



Caregiver Burden and Work Productivity Among Japanese Working Family Caregivers of People with Dementia

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Abstract

Background We examined the association between caregiver burden and work productivity (i.e., absenteeism, presenteeism, and overall work impairment) among working family caregivers of people with dementia and whether job characteristics (i.e., job demands, job control, supervisor and coworker support) moderate this association.

Methods A cross-sectional correlational study design using a web-based questionnaire survey was conducted among 379 Japanese working family caregivers of people with dementia (105 female, age range 20–77) in May 2016, which measured caregiver burden, work productivity, care situation, job characteristics, and demographics. Caregiver burden was designated as an independent variable and each aspect of work productivity as a dependent variable in a hierarchical multiple regression analysis, adjusting for demographics. Interaction terms between caregiver burden and each job characteristic were also included in the model.

Results Caregiver burden was significantly and positively associated with presenteeism ($\beta = 0.219, p < 0.001$) and overall work impairment ($\beta = 0.181, p < 0.001$), while the association of caregiver burden with absenteeism was not significant ($\beta = -0.003, p = 0.953$). Interaction effects of caregiver burden \times coworker support on presenteeism ($\beta = -0.189, p = 0.023$) and overall work impairment ($\beta = -0.172, p = 0.034$) were significant. According to simple slope analyses, caregiver burden was greater at lower levels of coworker support compared to higher levels of coworker support for both presenteeism and overall work impairment.

Conclusions Our study suggests that higher caregiver burden is associated with a decrease in work productivity. Additionally, coworker support appears to buffer the association of caregiver burden with presenteeism and overall work impairment among working family caregivers of people with dementia.

Keywords Caregivers · Dementia · Caregiver burden · Work productivity · Employment

Introduction

Worldwide, approximately 47.5 million people have dementia, and this number is expected to increase in the future [1]. In Japan, the number of people with dementia over 65 years of age will increase from 4.62 million in 2012 to 7 million in 2025 [2]. Dementia is a syndrome resulting from brain disease, characterized by disturbances of multiple higher-order cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment; it is usually of a chronic or progressive nature [1]. Most people with dementia suffer from the behavioral and psychological symptoms of dementia (BPSD), such as apathy, anxiety, delusions, agitation, and depression, during the course of their illness [3, 4]. The BPSD are associated with diminished quality of life [5] and activities of daily living (ADL) [6] among people with dementia, as well as greater caregiver burden [7]. Caregiver burden is defined as caregivers' perception of their health, psychological well-being,

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finances, social life, and the relationship between the caregiver and the impaired person [8]. Caregiver burden consists of two discrete components: personal strain, which refers to how personally stressful the experience is; and role strain, which refers to stress due to role conflict or overload [9, 10]. This can cause tremendous distress for both people with dementia and their family caregivers [11]. As the BPSD worsen, family caregivers of people with dementia also tend to experience higher levels of depression and distress, as well as worse physical and psychological health, in addition to greater caregiver burden [12–16].

In Japan, the proportion of primary caregivers living with a patient is 34.0% male and 66.0% female [17]. The family relationship of the caregiver is most likely to be the spouse (25.2%), followed by the patient's child (21.8%) and the child's spouse (9.7%) [17]. The most frequent age of the caregiver is in the 60s (31.5%), followed by the 70s (22.3%) and the 50s (21.2%) [17]. In the future, it is expected that as dementia rates increase, family caregivers of people with dementia will also increase. Such caregivers seem to be more involved in caregiving—in terms of hours and help provided for ADL and instrumental ADL—than caregivers of people with other diseases [18]. Additionally, the family caregivers of people with dementia experience greater physical and mental stress than do the caregivers of family members with other diseases [18, 19]. In the case of terminal diseases such as cancer, the disease itself is considered more predictable and ADL are often maintained until the late phase of terminal care, which means that greater caregiver burden is experienced only at this late phase [20, 21]. However, in the case of dementia, caregiving, either by family members and professional caregivers, is often needed as soon as cognitive function begins to decline. Therefore, family caregivers of people with dementia might experience long-term care with high stress and caregiver burden.

Advancements in medical care have extended the average life expectancy in Japan; on average, people can currently live to age 80, although some might need caregiving or minimum support as they approach age 65 or older [22]. Due to the declining birth rate since the baby boom, the number of elderly people has reached almost one third of the total population of Japan [23]. The burden of care for elderly people falls heavily on the shoulders of the working population, which makes up only half of the total population. Working family caregivers tend to have more health problems (e.g., depression, insomnia, and headache) and poorer health-related quality of life compared to non-caregivers [24, 25]. They also must contend with conflicts between their job and family responsibilities, and are more likely to be absent from work, experience increasing work productivity loss, which includes absenteeism (i.e., the amount of work time missed due to health problems), presenteeism (i.e., the degree of time impaired while on the job), overall work impairment (i.e., the degree

of overall work impairment/absenteeism plus presenteeism), and activity impairment (i.e., the degree of impairment during daily activities) [26], miss opportunities for advancement, and quit their jobs [27–31]. Previous studies of working caregivers of people with dementia have revealed that work demands are related to role strain and depression, and higher role overload is related to worry and strain [32, 33]. In addition, compared to non-caregiving workers, working caregivers of people with dementia had higher rates of absenteeism, presenteeism, and overall work impairment [30, 31]. These negative events are particularly severe in the working family caregivers of people with dementia [30, 31].

Occupational health focuses mainly on the “development of work organizations and working cultures in a direction which supports health and safety at work and in doing so also promotes a positive social climate and smooth operation and may enhance productivity of the undertakings” [34]. Work productivity among working family caregivers of people with cancer has been found to be associated with caregiver burden (e.g., financial problems, disrupted schedule, and health problems) [35]. Accordingly, we might expect that the working family caregivers of people with dementia would experience similar or even worse levels of caregiver burden, given that the duration of care for people with dementia is harder to predict than is that of people with terminal cancer. To the best of our knowledge, however, no study has examined the association between caregiver burden and work productivity among working family caregivers of people with dementia.

When we consider the association between caregiver burden and work productivity, the effect of job characteristics on the association cannot be ignored. For example, if working family caregivers are working under conditions of high job demands (or working long hours), work productivity loss caused by caregiver burden may be further increased due to dual burden of caregiving and work. On the other hand, in the occupational health research field, the job demands-control (or job strain) and demand-control-support (or iso-strain) models [36, 37] are well known as one of the theoretical models of job stress, suggesting that job control and worksite support buffer the adverse health effects of job demands. Although these theoretical models are not specifically set out to predict the situation of caregivers of people with dementia, we assumed that job control and worksite support could possibly buffer the stress reactions that come from caregiving situation as well as from work. Given the fact that stress reactions have been reported to decrease work productivity [38, 39], job control and worksite support may have a potential to mitigate work productivity loss caused by caregiver burden.

The objective of this study was to examine the association between caregiver burden and work productivity among working family caregivers of people with dementia and to determine the moderating effect of job characteristics (i.e.,

Table 1 The number of the email invitations to the web-based survey, the respondents to the web-based survey, and the participants who met inclusion criteria

Age	Email invitations to the web-based survey	Respondents to the web-based survey	Participants (respondents meeting inclusion criteria)	Percentage of respondents meeting inclusion criteria (%)
20–29	4505	813	19	2.3
30–39	8117	2166	69	3.2
40–49	10,997	3425	95	2.8
50–59	9903	3461	120	3.5
60–69	3583	1448	72	5.0
≥ 70	362	157	4	2.5

job demands, job control, and worksite support) on the association. We hypothesized that caregiver burden would be significantly associated with work productivity even after adjusting for demographic characteristics, care situation, and job characteristics. Furthermore, we hypothesized that job characteristics would moderate the association between caregiver burden and work productivity: specifically, job demands would enhance the association, whereas job control and worksite support would weaken it.

Method

Participants

Samples were recruited through NEO MARKETING Inc., a private Japanese online survey company. The data were collected using a self-administrated questionnaire containing scales of caregiver burden, work productivity, care situation, job characteristics, and demographic characteristics using a cross-sectional web-based survey. Sample inclusion criteria were the following: (1) aged above 19, (2) living in Japan, (3) consenting to the survey, (4) involved in caregiving for a family member with dementia, and (5) being employed. Respondents were screened out if they did not meet all of the five criteria listed above. The company ran a pilot test prior to the survey and suggested the proportion of respondents who would meet inclusion criteria was 2% (20 out of 1000 respondents fulfilled the inclusion criteria). However, as the response rate may fluctuate over time, so do the chances of respondents meeting the inclusion criteria. In this study, we needed a sample size of 300 to 350 effective participants. Sample size was calculated by software/methods to achieve minimum statistical power. Thus, to ensure enough effective participants (by estimating 30–50% response rate and 1% of the respondents meeting inclusion criteria), we sent the survey invitation to 37,467 registered members, randomly selected from the total list of 3.27 million registered members (as of May 20, 2016). The respondents were given online shopping points as an incentive. Once the responder had completed the

survey, the link to the questionnaire was disabled. Registration information (e.g., name, age, occupation, and email address) of the participants was also checked to ensure no duplication of registration. The aims and procedures of the study were fully explained on the webpage and consent was obtained from a respondent when he or she completed the questionnaire.

The study purpose and procedure were explained to the respondents prior to initiation of the study. The Ethics Committee of the Health Outcome Research Institute copyright reviewed and approved the aims and procedures of the study (No. 003).

Measures

Caregiver Burden

Caregiver burden was measured using the short version of the Japanese version of the Zarit Caregiver Burden Interview (J-ZBI_8) [9, 10, 40]. The scale comprises two subscales of personal strain and role strain. Personal strain comprises five items and role strain three items, each rated on a 5-point Likert response scale from 0 (*never*) to 4 (*nearly always*). The total score (ranging from 0 to 32) was calculated by summing all the items, with higher scores indicating greater caregiver burden. Cronbach's alpha coefficient was 0.93 for the J-ZBI_8 in this study.

Work Productivity

Work productivity was measured using the Work Productivity and Activity Impairment Questionnaire: General Health, version 2.0 [26, 31]. This scale measures the extent to which work productivity has been affected by health in the past 7 days. The scale measures four aspects of work productivity: (1) absenteeism (amount of work time missed), (2) presenteeism (degree of impairment at work/reduced on-the-job effectiveness), (3) overall work impairment (degree of overall work impairment/absenteeism plus presenteeism), and (4) activity impairment (degree of impairment during

daily activity). Higher values (expressed as percentages) indicate greater impairment and lower productivity. In this paper, we analyzed only absenteeism, presenteeism, and overall work impairment as components of work productivity, in order to focus on the work aspect of this construct. These variables range from 0 to 100%.

Care Situation

Care situation included caregiving time (hours/day), duration of caregiving (months), type of caregiver, living arrangements, night care situation, care recipient sex, and care recipient health status, which was measured by using the yes/no question “Is your recipient receiving treatment other than for dementia now?” to gather information on recipients’ disease status in treatment. These variables were assessed as confounding factors on the association between caregiver burden and work productivity.

Job Characteristics

Job demands, job control, worksite support (i.e., amount of support from supervisors and coworkers), and working days per week were assessed as job characteristics. The correlation between working days per week and work hours was high ($r = 0.76$); therefore, considering multicollinearity, only working days per week was used as a covariate. Job demands, job control, supervisor support, and coworker support were measured using the subscales of the Brief Job Stress Questionnaire [41]. Each subscale comprises three items rated with a 4-point Likert scale from 1 (*strongly disagree*) to 4 (*strongly agree*). The total score of each subscale (which ranges from 3 to 12) is calculated by summing all the item scores, with higher scores indicating greater job demands, job control, and supervisor or coworker support. Cronbach’s alpha coefficients were 0.83 for job demands, 0.78 for job control, 0.89 for supervisor support, and 0.85 for coworker support.

Demographic Characteristics

The demographic characteristics included caregiver sex, age, marital status, and education. Age was treated as a continuous variable. Marital status was dichotomized as *married* and *single* (including divorced and bereaved), while education was dichotomized as *less than vocational school* and *vocational school or above*.

Statistical Analysis

We examined the correlations to investigate the relationship between each variable and work productivity. Next, the work productivity variables were designated as the dependent variables in several hierarchical multiple regression analyses.

Table 2 Characteristics of the study participants ($n = 379$)

	Mean	(SD)	<i>n</i>	%
Caregivers				
Sex				
Male			274	72.3
Female			105	27.7
Age (years)	48.84	(11.37)		
Marital status				
Married			255	67.3
Single (including divorced and bereaved)			124	32.7
Education				
Less than vocational school			82	21.6
Vocational school or above			297	78.4
Caregiver burden (J-ZBI_8 ^a)	13.33	(8.02)		
Caregiving time (hours/day)	2.14	(2.89)		
Duration of caregiving (months)	53.49	(46.45)		
Type of caregiver				
Primary caregiver			127	33.5
Secondary caregiver			252	66.5
Living arrangements				
Lives with care recipient			171	45.1
Lives separately from care recipient			208	54.9
Night care situation				
Yes			242	63.9
No			137	36.2
Job characteristics (subscales of BJSQ ^b)				
Job demands	8.19	(2.16)		
Job control	8.68	(2.12)		
Supervisor support	7.09	(2.55)		
Coworker support	7.30	(2.30)		
Working days per week	4.87	(1.03)		
Work productivity (subscales of WPAI-GH ^c)				
Absenteeism	7.91	(17.52)		
Presenteeism	35.36	(23.67)		
Overall work impairment	40.02	(26.09)		
Care recipient				
Sex				
Male			164	43.3
Female			215	56.7
Health status ^d				
Yes			305	80.5
No			74	19.5

^a The short version of the Japanese version of the Zarit Caregiver Burden Interview

^b Brief Job Stress Questionnaire

^c Work Productivity and Activity Impairment Questionnaire: General Health

^d Receiving treatment other than for dementia

Table 4 Association between caregiver burden and work productivity (each subscale of WPAI-GH[†]) among employed family caregivers of people with dementia: hierarchical multiple regression analysis results (*n* = 379)

Variable	Absenteeism			Presenteeism			Overall work impairment		
	Standard partial regression coefficients (β)			Standard partial regression coefficients (β)			Standard partial regression coefficients (β)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Demographic characteristics									
Caregiver sex ^a	0.022	-0.006	-0.020	-0.052	-0.043	-0.034	-0.016	-0.024	-0.023
Age (years)	-0.159 **	-0.103 *	-0.100	-0.117 *	-0.060	-0.056	-0.157 **	-0.088	-0.082
Marital status ^b	0.127 *	0.045	0.041	-0.027	-0.022	-0.025	0.028	-0.009	-0.012
Education ^c	-0.180 **	-0.149 **	-0.148 **	-0.005	-0.001	0.009	-0.076	-0.056	-0.048
Care situation									
Caregiver burden (J-ZBI_8 [‡])	-0.023	-0.011	-0.003	0.232 **	0.215 **	0.219 **	0.179 **	0.170 **	0.181 **
Caregiving time (hours/day)	-0.096	-0.061	-0.059	0.004	0.011	0.003	-0.052	-0.030	-0.039
Duration of caregiving (months)	0.118 *	0.115 *	0.116 *	-0.028	-0.030	-0.026	0.033	0.030	0.033
Type of caregiver ^d	0.157 **	0.134 **	0.133 **	-0.063	-0.052	-0.050	0.005	0.002	0.003
Living arrangements ^e	0.096	0.051	0.037	-0.010	-0.028	-0.034	0.069	0.031	0.017
Night care situation ^f	0.105 *	0.068	0.062	0.074	0.084	0.075	0.115 *	0.108 *	0.096
Care recipient sex ^a	-0.142 **	-0.135 **	-0.123 *	-0.096	-0.060	-0.071	-0.145 **	-0.113 *	-0.114 *
Care recipient health status ^f	0.096 *	0.034	0.037	0.062	0.050	0.048	0.092	0.052	0.054
Job characteristics									
Job demands (subscales of BJSQ [¶])		0.141 **	0.137 **		0.211 **	0.187 **		0.246 **	0.224 **
Job control (subscales of BJSQ [¶])		0.003	-0.003		-0.151 **	-0.136 **		-0.114 *	-0.108 *
Supervisor support (subscales of BJSQ [¶])		0.223 **	0.204 **		0.092	0.081		0.171 *	0.156 *
Coworker support (subscales of BJSQ [¶])		-0.039	-0.029		-0.157 *	-0.131		-0.152 *	-0.127
Working days per week		-0.206 **	-0.199 **		0.051	0.038		-0.075	-0.079
Interaction (caregiver burden × job characteristics)									
Caregiver burden × job demands			-0.024			0.082			0.042
Caregiver burden × job control			-0.019			-0.074			-0.078
Caregiver burden × supervisor support			0.075			0.144			0.144
Caregiver burden × coworker support			-0.028			-0.189 *			-0.172 *
Caregiver burden × working days per week			0.089			-0.041			0.006
<i>R</i> ²	0.192 **	0.289 **	0.298 **	0.108 **	0.183 **	0.206 **	0.148 **	0.225 **	0.242 **
Adjusted <i>R</i> ²	0.166 **	0.256 **	0.254 **	0.079 **	0.144 **	0.157 **	0.120 **	0.188 **	0.195 **
ΔR^2	0.192 **	0.097 **	0.009 **	0.108 **	0.074 **	0.024 **	0.148 **	0.077 **	0.017 **

p* < 0.05, *p* < 0.01

[†] Work Productivity and Activity Impairment Questionnaire: General Health

[‡] The short version of the Japanese version of the Zarit Caregiver Burden Interview

[¶] Brief Job Stress Questionnaire

^a Male = 0, female = 1

^b Married = 1, single (including divorced and bereaved) = 0

^c Vocational school or above = 1, less than vocational school = 0

^d Primary caregiver = 1, secondary caregiver = 0

^e Lives with care recipient = 1, lives separately from care recipient = 0

^f Yes = 1, no = 0

conducted post hoc simple slope analyses according to the level of coworker support. These demonstrated that the simple slope of caregiver burden was greater at lower levels of coworker support (i.e., one SD below the mean) compared to higher levels of coworker support (i.e., one SD above the mean) for both presenteeism and overall work impairment (Fig. 1).

Discussion

To our knowledge, this is the first study to demonstrate significant and positive associations of caregiver burden with presenteeism and overall work impairment among working family caregivers of people with dementia, even after adjusting for demographic characteristics, care situation, and

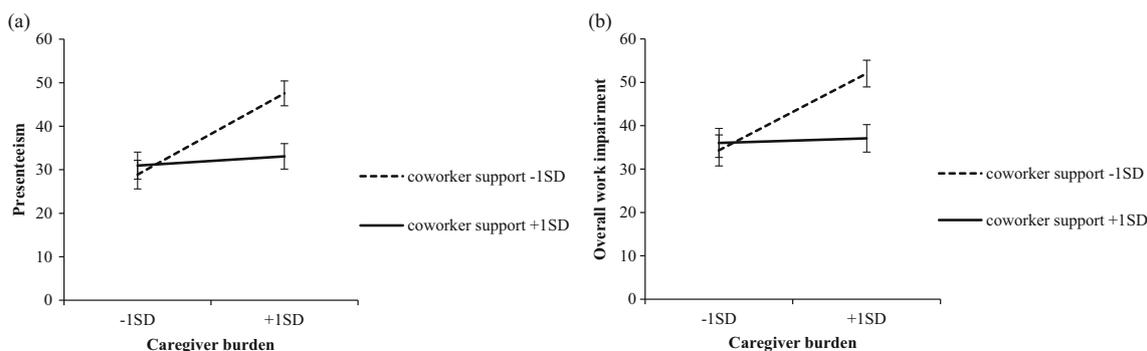


Fig. 1 Simple slopes data plots of the caregiver burden \times coworker support interaction for presenteeism (a) and for overall work impairment (b)

job characteristics (model 2). However, the association between caregiver burden and absenteeism was not significant. Furthermore, significant interaction effects of caregiver burden \times coworker support on presenteeism and overall work impairment were found—in other words, we found a buffering effect of coworker support on the associations of caregiver burden with presenteeism and overall work impairment.

The fact that caregiver burden was positively and significantly associated with presenteeism and overall work impairment accords with what was found in a previous prospective study [35] of employed family caregivers of patients with cancer. Highly burdened working family caregivers might not get enough rest at home and might be exhausted due to providing a greater amount of family care, which may have led to presenteeism and overall work impairment. On the other hand, caregiver burden was not significantly associated with absenteeism. Absenteeism might have been less likely to appear and not be significantly related to caregiver burden in the analysis because presenteeism generally precedes absenteeism [42, 43]. However, this study is cross-sectional, so we cannot interpret the temporal relationship between caregiver burden and absenteeism. Therefore, this association should be further examined in a longitudinal study.

Significant interaction effects of caregiver burden \times coworker support on presenteeism and overall work impairment were demonstrated. When further interpreted via simple slope analyses, this indicated that the associations of caregiver burden with presenteeism and overall work impairment were significant at lower levels of coworker support, but not at higher levels (indicating a buffering effect). In contrast, we found no significant interaction effect of caregiver burden \times supervisor support. This might be explained by the fact that coworkers are often more familiar to individuals, tend to be easier to consult, and are more likely to give support than are supervisors in Japanese culture, which is characterized by vertical collectivism [44]. Additionally, coworkers, rather than supervisors, engage in work sharing or support for presenteeism and overall work impairment.

While job demands and job control were found to be significantly associated with presenteeism and overall work

impairment, their interaction effects with caregiver burden were not significant. Some people who have higher levels of both caregiver burden and job demands might perceive the job demands as a greater challenge [45], which might explain the non-significant interaction effects of job demands on the association of caregiver burden with presenteeism and overall work impairment. Additionally, those with higher job control have enough discretion, but their responsibilities for work increase. Therefore, some people with higher levels of caregiver burden and job control might feel the burden of care as well as great responsibility for their work. This again suggests that it is difficult to suppress presenteeism and overall work impairment, which might explain the non-significant interaction effects of job control on the association of caregiver burden with presenteeism and overall work impairment.

The present study has certain noteworthy strengths. First, it utilized a larger sample than the previous study. Second, it suggested that caregiver burden was significantly and positively associated with work productivity even after adjusting demographic characteristics, care situation, and job characteristics. Finally, coworker support appears to buffer the association of caregiver burden with presenteeism and overall work impairment among working family caregivers of people with dementia.

However, the present study has several limitations. First, the causal relationships between caregiver burden and work productivity could not be determined because of the cross-sectional design. Therefore, longitudinal studies should be conducted as well. Second, we used online survey data, and past studies have shown that the socioeconomic and educational status of Internet users is higher than that of the general population [46]. This suggests the possibility of selection bias. Also, this research was conducted at home via web survey, and there is a possibility that the care receiver was nearby. Therefore, there is the possibility that respondents felt guilty about the care recipient and may not have honestly answered questions regarding the actual situation of their family care at home. On the other hand, because there is a distance from the workplace, there is a possibility that respondents honestly answered about their workplace environment. Therefore, due to

the potential problems with social desirability, the findings may not be fully generalizable. There is additional evidence for this as, compared with previous studies [25, 31, 35, 40], participants in the present study had relatively lower levels of caregiver burden and absenteeism. This suggests that those with lower levels of caregiver burden and absenteeism were more likely to participate in this study, possibly leading to the non-significant association of caregiver burden with absenteeism. Also, statistically, we adjusted for the age and type of caregiver, but there is a possibility that these effects may not be completely eliminated. Therefore, the participants of this study may be more likely to include those with lower caregiver burden and the results of this study may have been underestimated. Furthermore, those who had high levels of caregiver burden and job demands as well as high levels of presenteeism and overall work impairment might have been less likely to participate, thus leading to an underestimation of the interaction effect. Third, when recruiting participants, the survey invitation was randomly sent to 37,467 registered members who may or may not have met inclusion criteria. Therefore, a strict ratio of participants could not be calculated. Fourth, the participants of this study represented a relatively large share of male caregivers (72%). Of primary caregivers in Japan, 66% are women [17]; however, this study targeted Japanese workers. In Japan, as men are expected to play the role of family breadwinner [47], because they have to work to earn a living for their family, if they feel hard to work and care for their family, they will not quit work for the reason providing care their family. Given that this study included a larger proportion of men than women, this might explain the higher rate of presenteeism and overall work impairment than previous studies targeting Japanese [31]. Fifth, in this study, caregiver burden was measured using the J-ZBI_8 which has verified reliability and validity. However, the Resource Utilization in Dementia (RUD) [48] has been used globally. In the future, we will develop a Japanese version of the RUD and consider longitudinal studies and international comparison. Sixth, caregiver burden leads to diminished psychological health or even depression [49–51], but we did not have data on psychological health and depression in this study. Hence, future research should consider the model of psychological health and depression. Seventh, this research took place in Japan, where there is a declining birthrate and aging population. Although the results of this study may be applicable in countries with a declining birthrate and aging population such as China and South Korea, which in general have similar cultural values and family traditions as those in Japan, there is a limit to the generalizability of application to other countries. Finally, the adjusted R^2 of the hierarchical multiple regression analyses were not high and there might not have been enough statistical power in the present study. If variables such as dementia diagnosis and severity level, information concerning the BPSD, relationship with care recipient, and

work from home were added to the model, there might be a possibility that the explanation rate of outcomes would be increased. Hence, further prospective studies should include these variables potentially associated with work productivity and devise a model with better fit. This would verify and potentially reconsider the association between caregiver burden and work productivity.

Conclusion

This study found higher caregiver burden is associated with a decrease in work productivity after adjusting for demographic characteristics, care situation, and job characteristics. Additionally, coworker support appears to buffer the association of caregiver burden with presenteeism and overall work impairment among working family caregivers of people with dementia. As an intervention in the workplace, even if individuals experience caregiver burden, colleague support might prevent work productivity loss. In addition, it is important to create a structure that makes it easier to utilize local social resources to decrease caregiver burden.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and with 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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