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Research article

Influence of dioxin-related compounds on physical function in Yusho incident victims

Jun-ichi Fukushi [a,b,*], Hidetoshi Tsushima [a,b], Yoshihiro Matsumoto [b], Chikage Mitoma [c], Masutaka Furue [c], Hisaaki Miyahara [a], Yasuharu Nakashima [b]

[a] Department of Rheumatology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Jigyohama1-8-1, Chuoh-ku, Fukuoka 810-8583, Japan
[b] Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Maidashi3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
[c] Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

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ABSTRACT

Purpose: Few studies have examined the influence of dioxin-related compounds on human physical function, and existing results are inconsistent. In 1968, accidental human exposure to rice oil contaminated with dioxin-related compounds resulted in the development of Yusho oil disease in Japan. We aimed to determine whether the degree of exposure to dioxin-related compounds was associated with physical function in Yusho patients.

Methods: In 2016, 65 men (average age: 65.7 years) and 77 women (average age: 64.7 years) participated in a nationwide health examination in Fukuoka prefecture. Functional reach, gait speed, hand grip strength, and toe grip strength were evaluated as part of physical function. The serum levels of polychlorinated dibenzo-p-dioxin, polychlorinated dibenzofurans, and non-ortho polychlorinated biphenyls were measured using high-resolution gas chromatography and high-resolution mass spectrometry. We examined the association between physical function tests and serum toxic equivalency (TEQ) values.

Results: A 10-fold increase in serum TEQ levels was negatively associated with functional reach (adjusted b = -4.07, p = 0.017) and hand grip strength (adjusted b = -2.20, p = 0.0245) in men. No association was observed between serum TEQ level and physical function in women.

Conclusion: Our findings suggest that dioxin-related compounds have a negative influence on physical function in men. However, these findings should be interpreted carefully. Future studies examining additional data on musculoskeletal disorders are warranted.

1. Introduction

Exposure to persistent organochlorine compounds, including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxin (PCDDs), and polychlorinated di-benzofurans (PCDFs), is associated with various adverse health effects. These highly lipophilic compounds accumulate in fatty tissue, resulting in chronic exposure. Dioxins and dioxin-related compounds are shown to increase the risk of developmental defects (Walkowiak et al., 2001), reproductive toxicity (Tsukimori et al., 2008), and endocrine dysfunction (Pluim et al., 1993).

In 1968, over 1,900 people in Japan experienced accidental exposure to rice oil that was contaminated with PCBs, PCDFs, and PCDDs. The resulting food poisoning was referred to as Yusho oil disease, which presented various clinical symptoms, including those of a systemic, a dermatological, and an ophthalmological nature (Furue et al., 2005). Dioxin-related compounds persist for a long time in Yusho patients. Among the PCDF congeners that are now considered the primary causative agents of Yusho oil disease, 2,3,4,7,8-penta CDF has the strongest presence in these patients, at a concentration that is approximately 10-fold higher than that in controls (Todaka et al., 2009). Serum levels of dioxin-related compounds are associated with various conditions, including general fatigue, hyperlipidemia, osteoporosis, and symptoms in the extremities such as arthralgia and numbness (Akahane et al., 2018; Kanagawa et al., 2008; Fukushi et al., 2016)).

In vitro studies have shown that dioxin-related compounds have toxic effects on neuronal proliferation and differentiation *via* the aryl hydrocarbon receptor (AhR) (Juricek and Coumoul, 2018). However, few studies have investigated the toxic effects of dioxin-like compounds on neuro-muscular function in humans. PCB exposure resulting from the consumption of fish from the Great Lakes did not have an effect on hand

* Corresponding author.
E-mail address: junichifukushi@gmail.com (J.-i. Fukushi).

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steadiness (Schantz et al., 1999). In the Seveso Women's Health Study, an inverted U-shaped association was observed between hand grip strength and serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) levels; however, the biological implications of the association remained unclear (Ames et al., 2018).

The aim of the current study was to examine whether the degree of exposure to dioxin-related compounds is associated with physical function in Yusho patients. We selected a set of four physical function tests, including functional reach, gait speed, and hand/toe grip strength. These physical functions are associated with the risk of falling (Alenazi et al., 2018), frailty (Weiner et al., 1992; Bouillon et al., 2013), osteoporosis (Edwards et al., 2015), and various health problems including dyslipidemia (Fredman et al., 2010) and arthralgia (Hirano et al., 2013). This set of four tests could be performed using minimal space (5-meter walkway), time (10 min in total), and devices (hand/toe grip dynamometer) during the nationwide Yusho health examination.

2. Materials and methods

2.1. Participants

A nationwide Yusho health examination has been conducted annually in Japan since 1986 to monitor the health status of chronic Yusho patients (Furue et al., 2005). Officially registered Yusho patients are those registered by the prefecture office and the Ministry of Health, Labour and Welfare. In addition to to officially registered Yusho patients, the examination is open to those who were exposed to the contaminated rice oil, and regard themselves as potential victims.

In 2016, 142 individuals participated in the nationwide health examination at Fukuoka prefecture, including 65 men and 77 women with mean ages of 65.7 years and 64.7 years, respectively; among them 58 (89.2 %) men and 57 (74.0 %) women were officially registered Yusho patients. We obtained written informed consent from all participants prior to drawing blood and conducting interviews and physical function tests.

All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Ethics Committee approved the study design (No. 25–166, Kyushu University).

2.2. Clinical and biological parameters

The body height and weight were recorded, and the body mass index (BMI) was calculated as the weight (kg) divided by the height (m) squared. Bioelectrical impedance analyzers were used to estimate body composition, and fat mass (kg) and muscle mass (kg) were calculated using an algorithm provided by the manufacturer (InBody720, Biospace, Seoul, Korea).

The serum levels of dioxin-related compounds were measured during the nationwide Yusho health examination (Todaka et al., 2009). In summary, 10 mL blood samples were collected, and the levels of PCDDs, PCDFs, and non-ortho PCBs were measured using high-resolution gas chromatography and high-resolution mass spectrometry at the Fukuoka Institute of Health and Environmental Sciences (Iida and Todaka, 2003). The levels of 29 different congeners including 7 PCDDs, 10 PCDFs, and 12 PCBs were measured. Among the 29 congeners, 3 PCDDs, 1 PCDF, and 2 PCBs detected in more than two-third of the participants were used to determine toxic equivalency (TEQ) values (Table 1). TEQ values were determined using the World Health Organization 2005 toxic equivalence factors (Van den Berg et al., 2006).

2.3. Physical function assessment

2.3.1. Functional reach test

Functional reach is the maximum distance to which an individual can reach forward while maintaining a fixed base of support while in the standing position (Weiner et al., 1992). The participants were instructed to lift their preferred arm to the horizontal position and reach out as far as possible without stepping. Measurements were performed twice, and the longer of two reaches was used for the analyses.

2.3.2. Gait speed test (4-meter)

The gait speed test was performed using a 4-meter walkway, with a 1-meter start-up before timing was started. Participants were instructed to "walk at your usual speed" (Studenski et al., 2003). Measurement was performed twice, and the shorter duration required to walk 4 m was used for the analyses.

2.3.3. Hand grip strength

Hand grip strength was measured using a handgrip dynamometer (TKK5401; Takei Scientific Instruments Co., Ltd., Niigata, Japan). Participants stood with their shoulders adducted at the side, their elbows fully extended, and their palms facing inward. Measurements were

Table 1
Demographic characteristics of the participants.

	Men (n = 65)					Women (n = 77)				
	mean	SD	min	max	median	mean	SD	min	max	median
Age (years)	65.7	12.1	39	87	67	64.7	12.6	38	91	66
Height (cm)	165.6	6.5	147.4	177.6	165.5	152.9	6.7	132.1	171.6	153.3
Weight (kg)	65.7	9.9	42.2	91.5	64	52.1	8.9	27.9	74.5	52.3
BMI (kg/m^2)	23.9	2.8	19	31.8	23.5	22.4	3.4	16.1	33	22.1
Fat mass (kg)	15.4	4.7	6.2	29.4	14.8	16.3	5.9	5.2	34.3	16
Muscle mass (kg)	47.7	5.6	32.1	60.6	47.6	33.9	3.4	27.2	42.8	33.7
Body fat ratio (%)	22.9	4.1	12.6	32.1	22.7	30.3	6.7	12.0	46.1	30.2
Physical function										
Functional reach (cm)	30.8	7.7	2.8	48	31	29.4	8.5	7	48	29
4M gait time (s)	2.89	6.0	2.01	5.8	2.71	3.46	3.6	2	7.5	3.06
Hand grip strength (kg)	37.2	7.5	20.6	53.7	37.2	20.9	5.1	10	31.6	20.7
Toe grip strength (kg)	8.92	4.2	2.4	23.7	8.8	4.87	3.1	1	19.1	4.5
Congeners (pg/g lipid)										
1,2,3,7,8-PeCDD	6.31	4.0	0.5	21.3	5.18	8.72	6.4	0.5	32.2	7.13
1,2,3,6,7,8-HxCDD	24.2	19.8	1	115	19.2	39.4	42.2	5.3	254.1	24.3
1,2,3,4,6,7,8-HpCDD	43.5	76.8	10.9	638.8	31.2	39.9	28.4	9.55	231.9	36.5
2,3,4,7,8-PeCDF	54.0	85.1	4.42	478.9	20.9	117.9	179.1	3.46	851.3	29.5
3,3′,4,4′,5-PeCB(#126)	77.7	53.4	13.6	192.1	53.1	66.8	43.9	2.34	210.8	53.6
3,3′,4,4′,5,5′-HxCB(#169)	126.3	113.5	15.5	677.2	97.4	148.6	162.7	13.3	738.8	86.8
Total TEQ	44.5	43.4	7.9	241.4	33	64.2	79.9	7.6	415.7	27.9

performed on both the right and left hand, and the maximum force of each hand was used for the analyses.

2.3.4. Toe grip strength

Toe grip strength was measured using a toe grip dynamometer (TKK3364, Takei Scientific Instruments, Niigata, Japan). The interphalangeal joint of the first toe of the foot was positioned on a grip bar, and the heel was stabilized using a heel stopper. Measurements were performed on both the right and left foot. After the training trials, toe grip strength was measured twice, and the maximum force of each foot was used for the analyses. The interclass correlation coefficients (ICC) (1.1) (intra-rater reliability) and ICC (2.1) (inter-rater reliability) of this measuring method are 0.88 and 0.97, respectively (Uritani et al., 2012).

2.4. Data analysis and statistical methods

Since the results of physical function assessments differ significantly between women and men, we separately assessed the relationships between the concentrations of dioxin-related compounds and physical function assessments for each sex. Considering multicollinearity among the dioxin-related compounds, we introduced total TEQ values (total TEQ) into the analysis. Simple linear regression analyses were performed to detect the demographic factors and TEQ values associated with physical function assessment, with a significance level of 95%. Multiple regression analysis was conducted on significant factors to detect the independent factors associated with physical function assessment, with a significance level of 95%. Although not always associated with physical function tests, height and muscle mass were used as variables in the multiple regression models in view of possible confounding. Among the physical function tests, the gait speed test was not associated with other tests (functional reach or hand/toe grip strength). Therefore, gait speed was not used as a variable in the multiple regression model. A two-sided P value <0.05 was considered statistically significant in the statistical tests. All statistical analyses were performed using JMP software (version 12; SAS Institute, Cary, NC).

3. Results

3.1. Demographic data

The participants' demographic characteristics are shown in Table 1. Approximately 80% of the participants were officially registered Yusho patients, and more than 85% were aged over 50 years. One quarter (15 women, 19% and 19 men, 29%) of the participants were obese (BMI >25 kg/m^2).

The distributions of the serum dioxin-related compounds are shown in Table 1. As previously reported, the blood concentration of 2,3,4,7,8-PeCDF was higher in those who participated in the nationwide Yusho health examination (87.3 pg/g lipid) than in the normal controls (17 pg/g lipid) (Todaka et al., 2007).

3.2. Physical function assessment

The results of the physical function assessment are shown in Table 1. There were no significant differences in the functional reach between the men and women ($p = 0.0689$). The time required to walk 4 m was significantly shorter in the men ($p = 0.0012$). The hand grip and toe grip strength values were significantly higher in the men than women ($p < 0.0001$ and $p < 0.0001$, respectively). Functional reach, hand grip strength, and toe grip strength were significantly associated with each other (as shown in Tables 3, 5, 7, and 9).

3.2.1. Functional reach test

The association between functional reach and the patients' demographic data is shown in Tables 2 and 3. On simple linear regression analyses, age, height, muscle mass, hand grip strength, and toe grip strength were significantly associated with functional reach in both, men and women (Table 2). The functional reach was significantly associated with 10-fold increases in the total TEQ levels in both, men and women (Fig. 1). When these factors were analyzed together using multiple regression analysis (Table 3), the 10-fold increase in the total TEQ retained significance ($p = 0.017$) among men. Height ($p = 0.0141$) and hand grip strength ($p = 0.0372$) were significantly associated with functional reach in women (Table 4).

3.2.2. Gait speed test

The association between gait speed and patients' demographic data is shown in Tables 4 and 5. In the simple linear regression analyses, age in women ($p = 0.048$) and height in men ($p = 0.0138$) were significantly associated with gait speed. In women, total TEQ was negatively associated with gait speed ($p = 0.0002$) (Table 4). When these factors were analyzed together using multiple regression analysis (Table 5), height retained significance in both men and women ($p = 0.0226$ and 0.0004, respectively). Muscle mass ($p = 0.001$) and hand grip strength ($p = 0.0437$) also retained significance in women. There was a tendency towards a negative association between total TEQ and gait speed in women ($p = 0.0515$). No significant association between total TEQ and gait speed was observed in men.

3.2.3. Hand grip strength

The association between hand grip strength and patients' demographic data is shown in Tables 6 and 7. On simple linear regression analyses, age ($p < 0.0001$ and <0.0001), height ($p < 0.0001$ and <0.0001), muscle mass ($p < 0.0001$ and $p = 0.0056$), functional reach ($p = 0.0012$ and <0.0001), and toe grip strength ($p < 0.0001$ and <0.0001) were significantly associated with hand grip strength in both, men and women, respectively. When these factors were analyzed together using multiple regression analysis, the 10-fold increase in the total TEQ retained significance ($p = 0.0245$) in men (Table 7). Toe grip strength also retained significance in both men and women ($p = 0.0008$ and 0.007, respectively).

Table 2
Factors associated with Functional reach:simple linear regression.

	Men (n = 65)				Women (n = 77)			
	b	lower95%	upper95%	p	b	lower95%	upper95%	p
Age	-0.3286	-0.533	-0.088	0.0086	-0.5238	-0.6719	-0.3355	<.0001
Height	0.4407	0.2166	0.6207	0.0003	0.6292	0.468	0.7499	<.0001
Muscle mass	0.3483	0.1101	0.5487	0.0051	0.3951	0.1832	0.572	0.0005
Body fat ratio	-0.0608	-0.304	0.1898	0.6359	-0.0188	-0.2462	0.2106	0.874
BMI	0.0464	-0.2037	0.2909	0.7178	-0.1062	-0.3268	0.1253	0.3678
4M gait time	-0.1645	-0.3962	0.0868	0.1975	-0.1724	-0.3857	0.0584	0.1419
Hand grip strength	0.4011	0.1682	0.5916	0.0012	0.5719	0.395	0.7079	<.0001
Toe grip strength	0.3918	0.1595	0.5829	0.0015	0.4547	0.2524	0.6189	<.0001
Log [Total TEQ]	-0.4466	-0.6413	-0.1978	0.0009	-0.3567	-0.5498	-0.1274	0.003

Table 3
Factors associated with Functional reach:multiple regression.

	Men (n = 65)				Women (n = 77)			
	b	SE	t	p	b	SE	t	p
Age	0.1626322	0.128636	1.26	0.2128	-0.125487	0.091258	-1.38	0.1742
Height	0.3945988	0.288482	1.37	0.1783	0.4872851	0.192674	2.53	0.0141
Muscle mass	0.0918823	0.320907	0.29	0.776	-0.184179	0.306455	-0.6	0.5501
Hand grip strength	-0.050298	0.25642	-0.2	0.8454	0.4034887	0.189326	2.13	0.0372
Toe grip strength	0.5216215	0.336659	1.55	0.1284	0.2633973	0.289112	0.91	0.3659
Log [Total TEQ]	-4.078505	1.644629	-2.48	0.017	-0.9811	0.952079	-1.03	0.3069

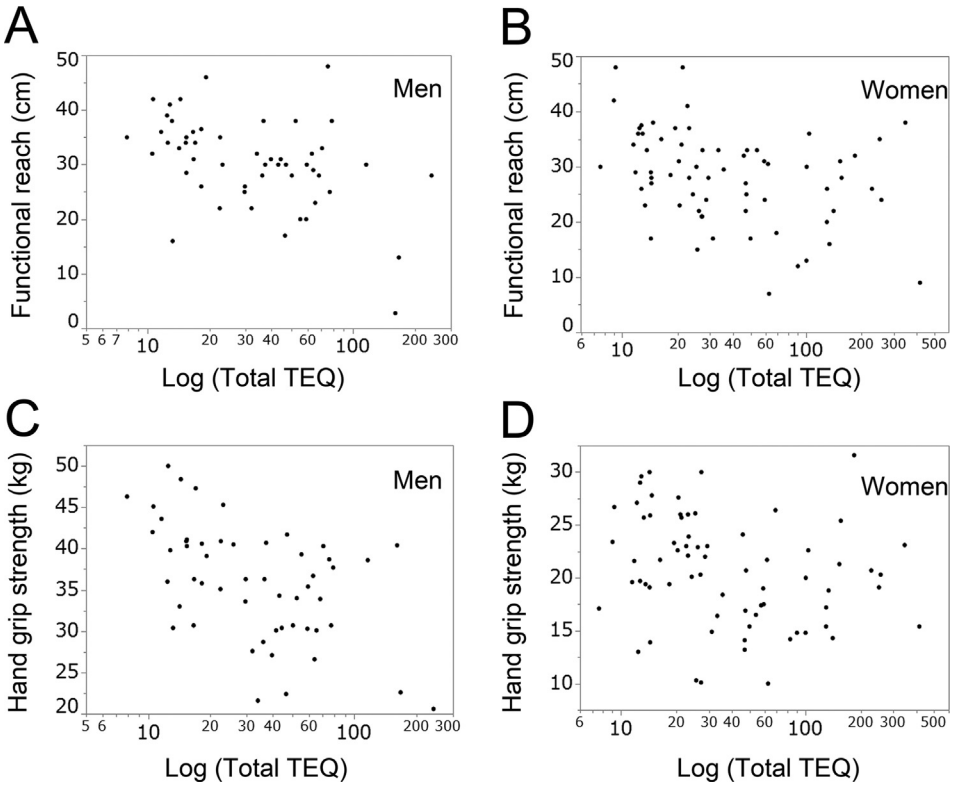

Fig. 1. (Upper) The distribution of functional reach and total TEQ in men (A) and women (B). (Lower) The distribution of hand grip strength and total TEQ in men (C) and women (D).

Table 4
Factors associated with 4M gait time:simple linear regression.

	Men (n = 65)				Women (n = 77)			
	b	lower95%	upper95%	p	b	lower95%	upper95%	p
Age	0.2102	-0.0375	0.4336	0.0954	0.2291	0.0023	0.4335	0.048
Height	-0.3065	-0.5136	-0.0656	0.0138	-0.2063	-0.4139	0.0217	0.0758
Muscle mass	-0.1209	-0.3561	0.1287	0.3412	-0.1418	-0.3573	0.088	0.2248
Body fat ratio	0.1614	-0.0879	0.3917	0.2027	0.1106	-0.1194	0.3293	0.345
BMI	0.1642	-0.085	0.3941	0.1947	0.1004	-0.1296	0.32	0.3916
Functionla reach	-0.1645	-0.3962	0.0868	0.1975	-0.1724	-0.3857	0.0584	0.1419
Hand grip strength	-0.207	-0.4326	0.043	0.1036	-0.1999	-0.4083	0.0284	0.0856
Toe grip strength	-0.0382	-0.2814	0.2095	0.7642	-0.1912	-0.4008	0.0374	0.1003
Log [Total TEQ]	0.1487	-0.1267	0.4028	0.2878	0.4433	0.2291	0.6166	0.0002

3.2.4. Toe grip strength

The association between toe grip strength and patients' demographic data is shown in Tables 8 and 9. In the simple linear regression analyses, age ($p = 0.0005$ and 0.0128), height ($p = 0.0002$ and <0.0001), functional reach ($p = 0.0015$ and <0.0001), and hand grip strength ($p < 0.0001$ and <0.0001) were significantly associated with toe grip strength in both men and women (men and women, respectively). No significant association between total TEQ and toe grip strength was observed in either the simple or multiple regression analysis among both men and women (Tables 8 and 9).

4. Discussion

In the present study, we examined whether the degree of exposure to

Table 5
Factors associated with 4M gait time:multiple regression.

	Men (n = 65)				Women (n = 77)			
	b	SE	t	p	b	SE	t	p
Age	-0.006762	0.114333	-0.06	0.9531	0.0206167	0.011568	1.78	0.0797
Height	-0.609405	0.258061	-2.36	0.0226	-0.088157	0.023294	-3.78	0.0004
Muscle mass	0.4899113	0.274994	1.78	0.0816	0.1333505	0.038684	3.45	0.001
Hand grip strength	-0.14679	0.226209	-0.65	0.5197	-0.049477	0.024021	-2.06	0.0437
Toe grip strength	0.295504	0.298024	0.99	0.3267	-0.048862	0.036686	-1.33	0.1878
Log [Total TEQ]	0.4234022	1.471497	0.29	0.7749	0.2401731	0.120897	1.99	0.0515

Table 6
Factors associated with hand grip strength:simple linear regression.

	Men (n = 65)				Women (n = 77)			
	b	lower95%	upper95%	p	b	lower95%	upper95%	p
Age	-0.6502	-0.7726	-0.4814	<.0001	-0.4374	-0.6023	-0.2365	<.0001
Height	0.6414	0.4697	0.7664	<.0001	0.5408	0.3604	0.6821	<.0001
Muscle mass	0.4709	0.2546	0.6424	<.0001	0.3127	0.0954	0.5016	0.0056
Body fat ratio	0.0111	-0.2353	0.2562	0.9304	0.0179	-0.207	0.2409	0.8775
BMI	0.1875	-0.0611	0.4142	0.1379	-0.0228	-0.2455	0.2023	0.8443
Functionla reach	0.4011	0.1682	0.5916	0.0012	0.5719	0.395	0.7079	<.0001
4M gait time	-0.207	-0.4326	0.043	0.1036	-0.1999	-0.4083	0.0284	0.0856
Toe grip strength	0.6105	0.429	0.7446	<.0001	0.5128	0.3234	0.6626	<.0001
Log [Total TEQ]	-0.5218	-0.6942	-0.2928	<.0001	-0.254	-0.4614	-0.0202	0.0339

Table 7
Factors associated with hand grip strength:multiple regression.

	Men (n = 65)				Women (n = 77)			
	b	SE	t	p	b	SE	t	p
Age	-0.054754	0.077114	-0.71	0.4812	-0.060692	0.060673	-1	0.321
Height	0.2518264	0.171928	1.46	0.1497	0.1866969	0.120852	1.54	0.1275
Muscle mass	0.1496828	0.179455	0.83	0.4084	0.1607535	0.203498	0.79	0.4326
Toe grip strength	0.6377272	0.1788	3.57	0.0008	0.51006	0.182821	2.79	0.007
Log [Total TEQ]	-2.204849	0.948922	-2.32	0.0245	-0.233044	0.638498	-0.36	0.7164

Table 8
Factors associated with toe grip strength:simple linear regression.

	Men (n = 65)				Women (n = 77)			
	b	lower95%	upper95%	p	b	lower95%	upper95%	p
Age	-0.4213	-0.6032	-0.1978	0.0005	-0.2863	-0.482	-0.0635	0.0128
Height	0.4529	0.235	0.6275	0.0002	0.4556	0.255	0.6186	<.0001
Muscle mass	0.2304	-0.0143	0.4491	0.0648	0.2252	-0.0019	0.4302	0.0521
Body fat ratio	-0.0304	-0.2722	0.2151	0.8103	0.011	-0.2165	0.2374	0.9251
BMI	0.0093	-0.2351	0.2526	0.9414	-0.0393	-0.2639	0.1894	0.7381
Functionla reach	0.3918	0.1595	0.5829	0.0015	0.4547	0.2524	0.6189	<.0001
4M gait time	-0.0382	-0.2814	0.2095	0.7642	-0.1912	-0.4008	0.0374	0.1003
Hand grip strength	0.6105	0.429	0.7446	<.0001	0.5128	0.3234	0.6626	<.0001
Log [Total TEQ]	-0.2254	-0.4651	0.0451	0.1012	-0.1309	-0.3581	0.111	0.2873

Table 9
Factors associated with toe grip strength:multiple regression.

	Men (n = 65)				Women (n = 77)			
	b	SE	t	p	b	SE	t	p
Age	-0.064577	0.055311	-1.17	0.2489	0.0049657	0.040042	0.12	0.9017
Height	-0.002612	0.127234	-0.02	0.9837	0.0939571	0.079752	1.18	0.2433
Muscle mass	-0.003309	0.130831	-0.03	0.9799	0.0345901	0.133844	0.26	0.7969
Hand grip strength	0.3340187	0.093649	3.57	0.0008	0.218682	0.078382	2.79	0.007
Log [Total TEQ]	0.9202673	0.712587	1.29	0.2029	0.0130998	0.418522	0.03	0.9751

dioxin-related compounds is associated with physical function in Yusho patients. Unlike previous studies, we measured the serum levels of 29 congeners and performed four different physical function assessments. The 10-fold increase in the total TEQ was significantly associated with the decrease in functional reach and hand grip strength in men. Although not significant, there was a tendency of a negative association between

total TEQ and gait speed in women.

The functional reach test is an assessment of functional balance, and is reportedly associated with age (Wallmann, 2001), risk of falling (Alenazi et al., 2018), frailty (Weiner et al., 1992), and various health problems including stroke and diabetes (Smith et al., 2004). In Yusho, symptoms in the extremities such as arthralgia and numbness are associated with serum levels of dioxin-related compounds (Akahane et al., 2018). Although these subjective symptoms were not evaluated in the present study, it seems possible that complex health problems associated with dioxin-related compounds could negatively affect functional reach distance in men; this represents the general health of the participants (Weiner et al., 1992).

Only two studies have reported the effect of dioxin-related compounds on physical function. PCB exposure from the consumption of fish from the Great Lakes did not impair hand steadiness, as measured using the static motor steadiness test (Schantz et al., 1999). In the Seveso Women's Health Study, an inverted U-shaped association observed between hand grip strength and a 10-fold increase in serum TCDD levels; however, the biological implication of the U-shaped association was not clarified (Ames et al., 2018). In the present study, we found a significant negative association between a 10-fold increase in the total TEQ and hand grip strength in men (Table 7). Previous studies have shown that handgrip strength is positively associated with leisure-time physical activity (Aadahl et al., 2011) and negatively associated with hospitalization (Cawthon et al., 2009) and all-cause mortality (Leong et al., 2015). Among those affected by the Yusho incident, the prevalence of various diseases, including orthostatic hypotension, Basedow's disease, cardiac insufficiency, and tachycardia, was higher than that in the general population (Akahane et al., 2018). It is unclear whether dioxin-related compounds directly affect neuro-muscular function. However, a plausible explanation for the observation in this study is that hand grip strength is an indicator of general health status (Reuben et al., 2013) and in men, it is affected by various conditions related to the Yusho incident (Akahane et al., 2018).

Gait speed has been shown to reflect health and functional status, and is considered a clinically useful indicator of well-being in elderly people (Hall, 2006). Both gait speed and hand grip strength are frequently used as objective components of frailty syndrome (Bouillon et al., 2013), and associated with mortality among older adults (Studenski et al., 2011). In the present study, there was a tendency of an association between higher TEQ values and slower gait speed in women ($p = 0.0515$). This lack of significance may result from the relatively small number of participants in the present study.

Toe grip strength was associated with the functional reach test and hand grip strength, but not with the total TEQ. Similar to hand grip strength, toe grip strength decreases with age (Uritani et al., 2014; Suwa et al., 2017), and is associated with the risk of falling among elderly people (Menz et al., 2006; Mickle et al., 2009). Although toe grip strength reflects patients' general physical condition and health status (Endo et al., 2002), hand grip strength may be a more sensitive marker of people's general health condition, which is possibly affected by dioxin exposure (Akahane et al., 2018).

Sex-related difference in the sensitivity to the toxicity of dioxin have been reported in various species including mice, rats, and humans (Pohjanvirta et al., 2012). Perinatal dioxin exposure has affected the development of language and gross motor skins only in boys exposed to Agent Orange in Vietnam (Pham et al., 2019). In a national survey in the United States, the negative association between serum levels of PCBs and cognitive scores was stronger in women than in men (Bouchard et al., 2014). These studies, along with our observations, indicate that the influence of dioxin-related compounds on neuro-muscular function depend on the sex. The functions of cells in neuro-muscular system are strongly affected by estrogen receptor signaling, which can cross-talk with aryl hydrocarbon receptor (AHR) (Juricek and Coumoul, 2018). Although this cross-talk may be modulated in the presence of dioxin-related compounds, the sex-related difference observed in the present study remains unexplained, and requires future investigation.

The present study has several limitations. First, the lack of information on participants' health conditions, including the presence of locomotive disability, may have resulted in a weakened estimation of the association between serum levels of dioxin-related compounds and physical function. To minimize possible confounding, we plan to follow this group in future studies, and intend to collect information on their lifestyle and health condition. Second, the individuals who had already died, or those who could not attend the annual health check were not included in the present study; this raises the possibility of a selection bias. In addition, the relatively small sample size raises concerns pertaining to statistical power. Despite these weaknesses, ours is among the few studies to have examined the effects of dioxin-related compounds on physical function. Unlike previous studies, we measured the serum levels of 29 congeners using a reliable method and evaluated four different physical function tests.

5. Conclusions

We observed a negative association of 10-fold increases in the total TEQ with hand grip strength and functional reach in men, based on data from the nationwide Yusho health examination. However, care should be taken in the interpretation of the observation, as residual confounding may be present. We plan to follow this group in future studies and collect information on the presence of locomotive disability and musculoskeletal disorders.

Declarations

Author contribution statement

Jun-ichi Fukushi: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Hidetoshi Tsushima: Performed the experiments; Wrote the paper.

Yoshihiro Matsumoto: Performed the experiments; Analyzed and interpreted the data.

Chikage Mitoma: Conceived and designed the experiments; Performed the experiments.

Masutaka Furue: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Hisaaki Miyahara: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Yasuharu Nakashima: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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