9) |
| Number of regularly consumed potentially xerogenic medications* | 0.9 ± 1.3 | 0.9 ± 1.3 |
|            | 0 (0; 2) | 0 (0; 2) |
| Saliva volume [μL/min] | — | 968.4 ± 432.5 |
| Time of the day when saliva was collected | | |
| 7-9 AM | 1350 (22.2%) |
| 9-11 AM | 2366 (39.0%) |
| 11 AM-1 PM | 1602 (26.4%) |
| 1-3 PM | 687 (11.3%) |
| 3-5 PM | 64 (1.1%) |

Note: Data are presented as mean ± standard deviation and median (25%; 75% quantile) or numbers (percentages). *Includes the following main therapeutic groups according to the ATC Classification System: A03, C02, C03, C07, C08, C09, N02, N05, N06, N07 and R06.
### DISCUSSION

Using data from two cohorts of the prospective SHIP (including 6753 Caucasian subjects in total), we showed that, firstly, average saliva volumes were lower with more medications. Secondly, potentially xerogenic medications, especially those with effects on the cardiovascular or the nervous system, were associated with lower saliva volumes. Thirdly, males more frequently took potentially xerogenic medications affecting the cardiovascular system, while females more often took potentially xerogenic medication affecting the nervous system.

A strength of this study is the use of strict protocols to collect data. Medical history data were collected with high accuracy. A computer-based questionnaire was used to determine medication, and in addition, participants had to bring the packages or an intake plan from a physician of all medications to gain further information. Also, saliva sampling and preparation were conducted according to a strict protocol, thereby minimizing any methodological biases. The spitting method of saliva collection, as used in this study, is the most reproducible and effective method even when chewing length (stimulation) is as much as 2 minutes.25

This study also has some limitations. Firstly, we determined salivary gland hypofunction as measured by stimulated saliva volumes per minute. Information on xerostomia (eg, acquired with the Simplified Xerostomia Index26) was not gathered. Secondly, including only Caucasians clearly narrows the generalizability of the study; however, it reflects the composition of the region's ethnicity. Thirdly, no information on dosages or treatment periods were collected, and no serum levels of different medications (in order to check whether patients take their medication as prescribed) were determined. The latter is important because of different pharmacokinetics. It is known that intake compliance is usually poor.27 Polypharmacy patients often feel they are taking unnecessary medications.28

Fourthly, medication consumption was classified as regularly or irregular (as needed) using self-reports, which is a further limitation. Finally, in addition to multiple medications, a range of medical conditions, including autoimmune diseases (ie, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and progressive systemic sclerosis29,30) and radiotherapy for head and neck cancer treatment,31 can reduce saliva secretion. As prevalences of these conditions are very low, effects on associations might be negligible.

In this study, 64.9% of participants regularly consumed medication from all ATC groups. Forty-one percent took at least one medication affecting the cardiovascular system. In a Swedish study based on prescribed medications, 4.2 million Swedes needed at least one medication, equaling a prevalence of 67.4%,32 which is in accordance with presented data. A German study, including over-the-counter medication such as dietary supplements, documented a prevalence of 75.3%.33

Advanced age is associated with disease and consequently with increased medication intake.34,35 This finding was also observed in the current study; prevalence of regularly consumed medication was 40.4% and 90.5% in 20-29- and 70- to 79-year-olds, respectively; average numbers of regularly consumed medication in those taking

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| TABLE 2 | Overview on the prevalence of regularly consumed potentially xerogenic medications classified according to the anatomical main group and the main therapeutic group of the ATC Classification System (N = 6753) |
|----------|---------------------------------------------------------------|
| **Anatomical main group** | **Main therapeutic group** | **N (%)** |
| Alimentary tract and metabolism (A) | A03- Drugs for functional gastrointestinal disorders | 33 (0.4) |
| Cardiovascular system (C) | CO2- Antihypertensives | 91 (1.4) |
|  | CO3- Diuretics | 515 (7.6) |
|  | CO7- Beta blocking agents | 1755 (26.0) |
|  | CO8- Calcium channel blockers | 555 (8.2) |
|  | CO9- Agents acting on the renin-angiotensin system | 2023 (30.1) |
|  | Total (C02, C03, C07, C08, C09) | 2750 (40.7) |
| Nervous system (N) | N02- Analgesics | 219 (3.2) |
|  | N05- Psycholeptics | 142 (2.1) |
|  | N06- Psychoanaleptics | 419 (6.2) |
|  | N07- other nervous system drugs | 60 (0.9) |
|  | Total (N02, N05, N06, N07) | 723 (10.7) |
| Respiratory system (R) | R06- Antihistamines for systemic use | 48 (0.7) |

Note: Data are presented as numbers (percentages).
FiguRe 1  Prevalence for intake of at least one regularly consumed medication for (A) all medications, (B) potentially xerogenic medications, (C) potentially xerogenic medications affecting the cardiovascular system, and (D) potentially xerogenic medications affecting the nervous system by age (N = 6753). In addition, mean numbers of medications among those taking at least one medication are provided at the top of each graph.

TABLE 3 Mean stimulated saliva volume by age and results from the linear mixed model (N = 6069)

| Age [years] | N (%)  | Stimulated saliva volume [µL/min] | Results from the linear mixed model |
|------------|--------|----------------------------------|-------------------------------------|
|             |        |                                  | B (95% CI)                      | P value |
| 20-29       | 351 (5.8) | 965.7 ± 447.4 | Ref. | |
| 30-39       | 863 (14.2) | 975.8 ± 416.6 | -61.0 (-146.0; 24.1) | .16 |
| 40-49       | 1271 (20.9) | 962.9 ± 434.6 | -57.6 (-134.5; 19.2) | .14 |
| 50-59       | 1326 (21.9) | 977.7 ± 449.2 | -74.5 (-149.4; 0.3) | .051 |
| 60-69       | 1265 (20.8) | 963.9 ± 420.1 | -60.5 (-135.2; 14.2) | .11 |
| 70-79       | 848 (14.0) | 943.5 ± 425.9 | -84.2 (-158.7; -9.7) | .027 |
| 80-93       | 145 (2.4) | 1079.3 ± 447.1 | -112.1 (-188.3; -36.0) | .004 |

Sex
|        |        |                                  |                                |
|--------|--------|----------------------------------|--------------------------------|
| Female | 3119 (51.4) | 959.1 ± 431.9 | Ref.                             |
| Male   | 2950 (48.6) | 978.2 ± 433.0 | 23.7 (2.0; 45.5)                |

Note: Data are presented as numbers (percentages) or mean ± standard deviation. Standard deviations were corrected for clustering of participants within studies.

Abbreviations: B, linear regression coefficient; CI, confidence interval.

*aDerived from linear mixed model adjusted for time point of saliva collection.
at least one medication were 1.4 and 5.0, respectively. Thirty-seven percent of 70- to 79-year-olds used 2-4 medications and 47% took ≥5 medications regularly. However, our study did not distinguish between polypharmacy and hyperpolypharmacy. In the Swedish registry, the number of dispensed medications was significantly related to age, with 2 medications (median) among the 20- to 29-year-olds and 7 medications (median) among the 70- to 79-year-olds, which are slightly higher than those in SHIP. In a Dutch study, 37% of the older adults (≥65 years) took 2 to 5 medications, and 4% were prescribed >5 medications in the year 1997. Given potentially xerogenic medications might promote hyposalivation, it is important to consider the association between ageing and multimorbidity and polypharmacy and hyperpolypharmacy given the rising numbers of older people and ageing populations.

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**TABLE 4** Mean stimulated saliva volume by the number of regularly consumed medication and by regularly consumed potential xerogenic medication (no potentially xerogenic medication versus at least one medication of the specified type) as classified by their main therapeutic group

| Number of regularly consumed medications | N (%) | Stimulated saliva volume [µL/min] | Linear mixed model | P value<sup>a</sup> |
|-----------------------------------------|-------|----------------------------------|--------------------|-----------------|
| **All medications**                     |       |                                  |                    |                 |
| 0                                       | 2160 (35.6) | 983.4 ± 443.4 | Ref.               |                 |
| 1-2                                     | 1902 (31.3) | 964.5 ± 425.2 | −17.6 (~44.9; 9.8) | .21             |
| ≥3                                      | 2007 (33.1) | 956.0 ± 427.1 | −36.4 (~67.0; −5.9) | .02             |
| **Potentially xerogenic medications (A03, C02, C03, C07, C08, C09, N02, N05, N06, N07, R06)** |       |                                  |                    |                 |
| 0                                       | 3406 (56.1) | 983.0 ± 437.4 | Ref.               |                 |
| 1-2                                     | 1942 (32.0) | 955.5 ± 420.1 | −37.5 (~64.1; −11.0) | .006            |
| ≥3                                      | 721 (11.9)  | 934.2 ± 439.4 | −66.8 (~105.0; −28.6) | .001            |
| **Potentially xerogenic medications affecting the cardiovascular system (C02, C03, C07, C08, C09)** |       |                                  |                    |                 |
| 0                                       | 3662 (60.3) | 981.7 ± 437.9 | Ref.               |                 |
| 1-2                                     | 1879 (31.0) | 952.0 ± 417.9 | −41.3 (~68.2; −14.4) | .003            |
| ≥3                                      | 528 (8.7)   | 934.5 ± 442.8 | −65.2 (~108.1; −22.3) | .003            |
| **Potentially xerogenic medications affecting the nervous system (N02, N05, N06, N07)** |       |                                  |                    |                 |
| 0                                       | 5442 (89.7) | 974.0 ± 431.2 | Ref.               |                 |
| 1-2                                     | 591 (9.7)   | 927.3 ± 446.6 | −52.0 (~89.2; −14.9) | .006            |
| ≥3                                      | 36 (0.6)    | 792.7 ± 314.2 | −190.9 (~331.9; −49.8) | .008            |
| **Medication classified by its main therapeutic group (excluding intake of medication from all other main therapeutic groups)** |       |                                  |                    |                 |
| Only C07                                 |       |                                  |                    |                 |
| 0                                       | 3406 (90.1) | 983.0 ± 437.4 | Ref.               | .004            |
| ≥1                                      | 375 (9.9)   | 924.5 ± 410.4 | −70.7 (~118.4; −23.1) | .58             |
| Only C09                                 |       |                                  |                    |                 |
| 0                                       | 3406 (87.3) | 983.0 ± 437.4 | Ref.               | .58             |
| ≥1                                      | 496 (12.7)  | 976.8 ± 411.8 | −12.1 (~55.0; 30.7) |                 |
| Only N06                                 |       |                                  |                    |                 |
| 0                                       | 3406 (96.6) | 983.0 ± 437.4 | Ref.               | .12             |
| ≥1                                      | 120 (3.4)   | 931.9 ± 426.9 | −62.7 (~142.3; 16.9) |                 |

Note: Linear mixed models evaluated associations of the number of regularly consumed medications and stimulated saliva volume. Data are presented as numbers (percentages) or means ± standard deviations. P values were derived from linear mixed models, adjusted for age, sex, and time point of saliva collection.

Abbreviations: B, linear regression coefficient; CI, confidence interval.

<sup>a</sup> P for differences compared to the references group.; <sup>b</sup> P for trend across categories.
sex-specific distributions of certain main therapeutic groups, our study showed that men more frequently were prescribed potentially xerogenic medication affecting the cardiovascular system than were women, while women more frequently took xerogenic medication affecting the nervous system. Interestingly, a Danish study reported comparable results.\textsuperscript{23} Sex-specific differences in medication use might indeed be restricted to certain main therapeutic groups. In Germany, cardiovascular diseases in women are diagnosed only half as often as in men,\textsuperscript{37} while women suffer from depression (eg, due to double burden of family/work and violence) nearly twice as often as men.\textsuperscript{38}

Current literature suggests that polypharmacy might be associated with lower salivary flow rates,\textsuperscript{22,39-42} even when distinguishing between poly- and hyperpolymedication.\textsuperscript{22} Although the values in the present study were within the range of normal stimulated saliva volumes, a high number of regularly consumed medications, potentially xerogenic medications, and those affecting the cardiovascular or the nervous system was significantly associated with lower stimulated saliva volumes. Only for beta-blocking agents (C07) medication intake was statistically significantly associated with lower saliva volumes (Δ70.7 µL/min). For agents acting on the renin-angiotensin system (C09) and psychoanalectics (N06), the sample size was too small to detect an association with saliva volumes, although regression coefficients indicated lower saliva volumes on average for participants with medication intake (Δ12.1 µL/min and Δ62.7 µL/min, respectively). These results are in agreement with other studies on cardiovascular medication,\textsuperscript{39} with special focus on beta-blocking agents (C07).\textsuperscript{40} Neurologic diseases and their pharmacologic treatment could result in hyposalivation and xerostomia, as they centrally block the inner-brain salivation centre.\textsuperscript{41,42} Psycholeptics (N05) and psychoanalectics (N06) block certain receptors\textsuperscript{43} and inhibit salivation. However mental pressure, depression and anxiety disorders are physiologically associated with hyposalivation, even without medication.\textsuperscript{29} Smidt et al (2010)\textsuperscript{23} found that stimulated salivary flow rates were lower in participants taking antidepressants (N05; primarily citalopram), cardiac agents (C01; mostly digitalis glycosides, digoxin) and calcium-channel blockers (C08; especially verapamil). Interestingly, unstimulated saliva flow was only reduced in psychoanalectics (N06).

Although certain ATC groups have been identified as being associated with lower saliva volumes, it remains to be clarified whether certain combinations of medication potentiate the effects on saliva volumes and therefore the limit clinical relevance of the present study. For example, using data from long-term hospital stays, stimulated parotid flow was lower among men taking combinations of tricyclic antidepressants (N06) and diuretics (C03).\textsuperscript{44} In this context, long-term effects of certain combinations of xerogenic medications on saliva volumes might be evaluated using prospective follow-up data from this cohort.

To conclude, polypharmacy is common in the older population. Higher consumption of medications, in general, but also intake of potentially ‘xerogenic’ medications from specific main therapeutic groups (eg, affecting the cardiovascular or the nervous system) are potentially associated with lower stimulated saliva volumes, thereby constituting a relevant oral health problem.

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**CONFLICT OF INTEREST**

The authors do not report any known competing financial interests or personal relationships that could have appeared to influence the work of this reported study.

**AUTHOR CONTRIBUTIONS**

OL contributed to interpretation of data and drafting the article. BH contributed to conception and design, analysis and interpretation of data, and drafting the article. CP contributed to analysis of data and critically revised the article for important intellectual content. SS contributed to acquisition of data and critically revised the article for important intellectual content. HV contributed to acquisition of data and critically revised the article for important intellectual content. TK contributed to conception and design and acquisition of data and critically revised the article for important intellectual content. All authors gave their final approval of the version to be published.

**DATA AVAILABILITY STATEMENT**

Data from SHIP are available after data application and signature of a data transfer agreement. The data dictionary and the online application form are available at: fvcm.med.uni-greifswald.de/dd_service/data_use_intro.php. Involving a local collaborative partner to facilitate the application process is recommended.

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