

Association Between Male Menopause Severity and Presenteeism: A Cross-sectional Study

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Funding Sources:

This study is supported by the research grant from Japanese Ministry of Health, Labour, and Welfare (22FB1001).

Conflicts of interest statement:

Dr. Fujino has the copyright to WFun with royalties paid from Sompo Health Support Inc., outside from this work. The other authors declare no conflicts of interest associated with this manuscript.

Acknowledgements:

1. Sources of Support

This study is supported by the research grant from Japanese Ministry of Health, Labour, and Welfare (22FB1001).

2. Author Contributions

HB: writing – original draft, formal analysis

MO: writing - data analysis advice, review, and editing

SY: writing – review and editing

ST, SH, and TY: writing – review, editing, and funding acquisition

YF writing – data analysis advice, review, editing, and supervision

3. Data Availability

Data are available from the authors on reasonable request.

4. EQUATER Network Reporting Guidelines (STROBE)

We adhered to the STROBE Guidelines as in the Supplementary Digital Content (SDC).

5. AI detailed statements as fully described in the AI section

No single sentence or ideas were derived from generative AI. We used ChatGPT (OpenAI, San Francisco, California, United States), only to enhance this paper's English quality, followed by checks from the authors and a professional English editing company.

Ethical Considerations & Disclosures:

Ethical approval: This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (Approval number: R4-008)

Informed Consent: N/A

Registry and the Registration No. Of the study: N/A

Animal Studies: N/A

ACCEPTED

Abstract

Objective: This study explored the association between symptoms of male menopause and presenteeism among middle-aged men in Japan.

Methods: We conducted a cross-sectional survey among 3,795 men aged 40 to 59 years who were in current employment in Japan. Male menopause symptoms were assessed using the Aging Male Symptoms (AMS) scale. Presenteeism was measured with the Work Functioning Impairment Scale (WFun). Poisson regression analysis was conducted.

Results: The prevalence of presenteeism increased with increasing total AMS scale score (p for trend <0.001). Severe AMS scale group showed prevalence ratio of 11.81 (95% confidence interval: 9.45-14.74) compared to no symptoms group. Each subscale demonstrated a dose-response relationship when evaluated independently.

Conclusions: We identified a strong association between male menopause symptoms and presenteeism. Addressing these symptoms, particularly the psychological and physical symptoms, in the workplace could reduce presenteeism.

Keywords: male menopause symptoms, presenteeism, occupational health, Japan, workers' health

Learning Outcomes

After completing this educational activity, the learner will be better able to:

- Comprehend the condition of male menopause symptoms.
- Discuss the impact of male menopause on presenteeism.
- Acknowledge the significance of addressing male menopause within the context of presenteeism.

ACCEPTED

Introduction

Male menopause, also known as andropause, is a condition characterized by various physical and mental disturbances that typically occur in middle-aged and older men¹. The prevalence of male menopause is reported to be 1.5% among men in their 40s and 1.7% among men in their 50s². The onset of male menopause is associated with factors such as aging, stress, and a decline in the secretion of male hormones³. This condition can affect men physically, mentally, and sexually⁴. Physical symptoms include fatigue, hot flashes, dizziness, headaches, and muscle pain. Mental symptoms include depressive mood, reduced concentration, insomnia, anxiety, and cognitive impairment. Sexual symptoms include decreased libido and erectile dysfunction. These male menopause-induced symptoms have been reported to lower quality of life⁵.

In recent years, attention has been drawn to the impact of male menopause on work performance. Middle age is a critical period in a worker's career, and physical and mental disturbances during this time can hinder work. This paper will discuss the disruptions caused by male menopause symptoms, focusing on physical, mental, and sexual aspects. Physical symptoms, such as decreased muscle strength and muscle pain, characteristic of male menopause, can directly affect work efficiency by making previously manageable tasks difficult. Mental symptoms, such as depressive mood, can impact work motivation, and reduced concentration can directly affect productivity. Additionally, irritability can strain interpersonal relationships. Sexual symptoms, explained by a decrease in testosterone, are also significant as testosterone is associated with vitality, and a decrease can lead to reduced vitality and sexual dysfunction⁶.

Through these symptoms, male menopause has the potential to influence work participation, work function, and overall work performance. Working while experiencing health

issues is referred to as presenteeism⁷. Major symptoms leading to presenteeism include pain, mental health issues, and sleep problems, all of which are associated with male menopause⁸⁻¹⁰. Presenteeism is detrimental to both individual workers and organizations. Workers experiencing presenteeism are more likely to delay treatment, experience symptom exacerbation, and face mismatches between health and job demands, leading to reduced working hours and changes in job duties. These factors ultimately increase the risk of taking leave or becoming unemployed. For organizations, employee presenteeism can result in decreased productivity, deteriorating workplace morale, and a decline in organizational discipline.

However, the actual status of male menopause in working men and the extent to which it affects work, including presenteeism, remain largely unknown. Male menopause often goes undiagnosed because its symptoms are subtle and men may not perceive the need for medical consultation. Patients may visit different specialists, such as psychiatrists or endocrinologists, under different diagnoses due to the diverse range of symptoms. For example, given the known association between the severity of male menopause and depression, men may consult psychiatrists for depression when they are actually experiencing male menopause¹¹. Additionally, the inclusion of sexual symptoms makes it difficult for men to seek medical advice, posing a barrier to hospital visits. Moreover, sexual dysfunction has not been widely recognized as a health issue that should be addressed in occupational health strategies.

The critical importance of research on male menopause among Japanese workers is highlighted by the aging of Japan's workforce. About 55% of Japan's labor force is male, and approximately 55.8% of this population is aged 45 and above¹². Elucidating the impact of male menopause on presenteeism among this significant portion of the workforce is socially important.

However, research clarifying this relationship is lacking.

The purpose of this study was to investigate the relationship between the symptoms of male menopause and presenteeism and to clarify the connection between them.

Methods

Study Design and Participants

This study was conducted under a cross-sectional design which targeted middle-aged men in Japan using an online self-administered questionnaire. An internet marketing company, Cross Marketing Inc. (Tokyo, Japan), was contracted to send invitation emails to panel monitors registered with the company. Eligibility criteria included men aged 40 to 59 years who were in current employment. The survey was conducted in September 2022. Participation was solicited until a total of 4,000 responses were obtained. After exclusion of 205 invitees who declined participation, the remaining 3,795 were included in the analysis. This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (Approval number: R4-008). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cross-sectional studies was used to prepare this report (see Table, Supplemental Digital Content 1, which is a STROBE checklist of this report, <http://links.lww.com/JOM/B786>).

Assessment of Male Menopause Symptoms

Male menopause symptoms were evaluated using the Aging Males' Symptoms (AMS)

scale⁴. AMS scale is a 17-item self-administered questionnaire designed to assess symptoms related to male menopause⁴. It includes three subscales: psychological symptoms, somatic symptoms, and sexual function. The AMS scale has been translated into multiple languages and is widely used internationally as a reliable assessment tool. Its validity has been thoroughly established, making it valuable for cross-cultural symptom comparisons¹³. Based on the total score, menopause symptoms were classified as none (17-26), mild (27-36), moderate (37-49), and severe (≥ 50). Additionally, the severity classification for the three subscales (psychological, somatic, and sexual symptoms) was based on Heinemann's criteria, namely psychological: none (≤ 5), mild (6-8), moderate (9-12), and severe (≥ 13); somatic: none (≤ 8), mild (9-12), moderate (13-18), and severe (≥ 19); and sexual, none (≤ 5), mild (6-7), moderate (8-10), and severe (≥ 11).

Assessment of Presenteeism

Presenteeism was assessed using the Work Functioning Impairment Scale (WFun)¹⁴. WFun comprises seven items, such as "I could not work carefully," and is a validated and reliable measure of work functioning impairment developed in accordance with COSMIN guidelines. This tool provides a straightforward and reliable method for evaluating presenteeism, with well-established validity¹⁵. The total WFun score ranges from 7 to 35; in this study, participants with a score of 21 or higher, indicating moderate to severe work functioning impairment, were considered to have presenteeism^{16,17}.

Potential Confounding Variables

Data were collected on potential confounding variables, including age, education (junior high or high school graduate, vocational school or junior college graduate, university or graduate

school graduate), marital status (married, divorced or widowed, single), income (less than 4,000,000; 4,000,000-6,000,000; 6,000,000-8,000,000; 8,000,000 or more Japanese yen), job type (mainly desk work, jobs mainly involving interpersonal communication, mainly physical work), company size (1 as self-employed, 2-49, 50-499, 500-4999, 5000 or more), and history of treatment for male menopause (current, past, never).

Statistical Analysis

There was no missing values as the survey used an internet-based response system which did not allow missing values. The prevalence ratios (PR) and 95% confidence intervals (CI) for presenteeism were calculated using Poisson regression analysis with robust variance for each severity classification of the total AMS score and subscales. Both univariable and multivariable models were constructed. The multivariable model adjusted for age, education, marital status, income, job type, company size, and history of treatment for male menopause. In preliminary analyses, each AMS subscale was further adjusted for the scores of the other AMS subscales in the multivariable model. Stata 18 (Stata Statistical Software: Release 18.0; StataCorp LLC, TX) was used for analysis, with significance level set at $p < 0.05$.

Results

Table 1 presents the basic characteristics of participants according to total AMS scale score. Age distribution was relatively even across the sample. Participants with severe male menopausal symptoms were more likely to belong to small and medium-sized enterprises and tended to have lower incomes.

Table 2 illustrates the relationship between total AMS scale scores, subscale scores, and the severity of symptoms of presenteeism. In the group with severe total AMS scores, the PR for presenteeism was 11.81 (95% CI: 9.45-14.74) compared to the group with no symptoms. The PR for presenteeism increased with higher AMS scores (p for trend <0.001). Each AMS subscale showed a dose-response relationship with presenteeism (p for trend <0.001). In the analysis, the group with high psychological symptom scores had a significantly PR for presenteeism, at 17.74 (95% CI: 12.99-24.22), compared to those with lower scores. Similarly, individuals with high somatic symptom scores had an PR for presenteeism of 11.36 (95% CI: 8.34-15.48) compared to those with lower scores. Furthermore, the group with elevated sexual symptom scores had an PR for presenteeism of 6.19 (95% CI: 4.77-8.02) compared to those with lower scores.

Discussion

In this cross-sectional study, we evaluated the relationship between the severity of male menopause symptoms as measured by the AMS scale and presenteeism. The total AMS scale score and the severity of each subscale were significantly associated with moderate or higher work functioning impairment, defined as presenteeism. A dose-response relationship was observed, with higher severity correlating with higher incidence rate ratios of presenteeism. To our knowledge, this study is the first to investigate the association between male menopause symptoms and presenteeism.

This study confirmed a robust association between menopausal symptoms and work functioning impairment. A dose-response relationship was observed between the AMS scale and work functioning impairment. Compared to the group with "no symptoms" as evaluated by the AMS scale, the group with "severe symptoms" had an adjusted PR for presenteeism of 11,

indicating a strong association. Moreover, as the severity of psychological, somatic, and sexual components of the AMS scale increased, the PR of presenteeism also increased.

The results of this study indicate that the psychological aspects of male menopause significantly affect presenteeism. Mental health symptoms such as depression, insomnia, irritability, and reduced motivation associated with male menopause are closely linked to presenteeism. These mental health issues, particularly insomnia and irritability related to depressive symptoms, are known to correlate with presenteeism¹⁸. One cause of these psychological symptoms during male menopause is the decline in testosterone secretion. Testosterone, produced by Leydig cells in the testes, decreases with age as the number of Leydig cells declines. Additionally, the secretion of GnRH in the hypothalamus also decreases with age, further reducing testosterone levels. Although the exact mechanism by which decreased testosterone leads to depressive symptoms is not fully understood, studies have shown that lower testosterone levels are associated with higher incidences of depressive symptoms^{19,20}. For instance, individuals with low testosterone levels are approximately three times more likely to be diagnosed with depression compared to those with normal levels²¹. Furthermore, higher testosterone levels are associated with a stronger sense of fairness and increased social contribution^{22,23}. The decline in testosterone in middle-aged and older men may lead to a reduction in the sense of fairness and social contribution, resulting in decreased motivation. From a societal perspective, this decline in productivity can contribute to presenteeism.

The physical symptoms of male menopause significantly impact presenteeism. Male menopause encompasses a variety of physical symptoms, including fatigue, decreased muscle strength, muscle pain, headaches, dizziness, tinnitus, and frequent urination. Many of these

symptoms can directly influence presenteeism. For example, fatigue can lead to insufficient performance in physically demanding tasks, while decreased muscle strength and muscle pain can impair the ability to perform tasks that require heavy lifting or significant physical movement. Hot flashes and sweating can reduce work efficiency, leading to presenteeism. Additionally, symptoms such as headache, dizziness, and tinnitus can decrease concentration, contributing to presenteeism. Frequent urination necessitates multiple breaks from work, further impacting presenteeism. Studies on physical symptoms and presenteeism have reported that conditions like headaches and lower back pain affect presenteeism^{8,24}. Given the diverse range of physical symptoms associated with male menopause, it is reasonably assumed that the impact of these symptoms on presenteeism is substantial.

Sexual factors may be linked to presenteeism through both physical and psychological components. Sexual dysfunction in male menopause is influenced by biological and socio-psychological factors, particularly the decline in testosterone secretion associated with reduced gonadal function. The decrease in testosterone affects both physical and psychological symptoms. Although not directly shown in the results, sexual factors measured by the AMS were associated with work functioning impairment when adjusted for age. However, when further adjusted for physical and psychological factors, the significance of the association between sexual factors and work functioning impairment disappeared. This suggests that the relationship between sexual factors and work functioning impairment is mediated by psychological and physical factors.

We propose that the results of this study have two significant implications. First,

addressing male menopause in working men can potentially improve presenteeism and contribute to increased workplace productivity. Despite its importance, addressing male menopause in the workplace has largely been overlooked. Although 15-20% of men score moderate or higher on the AMS scale for male menopause, only 0.13% seek medical consultation²⁵. Testosterone replacement therapy is effective for male menopause, so workplace screening for symptoms and proactive encouragement for medical consultation would be beneficial. Second, this study provides a rationale for implementing measures to address male menopause in the workplace. Gonadal dysfunction, a hallmark of male menopause, manifests in symptoms such as loss of early morning erections, erectile dysfunction, decreased libido, and fatigue.³ These symptoms significantly impact men's quality of life but have been rarely considered in workplace health management. However, the association between sexual symptoms of male menopause and work functioning impairment supports the need for more proactive management of male menopause in the workplace. A considerable proportion of men over 40 who experience male menopause are key personnel in their workplace, and maintaining their health is desirable from a productivity standpoint for companies.

This study has several limitations. First, as the survey was conducted online, it may not be representative of the entire Japanese workforce. Therefore, the prevalence rates of male menopause symptoms and presenteeism in this study may differ from those of the general working population. However, the observed relationship between the severity of male menopause symptoms and presenteeism within the sample is likely to be maintained unless there is some special sampling that biases this relationship, and to the best of our knowledge, the study has no such special situation. Second, this study used the AMS scale to evaluate male menopause symptoms. Although the AMS scale has been validated as a tool for the screening of male

menopause symptoms, actual diagnosis of male menopause requires the measurement of testosterone levels. Third, there may be unmeasured confounding factors, such as job position, workplace stress, and workplace accommodations. The size and direction of the bias caused by these factors is uncertain.

Conclusion

The study suggests a significant association between the severity of male menopause symptoms and presenteeism. Male menopause is a condition with low awareness which is challenging for affected individuals to recognize, and consideration from those around them is often lacking. Increasing awareness and creation of an environment in which male menopause is acknowledged and accommodated may help improve presenteeism. To support workers experiencing male menopause, it is crucial to promote understanding of this condition, encourage medical consultation and self-care, and develop workplace awareness and support measures.

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Table 1. Participants' demographic and sociological characteristics

	Aging Male Symptoms scale score				
	Total	Low (17-26)	Middle (27-36)	High (37-49)	Very high (50-85)
	n=3,795 n (%)	n=1,798 n (%)	n=876 n (%)	n=639 n (%)	n=482 n (%)
Age, years, median (IQR)	50 (46-55)	49 (45-54)	50 (46-55)	50 (46-55)	49 (46-55)
Education					
Junior high or high school	1,044 (27.5)	480 (26.7)	226 (25.8)	194 (30.4)	144 (29.9)
Vocational school, junior college, or technical college	577 (15.2)	264 (14.7)	135 (15.4)	101 (15.8)	77 (16.0)
University or graduate school	2,174 (57.3)	1,054 (58.6)	515 (58.8)	344 (53.8)	261 (54.1)
Marital status					
Married	2,368 (62.4)	1,135 (63.1)	558 (63.7)	404 (63.2)	271 (56.2)
Divorced or bereaved	286 (7.5)	124 (6.9)	59 (6.7)	55 (8.6)	48 (10.0)
Never married	1,141 (30.1)	539 (30.0)	259 (29.6)	180 (28.2)	163 (33.8)
Annual income (Japanese Yen)					
<4000000	1,144 (30.1)	484 (26.9)	256 (29.2)	201 (31.5)	203 (42.1)
4000000-6000000	1,024 (27.0)	468 (26.0)	231 (26.4)	190 (29.7)	135 (28.0)
6000000-8000000	794 (20.9)	379 (21.1)	204 (23.3)	128 (20.0)	83 (17.2)
>8000000	833 (21.9)	467 (26.0)	185 (21.1)	120 (18.8)	61 (12.7)
Job type					
Mainly desk work	1,898 (50.0)	936 (52.1)	419 (47.8)	313 (49.0)	230 (47.7)
Jobs mainly involving interpersonal communication	803 (21.2)	374 (20.8)	201 (22.9)	142 (22.2)	86 (17.8)
Mainly physical work	1,094 (28.8)	488 (27.1)	256 (29.2)	184 (28.8)	166 (34.4)
Number of employees					
1	350 (9.2)	176 (9.8)	69 (7.9)	51 (8.0)	54 (11.2)
2-49	937 (24.7)	421 (23.4)	218 (24.9)	172 (26.9)	126 (26.1)
50-499	1,025 (27.0)	475 (26.4)	251 (28.7)	176 (27.5)	123 (25.5)
500-4999	832 (21.9)	385 (21.4)	177 (20.2)	155 (24.3)	115 (23.9)
≥5000	651 (17.2)	341 (19.0)	161 (18.4)	85 (13.3)	64 (13.3)
Experience of treatment of male's menopausal disorders					
Current	83 (2.2)	18 (1.0)	16 (1.8)	22 (3.4)	27 (5.6)
Past	78 (2.1)	14 (0.8)	9 (1.0)	28 (4.4)	27 (5.6)
Never	3,634 (95.8)	1,766 (98.2)	851 (97.1)	589 (92.2)	428 (88.8)

Table 2. Association between Aging Male Symptoms Score in working male and work functioning impairment

	Total		WFun ≥ 21		Model 1			Model 2			
	n	%	Prevalence ratio	95% Confidence Interval	p	Prevalence ratio	95% Confidence Interval	p			
Aging Male Symptoms Score (AMS)											
17-26	1798	5	reference		< 0.001 †	reference		< 0.001 †			
27-36	876	14	3.04	2.34 3.96	< 0.001	3.09	2.38 4.01	< 0.001			
37-49	639	37	7.81	6.20 9.84	< 0.001	7.83	6.22 9.86	< 0.001			
50-85	482	56	11.81	9.45 14.74	< 0.001	11.81	9.43 14.80	< 0.001			
Subscales of AMS											
Psychological score											
5	1412	3	reference		< 0.001 †	reference		< 0.001 †			
6-8	728	10	3.45	2.41 4.93	< 0.001	3.49	2.45 4.98	< 0.001			
9-12	784	28	9.64	6.97 13.34	< 0.001	9.61	6.96 13.28	< 0.001			
13-25	871	52	18.02	13.22 24.55	< 0.001	17.74	12.99 24.22	< 0.001			

Somatic score

7-8	981	4	reference				< 0.001 †				< 0.001 †
9-12	1087	8	1.80	1.25	2.60		0.002	1.85	1.28	2.65	0.001
13-18	883	25	5.89	4.28	8.03		< 0.001	5.98	4.36	8.22	< 0.001
19-35	844	48	11.40	8.37	15.54		< 0.001	11.36	8.34	15.48	< 0.001

Sexual score

5	1029	6	reference				< 0.001 †				< 0.001 †
6-7	1175	8	1.40	0.97	2.02		< 0.001	1.43	1.00	2.06	0.051
8-10	658	17	2.93	2.19	3.92		< 0.001	3.08	2.31	4.11	< 0.001
11-25	933	35	6.17	4.77	7.99		< 0.001	6.19	4.77	8.02	< 0.001

Model 1: univariable model

Model 2: adjusted for age, education, job type, income, company size, treatment for LOH

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/	8*	For each variable of interest, give sources of data and details of	6

measurement		methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	N.A
		(c) Explain how missing data were addressed	N.A
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A
		(e) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N.A
		(c) Consider use of a flow diagram	N.A

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N.A
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(b) Report category boundaries when continuous variables were categorized	7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	8-10

similar studies, and other relevant evidence

Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
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Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

The severity of male menopause symptoms is associated with presenteeism

The study explored the association between symptoms of male menopause and presenteeism among middle-aged men.



The prevalence of presenteeism increased with increasing severity of male menopause.



The study highlights a strong association between symptoms of male menopause and presenteeism, emphasizing the need for greater awareness and workplace support to enhance the performance of affected workers.



Association Between Male Menopause Severity and Presenteeism: A Cross-sectional Study

Hiroki Beppu, MD; Makoto Okawara, MD, PhD; Satoshi Yamashita, MD, PhD; Seiichiro Tateishi, MD, PhD; Shigeo Horie, MD, PhD; Toshiyuki Yasui, MD, PhD; Yoshihisa Fujino, MD, MPH, PhD



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