ORIGINAL

Long-term impact of COVID-19 pandemic on secular changes in metabolic parameters in Japanese workers : Tokushima Cohort Study

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Abstract : Objective : The coronavirus disease 2019 (COVID-19) pandemic has caused unprecedented changes in people's lifestyles. Since then, our lifestyle has remained different from what it used to be in the pre-pandemic era. This study investigated the long-term impact of the COVID-19 pandemic on secular changes in metabolic parameters in Japanese workers. Methods : A total of 519 eligible subjects completed fiscal year (FY) 2017, FY2019 and FY2021 surveys. Comparison between pre-COVID-19 (Δpre-covid19 : FY2019-2017) and during COVID-19 (Δcovid19 : FY2021-2019) was performed in each sex. Results : Increment of diastolic blood pressure (DBP) in Δcovid19 was significantly greater than that in Δpre-covid19 (Δpre-covid19 to Δcovid19 : 0.22 ± 6.17 to 2.59 ± 6.69 mmHg, p = 0.0002 in males, -0.18 ± 6.26 to 2.16 ± 6.60 mmHg, p = 0.01 in females). In females, increments of waist circumference and fasting plasma glucose in Δcovid19 were also significantly greater than those in Δpre-covid19 (both p < 0.05). Conversely, increments of BMI and body fat in Δcovid19 were significantly smaller than those in Δpre-covid19 in males (both p < 0.05). Conclusion : Our findings suggest that there was an apparent metabolic impact of the COVID-19 pandemic on DBP increment in Japanese workers. In addition, COVID-19 may have influenced males and females differently in relation to glucose metabolism and anthropometric measurements related to obesity/adiposity. J. Med. Invest. 71 : 47-53, February, 2024

Keywords **:** *Covid-19, pandemic, prospective study, secular change, diastolic blood pressure*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This disease first emerged in Wuhan, China in December, 2019 (1). The new virus spread rapidly to other countries around the world. The World Health Organization (WHO) declared the outbreak as a pandemic on March 11, 2020. Many countries introduced COVID-19 lockdown and strict restrictions to prevent human-to-human transmission of SARS-CoV-2. The Japanese government also requested, but did not force, people to refrain from nonessential and non-urgent outings. A nationwide state of emergency was declared in Japan on April 16, 2020. Such a state of emergency declaration carried on with some short intervals of lifting, and even after the declaration was lifted, the Japanese government strongly prioritized preventative measures, which included shorter operating hours for dining and drinking establishments. Additionally, local governments in Japan requested residents not to hold events and to refrain from moving across prefectural borders, to prevent SARS-CoV-2 transmission. Although the Japanese government, unlike those of other countries, chose not to enforce strict restrictions, newly confirmed COVID-19 cases per 100,000 population in Japan remained low until February 2022 (2).

When the COVID-19 pandemic started, many governments imposed unprecedented changes in citizens' daily lives by placing lockdowns (i.e., staying at home, school closure, maintaining social distance, and missing social gatherings and eating out). In places lockdown was implemented, it caused physical and social isolation. In the US, increased sedentary time and decreased physical activity were observed, based on an analysis of questionnaires conducted during the early stage of the COVID-19 pandemic (3). Thus, although lockdown and strict restrictions due to COVID-19 may have been effective in preventing SARS-CoV-2 transmission, accompanying lifestyle changes during the early stage of the pandemic had a negative influence on the metabolic profile, with an increase in cardiometabolic risk (4, 5).

In Japan, the government did not impose lockdown but instead made a request to people to change their lifestyle. Such mild restrictions, which were based on voluntary changes in behavior, were still effective in containing the pandemic, as the number of confirmed cases and the fatality of COVID-19 were low in Japan (2). However, it is still not clear whether or not such mild restrictions had a negative impact on the metabolic profile. In addition, although the impact of lockdown, which is a relatively short-term exposure, on lifestyle and the metabolic profile has been reported (3, 4), studies regarding the long-term impact of the COVID-19 pandemic are still limited.

Hence, the aim of this study was to investigate the long-term impact of the COVID-19 pandemic on secular changes in metabolic parameters in office workers in Japan.

SUBJECTS AND METHODS

Study participants and design

This prospective cohort study has been underway since 2008 in Tokushima Prefecture, Japan. We recruited employees working for local governments, large scale companies, or small businesses, aged 20 to 60 years in a fiscal year (FY) 2008 survey. Participants were followed-up prospectively from FY2008 to

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FY2022 by repeated annual health examinations at their workplace. During the COVID-19 pandemic, annual follow-up health examinations were temporarily interrupted in some workplaces.

The aim of this study was to investigate the impact of the COVID-19 pandemic on secular changes in metabolic parameters. For this purpose, we focused on only participants who attended FY2017 (Jun 2017-Feb 2018), FY2019 (Jun 2019-Feb 2020) and FY2021 (Jul 2021-Jan 2022) surveys.

Among the FY2017, FY2019 and FY2021 surveys, 1775 subjects (male : 1241, female : 534) participated in at least one of three surveys. Out of those, 523 subjects (male : 379, female : 144) completed all three surveys with blood sampling and anthropometric measurements at their workplaces. After exclusion of 4 pregnant subjects, the remaining 519 subjects were enrolled in this analysis.

Definition of metabolic abnormality

Hypertension was defined as either : 1) systolic blood pressure (SBP) ≥ 140 mmHg, 2) diastolic blood pressure (DBP) ≥ 90 mmHg or 3) medication for hypertension (6). Metabolic syndrome (MetS) was determined using the Japanese criteria based on abdominal obesity (increased waist circumference ≥ 85 cm for males and ≥ 90 cm for females), and two of the following three criteria : 1) elevated blood pressure (SBP/DBP ≥ 130/85 mmHg or use of antihypertensive medication), 2) dyslipidemia (fasting triglycerides ≥ 150 mg/dl or serum high density lipoprotein cholesterol (HDL-C) < 40 mg/dl or medication for dyslipidemia), and 3) glucose intolerance (fasting plasma glucose ≥ 110 mg/dl or hemoglobin A1c (HbA1c) ≥ 6.0% or medication for diabetes) (7).

Metabolic parameters and lifestyle measurements

Participants were requested to fast overnight for at least 10 hours before blood collection. However, postprandial blood samples were collected for some participants, which were still included in this analysis as long as their test results fell within the normal range, except for blood glucose level and triglyceride level. Plasma glucose level was determined by a glucose-oxidase method. A high-performance liquid chromatographic method was used for determination of HbA1c level. HDL-C and low density lipoprotein cholesterol (LDL-C) were determined by a direct method. Total-cholesterol and triglyceride levels were determined enzymatically. Seated blood pressure was obtained in each arm, and the average value was used in the analyses. Blood pressure measurements were performed using an appropriately sized cuff (HBP-T1055-N, Omron Co., Japan). Pulse pressure was calculated as the difference between SBP and DBP. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated. Body fat percentage and skeletal muscle mass were measured with a bioimpedance analyzer (Inbody 230, InBody Co., Ltd., Korea).

Each subject completed a self-administered questionnaire covering medical history, anti-diabetic, anti-dyslipidemic, and anti-hypertensive medication, smoking habit and alcohol intake, which were confirmed by interview of participants by medical professionals each year. Smoking habit and alcohol intake at annual health examinations were classified as either current or not current.

Statistical analysis

Comparisons of metabolic parameters and physical measurements between each group were carried out using repeated measures analysis of variance (ANOVA) with Bonferroni post hoc tests. Data are expressed as mean value ± standard deviation, or geometric mean (95% confidence interval) if the distribution of data was skewed. Because the distributions of plasma glucose, HbA1c, and triglycerides were skewed, these values were natural log transformed for statistical analyses. Comparison of frequencies was performed using McNemar's test. All comparisons were adjusted by Bonferroni correction method to counteract the multiple comparison problem.

We also calculated the 2-year difference in metabolic parameters and physical measurements for each subject using the following formulas :

Δpre-covid19 = metabolic profile (FY2019) - metabolic profile (FY2017)

Δcovid19 = metabolic profile (FY2021) - metabolic profile (FY2019)

Comparisons between Δpre-covid19 and Δcovid19 values of metabolic parameters and physical measurements were carried out using paired t-test or Wilcoxon's signed rank test. Data are expressed as mean value ± standard deviation, or median (25^{th}, 75^{th} percentile) if the distribution of data was skewed. Values of $p < 0.05$ were considered statistically significant in all analyses. SAS software package version 9.4 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses.

Ethical considerations

This study was conducted with the approval of the Ethics Committee of Tokushima University Hospital (ethical approval number : 662), and written informed consent was obtained from the participants.

RESULTS

According to the criteria described in Subjects and Methods, 519 subjects (379 male and 140 female) were selected for the present study. Mean age in FY2017 was 44.1 ± 10.8 years (males) and 45.7 ± 8.8 years (females). Table 1A and 1B present the characteristics of subjects in each FY. SBP, DBP, pulse pressure, HbA1c, total-cholesterol, HDL-C, and LDL-C were analyzed, excluding subjects with medication for each condition. In addition, fasting plasma glucose and fasting triglycerides were analyzed, excluding subjects with medication for each condition and subjects without fasting. In males (Table 1A), waist circumference (86.4 ± 9.5 cm), SBP (128.6 ± 14.2 mmHg), DBP (79.6 ± 10.6 mmHg), fasting plasma glucose [96.0 (94.8-97.2) mg/dl], HbA1c [5.53 (5.49-5.58) %] and total-cholesterol (208.2 ± 33.2 mg/dl) in FY2021 were significantly higher compared to FY2017 and FY2019 (all $p < 0.05$). LDL-C (125.7 ± 31.1 mg/dl) significantly increased with aging ($p < 0.05$ vs FY2017). In females (Table 1B), waist circumference (80.5 ± 11.7 cm), DBP (71.0 ± 10.0 mmHg), fasting plasma glucose [89.9 (88.5-91.2) mg/dl], total-cholesterol (218.2 ± 33.1 mg/dl) and LDL-C (124.7 ± 28.9 mg/dl) in FY2021 were significantly higher compared to FY2017 and FY2019 (all $p < 0.05$). HDL-C (males : 59.5 ± 15.5 mg/dl, females : 74.8 ± 16.6 mg/dl) in FY2021 was significantly higher compared to FY2017 in males and females ($p < 0.05$, respectively). Additionally, body fat (24.5 ± 6.2%) in FY2019, but not in FY2021, was significantly increased compared to FY2017 in males ($p < 0.05$).

Frequencies of lifestyle factors and metabolic abnormalities in each FY are shown in Table 2. Dyslipidemia and glucose intolerance as MetS components were analyzed. Participants who had postprandial blood collection and exhibited either abnormal triglyceride or glucose level were excluded from the analysis. In males, frequencies of hypertension (37.7%), elevated blood pressure (56.7%) and glucose intolerance (18.3%) as components of MetS in FY2021 were significantly higher compared to FY2019 and FY2017 (all $p < 0.05$). In addition, frequency of abdominal obesity was significantly higher in FY2019 and FY2021, when compared with that in FY2017 (FY2019 : 50.4%, FY2021 : 55.4%, $p < 0.05$). On the other hand, frequency of using

Table 1A. Characteristics of metabolic parameters and physical measurements in each fiscal year in males

	Male			
	n	FY2017	FY2019	FY2021
BMI, kg/m^2	379	24.1 ± 3.6	24.3 ± 3.5	24.3 ± 3.4
Waist circumference, cm	379	84.7 ± 9.4	85.8 ± 9.4*	86.4 ± 9.5*†
Body fat, %	379	24.1 ± 6.2	24.5 ± 6.2*	24.5 ± 6.0
Skeletal muscle mass, kg	379	29.9 ± 3.6	29.9 ± 3.7	29.9 ± 3.8
SBP, mmHg	312	126.2 ± 13.1	126.6 ± 12.9	128.6 ± 14.2*†
DBP, mmHg	312	76.8 ± 9.8	77.0 ± 9.7	79.6 ± 10.6*†
Pulse pressure, mmHg	312	49.4 ± 7.9	49.6 ± 7.3	48.9 ± 8.4
Fasting plasma glucose, mg/dl	327	92.7 (91.7-93.7)	94.0 (93.0-95.1) *	96.0 (94.8-97.2) *†
HbA1c, %	361	5.50 (5.46-5.53)	5.50 (5.47-5.54) *	5.53 (5.49-5.58) *†
Total-cholesterol, mg/dl	333	203.0 ± 32.0	204.5 ± 32.2	208.2 ± 33.2*†
HDL-cholesterol, mg/dl	333	58.4 ± 14.4	58.6 ± 14.2	59.5 ± 15.5*
LDL-cholesterol, mg/dl	333	119.8 ± 28.0	124.1 ± 29.7*	125.7 ± 31.1*
Fasting triglycerides, mg/dl	299	93.7 (87.6-100.3)	94.8 (88.9-101.1)	94.3 (88.4-100.5)

Values are presented as mean ± SD or geometric mean (95% CI).
* Bonferroni adjusted $p < 0.05$ vs FY2017, † Bonferroni adjusted $p < 0.05$ vs FY2019.
SBP, DBP, pulse pressure, HbA1c, total-cholesterol, HDL-cholesterol, and LDL-cholesterol were analyzed in subjects without medication for each condition.
Fasting plasma glucose and fasting triglycerides were analyzed in subjects without medication for each condition and without breakfast.

Table 1B. Characteristics of metabolic parameters and physical measurements in each fiscal year in females

	Female			
	n	FY2017	FY2019	FY2021
BMI, kg/m^2	140	21.8 ± 3.4	21.9 ± 3.4	22.1 ± 3.9
Waist circumference, cm	140	77.7 ± 9.8	78.3 ± 10.4	80.5 ± 11.7*†
Body fat, %	140	31.0 ± 6.6	31.0 ± 7.0	31.6 ± 7.4
Skeletal muscle mass, kg	140	20.2 ± 2.4	20.3 ± 2.3	20.3 ± 2.6
SBP, mmHg	127	117.8 ± 14.2	117.6 ± 13.9	119.9 ± 16.4
DBP, mmHg	127	69.0 ± 8.7	68.8 ± 9.6	71.0 ± 10.0*†
Pulse pressure, mmHg	127	48.8 ± 9.9	48.8 ± 8.3	48.9 ± 10.8
Fasting plasma glucose, mg/dl	129	88.2 (87.0-89.4)	87.9 (86.7-89.1)	89.9 (88.5-91.2) *†
HbA1c, %	137	5.45 (5.41-5.50)	5.46 (5.41-5.50)	5.46 (5.42-5.51)
Total-cholesterol, mg/dl	128	205.9 ± 36.1	211.7 ± 32.9*	218.2 ± 33.1*†
HDL-cholesterol, mg/dl	128	72.5 ± 17.3	74.0 ± 16.6	74.8 ± 16.6*
LDL-cholesterol, mg/dl	128	114.0 ± 28.2	120.4 ± 27.8*	124.7 ± 28.9*†
Fasting triglycerides, mg/dl	121	59.6 (55.7-63.8)	60.9 (56.8-65.3)	63.5 (58.4-69.0)

Values are presented as mean ± SD or geometric mean (95% CI).
* Bonferroni adjusted $p < 0.05$ vs FY2017, † Bonferroni adjusted $p < 0.05$ vs FY2019.
SBP, DBP, pulse pressure, HbA1c, total-cholesterol, HDL-cholesterol, and LDL-cholesterol were analyzed in subjects without medication for each condition.
Fasting plasma glucose and fasting triglycerides were analyzed in subjects without medication for each condition and without breakfast.

antihypertensive drugs in FY2019 (14.8%) and FY2021 (16.6%) was significantly higher only when compared to FY2017 (12.4%) (both $p < 0.05$ vs FY2017). Also, frequency of using antihyperglycemic drugs (4.8%) and using antilipidemic drugs (10.8%) significantly increased in FY2021, when compared to those in FY2017 (both $p < 0.05$). In females, abdominal obesity as a component of MetS tended to increase with aging ($p < 0.05$ vs FY2017). In regard to smoking habit and alcohol intake, their frequencies during the COVID-19 pandemic tended to decrease compared to those before the pandemic. Especially, FY2021 alcohol intake (18.6%) in females significantly declined compared to FY2017 (25.7%) ($p < 0.05$).

Increments in metabolic parameters and physical measurements pre-COVID-19 and during COVID-19 are summarized in Table 3. DBP increment significantly increased during COVID-19 compared to pre-COVID-19 in males and females (Δpre-covid19 to Δcovid19 : 0.22 ± 6.17 mmHg to 2.59 ± 6.69 mmHg, p = 0.0002 in males, -0.18 ± 6.26 mmHg to 2.16 ± 6.60 mmHg, p = 0.01 in females). In females, increments of waist circumference and fasting plasma glucose during COVID-19 also increased significantly compared to pre-COVID-19 [waist circumference : 0.59 ± 4.65 cm to 2.13 ± 5.25 cm, p = 0.03, fasting plasma glucose : 0.0 (-4.0, 4.0) mg/dl to 2.0 (-1.0, 5.0) mg/dl, p < 0.01]. Meanwhile, increments of BMI and body fat during

Table 2. Frequency of lifestyle factors and metabolic abnormality in each fiscal year by sex

	Male				Female			
	n	FY2017	FY2019	FY2021	n	FY2017	FY2019	FY2021
Smoking habit, %	379	97 (25.6)	98 (25.9)	93 (24.5)	140	4 (2.9)	4 (2.9)	3 (2.1)
Alcohol intake, %	379	220 (58.1)	223 (58.8)	213 (56.2)	140	36 (25.7)	32 (22.9)	26 (18.6) *
Hypertension, %	379	109 (28.8)	123 (32.5)	143 (37.7)*†	140	20 (14.3)	19 (13.6)	26 (18.6)
Using antihypertensive drug, %	379	47 (12.4)	56 (14.8) *	63 (16.6) *	140	5 (3.6)	11 (7.9)	12 (8.6)
Using antihyperglycemic drug, %	379	10 (2.6)	12 (3.2)	18 (4.8) *	140	1 (0.7)	1 (0.7)	3 (2.1)
Using antilipidemic drug, %	379	28 (7.4)	33 (8.7)	41 (10.8) *	140	6 (4.3)	7 (5.0)	12 (8.6)
MetS, %	379	75 (19.8)	71 (18.7)	79 (20.8)	140	0 (0)	3 (2.1)	5 (3.6)
Components of MetS								
Abdominal obesity, %	379	172 (45.4)	191 (50.4) *	210 (55.4)*†	140	12 (8.6)	18 (12.9)	23 (16.4) *
Dyslipidemia, %	367	106 (28.9)	105 (28.6)	105 (28.6)	140	11 (7.9)	10 (7.1)	17 (12.1)
Elevated blood pressure, %	379	186 (49.1)	189 (49.9)	215 (56.7)*†	140	39 (27.9)	41 (29.3)	39 (27.9)
Glucose intolerance, %	378	52 (13.8)	55 (14.6)	69 (18.3)*†	140	10 (7.1)	7 (5.0)	8 (5.7)

Values are presented as number (%).
MetS, metabolic syndrome ; * Bonferroni adjusted p < 0.05 vs FY2017, † Bonferroni adjusted p < 0.05 vs FY2019.

Table 3. Changes in metabolic parameters and physical measurements pre COVID-19 and under COVID-19 by sex

	Male				Female			
	n	Δpre-covid19	Δcovid19	P-value	n	Δpre-covid19	Δcovid19	P-value
BMI, kg/m^2	379	0.15 ± 1.06	-0.04 ± 1.50	**0.04**	140	0.09 ± 1.18	0.23 ± 1.40	0.47
Waist circumference, cm	379	1.07 ± 3.57	0.57 ± 4.80	0.15	140	0.59 ± 4.65	2.13 ± 5.25	**0.03**
Body fat, %	379	0.48 ± 2.66	-0.09 ± 3.42	**0.02**	140	0.06 ± 2.85	0.58 ± 3.83	0.27
Skeletal muscle mass, kg	379	0.01 ± 0.10	0.02 ± 1.13	0.93	140	0.05 ± 0.72	-0.03 ± 0.85	0.47
SBP, mmHg	312	0.43 ± 9.78	1.94 ± 11.15	0.13	127	-0.22 ± 10.21	2.25 ± 11.08	0.11
DBP, mmHg	312	0.22 ± 6.17	2.59 ± 6.69	**0.0002**	127	-0.18 ± 6.26	2.16 ± 6.60	**0.01**
Pulse pressure, mmHg	312	0.21 ± 7.33	-0.66 ± 8.55	0.18	127	-0.05 ± 7.38	0.09 ± 8.92	0.91
Fasting plasma glucose, mg/dl ¶	327	2.0 (-2.0, 5.0)	1.0 (-2.0, 5.0)	0.85	129	0.0 (-4.0, 4.0)	2.0 (-1.0, 5.0)	**< 0.01**
HbA1c, % ¶	361	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.50	137	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.86
Total-cholesterol, mg/dl	333	1.54 ± 21.84	3.65 ± 23.19	0.31	128	5.80 ± 23.07	6.52 ± 20.20	0.82
HDL-cholesterol, mg/dl	333	0.21 ± 7.08	0.94 ± 8.74	0.30	128	1.48 ± 9.12	0.84 ± 8.86	0.62
LDL-cholesterol, mg/dl	333	4.30 ± 19.68	1.64 ± 20.70	0.15	128	6.40 ± 17.67	4.31 ± 16.94	0.41
Fasting triglycerides, mg/dl ¶	299	-1.0 (-23.0, 24.0)	0.0 (-22.0, 21.0)	0.28	121	0.0 (-13.0, 15.0)	2.0 (-13.0, 16.0)	0.58

Values are presented as mean ± SD, median (25^{th}, 75^{th} percentile). p values were calculated by paired t-test or Wilcoxon's signed rank test¶.
Δpre-covid19 = metabolic profile (FY2019) - metabolic profile (FY2017), Δcovid19 = metabolic profile (FY2021) - metabolic profile (FY2019).
SBP, DBP, pulse pressure, HbA1c, total-cholesterol, HDL-cholesterol, and LDL-cholesterol were analyzed in subjects without medication for each condition.
Fasting plasma glucose and fasting triglycerides were analyzed in subjects without medication for each condition and without breakfast.

COVID-19 were significantly smaller than those pre-COVID-19 in males (BMI : 0.15 ± 1.06 kg/m^2 to -0.04 ± 1.50 kg/m^2, p = 0.04, body fat : 0.48 ± 2.66% to -0.09 ± 3.42%, p = 0.02).

DISCUSSION

In the present study, we used longitudinal data to evaluate the long-term impact of the COVID-19 pandemic on metabolic parameters in Japanese office workers. This study demonstrated that prolonged mild COVID-19 restrictions significantly increased DBP increment over 2 years above that with aging in both sexes. In addition, increments of waist circumference and fasting plasma glucose level during the COVID-19 pandemic were also significantly greater than those before the pandemic in females. Conversely, increments of BMI and body fat during the COVID-19 pandemic were significantly smaller than those before the pandemic in males.

Previous studies concerning changes caused by the COVID-19 pandemic have focused on the short-term impact of strict COVID-19 restriction periods, like lockdowns. During the COVID-19 lockdown and strict restriction period, morning SBP level was significantly higher in Chinese elderly hypertensive patients with anxiety (8). In addition, office blood pressure management worsened in Japanese outpatients (9). These results are highly likely to be attributable to blood pressure increase due to anxiety, psychological distress caused by COVID-19-related behavioral restrictions, financial stress, interrupted social interaction, and insufficient information on SARS-CoV-2. With the passage of time, COVID-19 lockdown and strict restrictions gradually eased. In Japan, milder restrictions gradually eased in FY2021. Anxiety about COVID-19 was also alleviated by the development of COVID-19 vaccines and medications. The results from this study indicate that the long-term impact of the COVID-19 pandemic has especially affected DBP in individuals without medication. The exact reasons underlying this result remain unclear but it could be due to increased visceral fat and peripheral resistance. In females, waist circumference in FY2021 was significantly larger because the increment in waist circumference in Δcovid19 was significantly larger than that in Δpre-covid19. In males, BMI and body fat in FY2021 were similar to those in FY2019 because BMI and body fat increments in Δcovid19 were significantly smaller than those in Δpre-covid19. On the other hand, waist circumference in FY2021 and the frequency of abdominal obesity in FY2021 were significantly higher than those in FY2019 because the increment in waist circumference in Δcovid19 was not very different from that in Δpre-covid19. In short, only waist circumference continued to increase although BMI and body fat were unchanged during the COVID-19 pandemic in males. Angiotensinogen expression from excessive visceral fat, hyperinsulinemia and insulin resistance may contribute to increased blood pressure (10, 11). Moreover, increased peripheral vascular resistance in small vessels leads to a greater increase in DBP than in SBP (12, 13). It was reported that increased peripheral vascular resistance may be attributable to less physical activity (14). It was obvious that individuals became less active due to the preventive measures against SARS-CoV-2 transmission during the COVID-19 pandemic (15, 16). Consistent with our findings, similar results were reported that SBP, DBP, and BMI during the pandemic were significantly increased in women's health checkups in Bangladesh (17). Incidentally, the frequency of antihypertensive medication use did not significantly increase during the COVID-19 pandemic in this study, as patients with hypertension may have become more reluctant to visit clinics because of the risk of COVID-19 infection in the early stage of the pandemic, although people may have paid more attention to their health conditions because comorbidity of hypertension (18), diabetes (19), heart disease (20, 21), hepatic cirrhosis (22), obesity (23), chronic kidney disease (24), cancer (25) and chronic obstructive pulmonary disease (26) may be associated with more severe COVID-19 outcomes. The same trends were observed in antilipidemic and antihyperglycemic drug use (data not shown). This implies that DBP increment and the frequency of hypertension were affected by the long-term impact of the COVID-19 pandemic, and not by the influence of antihypertensive medication during the pandemic. Therefore, increased visceral fat and peripheral resistance may have led to exacerbation of DBP in the long-term during the COVID-19 pandemic.

We found that increments of waist circumference and fasting plasma glucose in Δcovid19 in females were significantly greater than expected when accounting for the previous upward trends between FY2017 and FY2019, without significant increments in BMI and body fat. As a result, the frequency of abdominal obesity in FY2021 was significantly higher than that in FY2017. Kutac *et al*. also reported the same results in boys in the Czech Republic. COVID-19 restrictions reduced physical activity, resulting in a significant increase in visceral fat volume and decrease in skeletal muscle mass (27). Although the present study did not analyze physical activity level, physical activity seems to have decreased due to a request to refrain from non-essential and non-urgent outings. In addition, skeletal muscle mass in Δcovid19 tended to decrease in females (Table 3). As a result, less physical activity during the COVID-19 pandemic led to increased visceral fat and worsened glucose metabolism (i.e., increased fasting plasma glucose).

Contrary to our expectations, increments of BMI and body fat in Δcovid19 were significantly smaller compared to those in Δpre-covid19 in males. Hence, BMI and body fat level in FY2021 did not increase with aging during the COVID-19 pandemic in males. One potential explanation is that the frequency of eating-out was drastically reduced. To prevent transmission, the Japanese government and the Tokushima prefectural government (until Sep 30, 2021) strongly requested dining and drinking establishments to shorten their opening hours. Before the COVID-19 pandemic, the frequency of eating-out more than once a week was 41.6% for men and 26.7% for women, derived from the National Health and Nutritional Survey in 2019 (28). Hayashi *et al*. reported that the frequency of eating-out was decreased compared to usual during the COVID-19 pandemic in Japanese (29). The frequency of eating-out is higher in males than in females. Moreover, eating-out tends to be accompanied by alcohol consumption in males. Thus, there is a tendency for total energy intake due to eating-out to be higher in males, and abstention from eating-out had a greater influence on BMI and body fat in males.

Cumulative confirmed COVID-19 cases (4,983 confirmed cases until January 2022) in Tokushima (30) was quite low until FY2022, as well as in Japan (2,721,084 confirmed cases until January 2022) (2). Also, there were no confirmed COVID-19 cases in our cohort of subjects until FY2022. Therefore, the secular changes in metabolic parameters were derived from the COVID-19 pandemic and mild restrictions, and not from infection with SARS-CoV-2, COVID-19 itself and long COVID (post-COVID conditions).

The major strength of the present study is that we analyzed longitudinal data from the same subjects. Also, we didn't focus on the temporary impact of COVID-19 quarantine. However, there are some limitations. First, this cohort study focused on Japanese office workers, who may differ in various ways from those in other countries under the COVID-19 pandemic situation. However, we recruited subjects with various job types and working practices, so it is likely that the findings on the impact of COVID-19 are meaningful for populations under similar COVID-19 situations in other countries, as well as in Japanese. Second, blood sampling and physical measurements were conducted once in a FY. Third, we did not analyze the impact of lifestyle changes precisely except for smoking habit and alcohol intake. Fourth, the influence of COVID-19 vaccination and drugs, with the exception of antihyperglycemic drugs, antilipidemic drugs and antihypertensive drugs, cannot be excluded. Finally, the sample size may not be sufficiently large.

In conclusion, the present analysis has shown that the impact of the COVID-19 pandemic might have affected health over the long term. DBP management in males and females, and fasting plasma glucose and waist circumference management in females worsened during the COVID-19 pandemic. These findings may contribute to identifying metabolic profiles that have been influenced during the COVID-19 pandemic, on which to focus.

CONFLICT OF INTEREST / DISCLOSURE OF ANY FINANCIAL SUPPORT

Akiko Hata and Makoto Funaki declare no conflict of interest associated with this manuscript.

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