厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

コホート対象者の食事調査の研究

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佐久総合病院人間ドック受診者からコホート集団を組み、サブコホート（総計5000人程度）には、糖尿病・メタボリックシンドローム予防のための、食生活と運動の介入を行い、栄養摂取量をDHQアンケートにより把握して、介入効果との関係を評価した。

A. 研究目的

人間ドック受診者を対象として研究を拡げ、栄養摂取・身体活動状況、過去の健診データの収集と追跡調査から、メタボリックシンドロームの自然史を明らかにし、同時にSCOP対象者をサブコホートとして栄養指導及び運動指導を継続実施して、長期の介入効果を検証し、特に脱落者の要因を明らかにして対策を考える事を目的とする。本研究は、専門家グループにより認知行動変容療法により食事と運動による介入を徹底しておこなうが、栄養摂取に関して正確に把握する点に特色がある。食事を通じて疾病の予防や治療を行なうときに、その科学的根拠が必要であるが、日本ではこの分野の研究は立ち遅れている。本研究は日本人のデータにもとづくエビデンスの構築に貢献できる。

B. 研究方法

また新規に21年度からの受診者、40～75歳の男女を対象に5歳階級ごとに分け、年齢層毎に男女各50人以上、各年度1000人以上の対象者を募り、サブコホート参加者には一般健診項目に加えメタボリックシンドロームに関連する検査を追加実施する。栄養調査は佐々木らが開発した半定量SDQを用いる。これらを入力し、栄養素の摂取状況を推定し、身体活動や検査データと比較検討して栄養の影響を明らかにする。

C. 研究結果

佐久総合病院人間ドック受診者から同意を得た参加したサブコホート対象者は総計 3000人を超えた。DHQアンケートの入力は終了し分析中である。

D. 発表業績

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E. 健康危険情報

特になし

F. 知的財産権の出願・登録状況

(1) 特許取得　なし

(2) 実用新案　なし

(3) その他　なし

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

糖尿病進展及び合併症進展予防に関する生物統計学的研究

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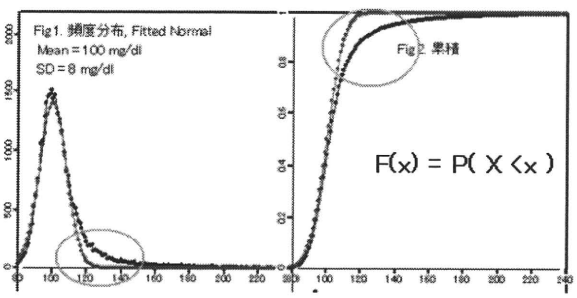
一般健常者での糖尿病の新規発症は年あたり 1/100、合併症としての腎症はそのなかで1/100 程度であり、糖尿病性腎症年あたり新規発生確率は 1/10,000 と小さな確率も全国 1億人にて万の数を数え対策が急がれる。今回、我々は、一地域住民を対象としての 30 年近い健診成績を 栄養疫学的 Retrospective Cohort として縦断評価し、糖尿病進展と、腎症進展の関連を解析したので報告する。

A. 研究目的

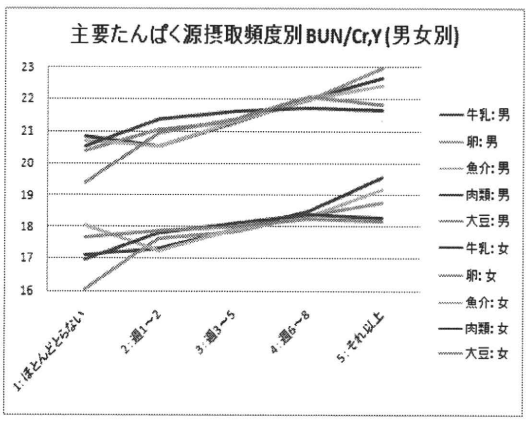
糖尿病合併症なかでも腎症は、近年増加傾向にあり対策がいそがれる。糖尿病初期には過剰濾過状態があるが、その後の腎機能低下との関連は、分からないことが多い。糖尿病性腎症では、腎機能が低下し始めると、進展が早いことが言われているが、病期の長いことと、臨床データとの突き合わせが十分でないことから実際分からないことが多い。我々は早期からの糖尿病進展予防が重要との視点から、長年にわたる地域住民健診および人間ドック成績を栄養疫学的 Retrospective Cohort として縦断データベースを構築し、その評価と解析を提案した。ここでは、タンパク質摂取との関連を解析したので報告する。

B. 研究方法

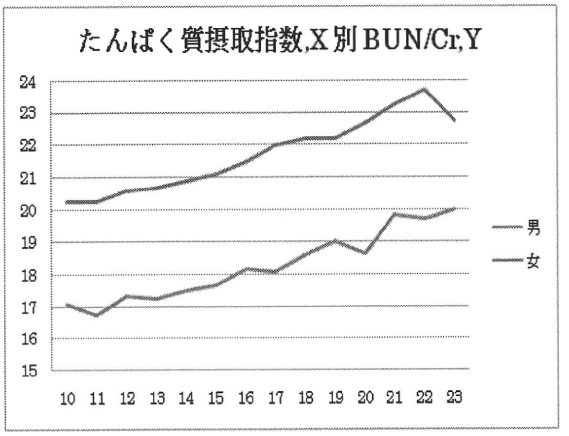


血糖値の分布をみると 110mg/dl 以上で べき乗分布が認識される。このことの背景には、不可逆的変化の蓄積効果があり、膵β細胞の枯渇が大きいが、これにインスリン抵抗性の増大（付図１）がからみ、時間発展は個人差が大きく複雑である。

栄養疫学的に、タンパク質摂取に注目すると、供給源は 1. 牛乳, 2. 卵, 3. 魚介, 4. 肉類, 5. 大豆等における一週間の摂取頻度とし、タンパク質摂取量的指標としては BUN/Cr を用いると両者に良い相関が認められる。



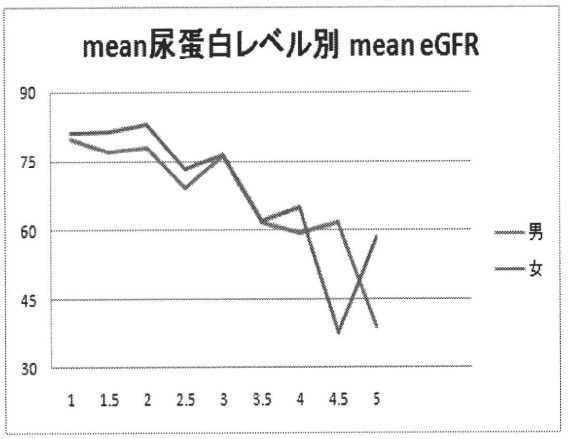
総合スコアでの相関はさらに良い。



以上の観察から糖コントロール状態は血糖値、タンパク質摂取量的指標は BUN/Cr，腎機能コントロール指標としては eGFR を用いて時間発展を解析した。

C. 研究結果

(1) 尿タンパク＋顕在化と腎機能低下



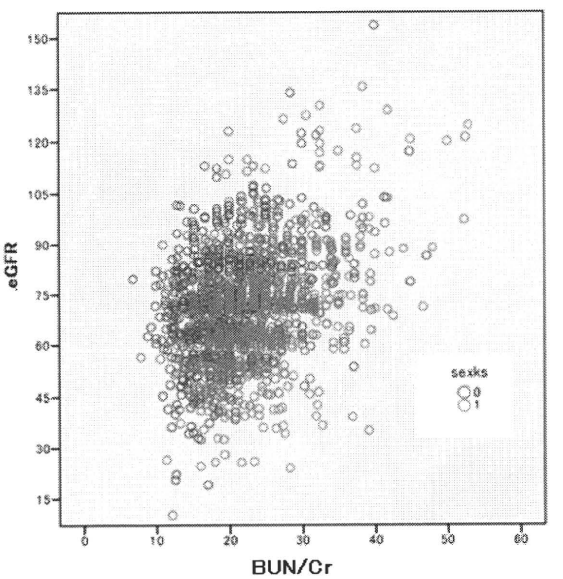
尿タンパク＋(1:-, 2:+-, 3:+, 4:++, 5:+++)顕在化と腎機能低下指標 eGFR との相関は図の如く分かり易かった（10 年間の平均)。

(2) タンパク質摂取の量的指標として BUN/CR を用い 尿タンパクをみると、付図２の如く 尿タンパク(-) vs (+-) の比較にて 有意差(P<0.001) が得られた。

(3) 糖尿病域に限って血糖（含む随時血糖）レベル別に eGFR をみると 血糖値が 200～ 300 mg/dl を超えるようになると全体的な eGFR の低下傾向がみられたが、 eGFR 50 程度未満に注目すると 一定の傾向は観察されなかった。eGFR 100 を超える対象は 血糖値 200 未満に多く見られた（付図３）

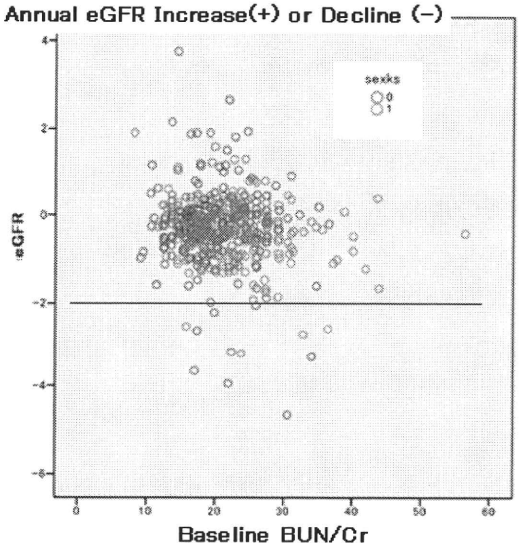
(4) 糖尿病既往期間 20 年以上に限って eGFR レベル別に eGFR 年低下を観察すると(1990→2005) eGFR 値の低い方で年低下傾向の大きいことが観察された（付図３）

(5) タンパク質摂取量的指標 BUN/Cr と eGFR の相関解析結果



図の如く BUN/Cr が 30 を超えると eGFR 100 以上(過剰濾過)の出現が増加して観察された。

(6) 年令 60 歳以上での Baseline 時 BUN/Cr 別 eGFR 年低下の相関



図の如く負の相関が得られた。

D. 考察とE. 結論

近年、透析患者数の増加は著しく、治療成績のよいこともあって、prevalence は世界１のレベルである。新規透析導入に占める糖尿病性腎症は増加の傾向にあって、糖尿病進展予防、腎症進展予防には切実なものがある。

今回、長年の健診および人間ドック成績を用いて、栄養疫学的観点からタンパク質摂取との量的関係の解析をこころみた。タンパク供給源はいろいろであるが、BUN/Cr を量的指標として採用すれば、尿タンパク (-) から (+-) の出現頻度の増加が示唆された。 健診人間ドックの現場では 尿タンパク (+-) 程度は Risk Factor としては認識されるがさらなる情報が望まれる。しかしながらタンパク質摂取量を減らすことが尿タンパクの改善につながることは分かりやすいと考えられた。

BUN/Cr と eGFR の関係は BUN/Cr が 30 以上で eGFR 100 以上の過剰濾過状態の出現頻度が増していて、これもタンパク質摂取との量的関係が背景に示唆された。

糖尿病初期における過剰濾過状態の善し悪しや、血糖値コントロールとその後の腎症進展との関係（付図３）は一定の傾向がみられなかったが、これには、病期の把握、糖尿病薬服薬状況、さらには臨床データとの突き合わせの必要性が示唆された。

糖尿病罹病期間 20 年以上に限っての観察（付図４）は、糖尿病では腎機能が低下をはじめるとその進展が早まるということが示唆され、今回解析結果のなかで特に注目された。

最近では 30～40 歳からの糖尿病罹病も多く罹病期間との関係は重要である。現在 60 歳以上で 糖尿病罹病期間が 20 年以上という対象では、過去にさかのぼってのタンパク質摂取状況の把握、また今後のタンパク質摂取状況の適正化にて将来における腎機能の低下予防に資する面が大きいと考えられる。糖尿病性腎症、年あたり新規発生 1/100,00 の確率に迫るには、個人差の大きな分野であり今後の栄養疫学研究の発展が望まれる。

F. 健康危険情報

特になし

G. 研究発表

1. 論文発表

なし

2. 学会発表

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2. 水野正一： 最近の動向を加味した Age Cohort 解析の提案（肝癌を例として）. 第 23 回日本疫学会総会 平成 23 年 1 月 21 札

幌

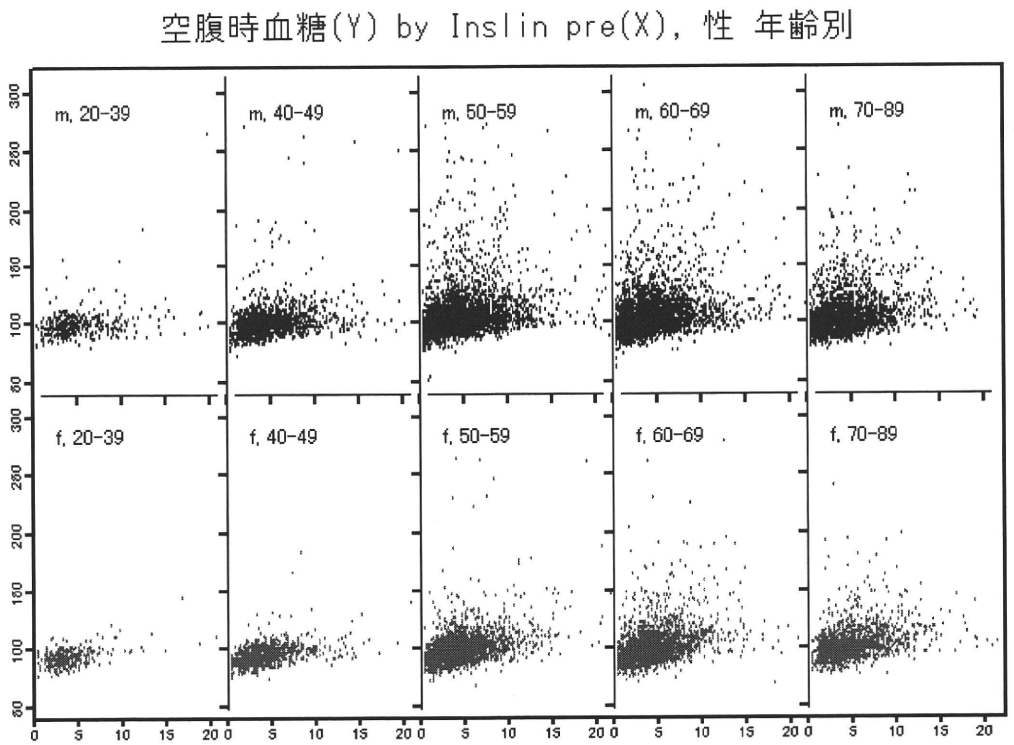
3. 森本明子、大野ゆう子、辰巳友佳子、前島文夫、西垣良夫、渡邊昌、水野正一：健康診断受診者の BMI 値のパーセンタイル曲線. 第 23 回日本疫学会総会 平成 23 年 1 月 22 札幌
4. 辰巳友佳子、大野ゆう子、森本明子、前島文夫、西垣良夫、渡邊昌、水野正一：健康診断受診者の血圧値のパーセンタイル曲線. 第 23 回日本疫学会総会 平成 23 年 1 月 22 札幌

H. 知的所有権の取得状況

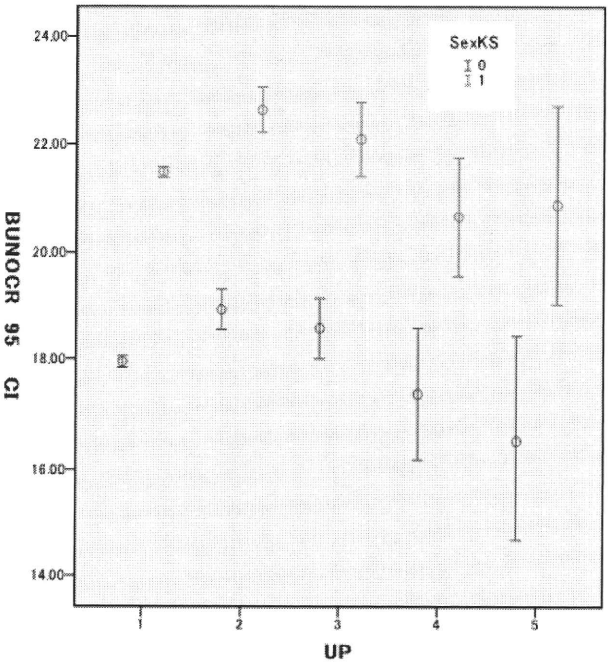
1．特許取得 なし

2．実用新案特許　なし

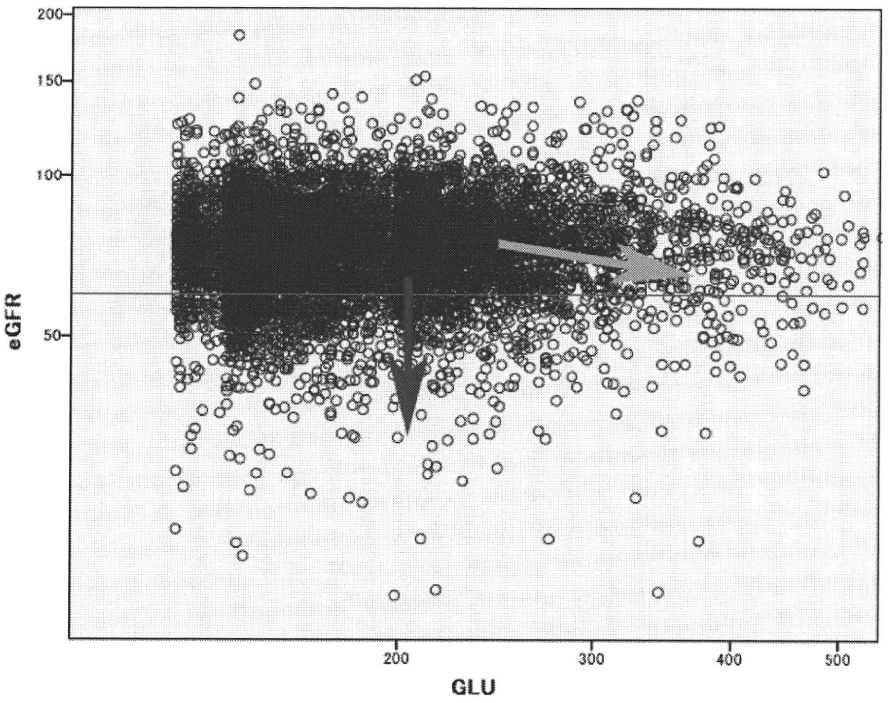
3. その他　なし



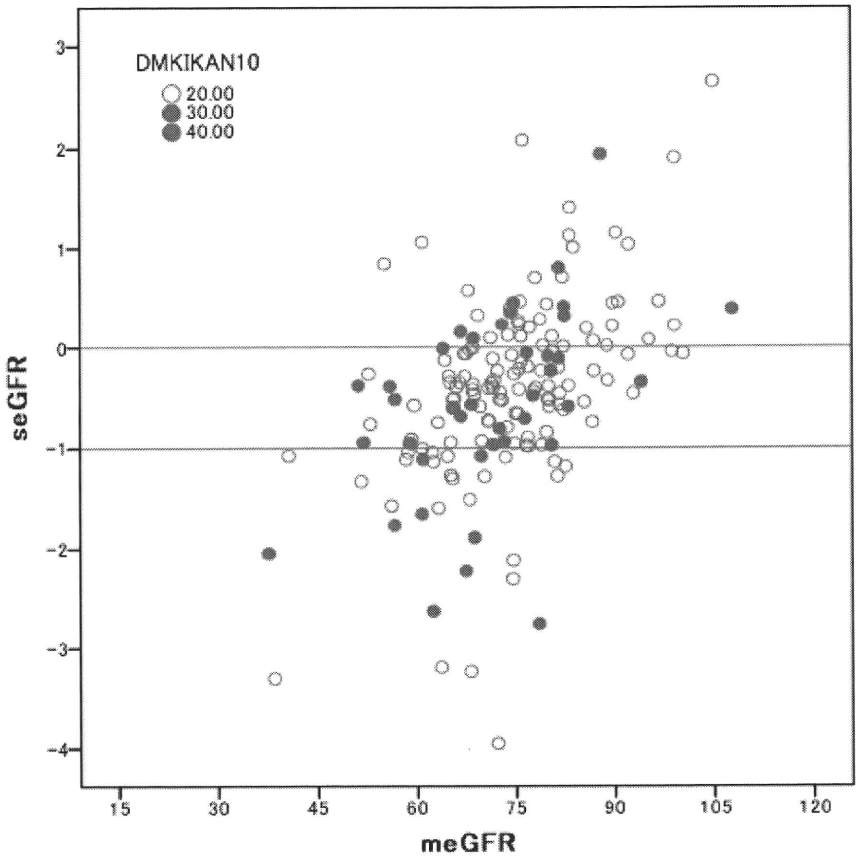
付図 1. 空腹時インスリン値(X)と血糖値(Y) の相関 男女年齢別



付図 2. タンパク質摂取量的指標 BUN/CR(Y) と 尿タンパク(1:−,2:+−,3:+,4:++,5+++)との相関 (1990−1993 年)



付図 3. (血糖値,eGFR) 相関図



付図4. 糖尿病既往期間 20 年以上の対象に限っての eGFR レベル(X)別 eGFR 年低下(Y)

Ⅲ. 研究成果の刊行物・別冊

ORIGINAL

Advance Publication
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Congener-specific polychlorinated biphenyls and the prevalence of diabetes in the Saku Control Obesity Program

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Abstract. The prevalence of diabetes is increasing globally. In addition to established risk factors for diabetes, such as diet, inactivity, overweight and obesity, the involvement of persistent organic pollutants, including dioxins and polychlorinated biphenyls (PCBs), has also been suggested to be a possible, but controversial, cause of this epidemic. The present study investigated the association between blood PCB congener levels and the prevalence of diabetes among middle-aged, overweight and obese Japanese participants in the Saku Control Obesity Program. One hundred seventeen participants had their congener-specific PCB levels measured in addition to undergoing routine blood analyses at the time of a medical checkup. Prevalent diabetes was defined according to two methods: definite diabetes was defined as people with an HbA1c level ≥ 6.9% or who were taking medication for diabetes, and all diabetes was defined as people with an HbA1c level ≥ 6.5%, a fasting plasma glucose level ≥ 126 mg/dL, or a history of doctor-diagnosed diabetes. A multiple logistic regression analysis was performed to analyze the association between the PCB levels and the prevalence of diabetes, with adjustments for sex, age, body mass index and total lipids. As a result, PCB 146 and 180 were positively associated and PCB 163/164 and 170 were negatively associated with the prevalence of definite diabetes. The significance of the association of PCB 180 and 163/164 with the prevalence of diabetes persisted regardless of the definition of diabetes or adjustments for total lipids, suggesting the possibility that these parameters may modify the risk of diabetes.

Key words: Diabetes, Polychlorinated biphenyl, Risk factor, Saku Control Obesity Program

DIABETES mellitus is increasing in Japan and other countries worldwide. The global prevalence of diabetes is estimated to be 285 million people among adults aged 20 to 79 years in 2010, and it is projected to increase to 439 million by 2030, accounting for 7.7% of the world population [1].

Well-established risk factors for the development of type 2 diabetes include excessive food consumption, a lack of physical activity, overweight and obesity, aging, smoking, socioeconomic status, and genetic predisposition [2, 3]. In addition to these factors, the involvement of persistent organic pollutants (POPs), such as dioxins and polychlorinated biphenyls (PCBs), in the increasing prevalence of diabetes has also been considered. Observations of occupational or accidental exposure to high levels of POPs have suggested a relationship between POPs and diabetes [4-9]. US Air Force veterans who participated in the spraying of aerial herbicide during the Vietnam War had higher levels of serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), compared with veterans who performed other tasks, and exhibited a significantly higher prevalence of diabetes, increased use of medicines for diabetes, and a shorter duration until the onset of diabetes [4]. A cross-sec-

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tional study examining the effect of occupational exposure to TCDD among US workers showed a positive association between the TCDD concentration and the risk of diabetes and a higher fasting serum glucose level [5]. In a follow-up study of Italian citizens who were exposed to TCDD as a result of an industrial accident that occurred in 1976, a significantly elevated diabetes-related mortality was observed among women [6-9].

However, the relationship between exposure to low levels of POPs and diabetes is less consistent. A cross-sectional study of a general population in the USA indicated that the prevalence of diabetes, as determined by a fasting plasma glucose (FPG) level ≥ 126 mg/dL, a non-FPG level ≥ 200 mg/dL, or a self-report of diabetes diagnosed by a physician, was associated with the concentrations of 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153), 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HpCDD), 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD), oxychlordane, *p,p'*-dichlorodiphenyltrichloroethane (DDE), and trans-nonachlor [10]. Another cross-sectional study of a Native American population concluded that the total PCB concentrations of 101 PCB congeners, PCB 153, PCB 74, DDE, and hexachlorobenzene (HCB) were positively associated with diabetes, as defined by an FPG level > 125 mg/dL or the use of hypoglycemic medication [11]. PCB 126, along with polychlorinated dibenzo-*p*-dioxin and *p,p'*-DDT, was considered in a general population in the USA, and a significant association was found with diagnosed diabetes and undiagnosed diabetes, which was defined as an HbA1c level > 6.1% [12]. Among the general population of Japan, a cross-sectional study measured seven polychlorinated dibenzo-*p*-dioxins (PCDDs), ten polychlorinated dibenzofurans (PCDFs) and 12 dioxin-like PCBs and showed that the accumulated toxic equivalents (TEQs) of these compounds were positively correlated with the HbA1c level [13]. In addition, the prevalence of diabetes, as defined by the self-reporting of physician-diagnosed diabetes or an HbA1c level > 6.5%, was positively associated with the accumulated TEQs of dioxin-like PCBs [13].

On the other hand, some studies have not confirmed a positive relationship. A cross-sectional study among Greenland Inuit did not find any association between subclasses of 13 PCB congeners and organochlorine pesticides and the prevalence of diabetes, as detected using a 75-g oral glucose tolerance test (OGTT) or self-reporting [14]. A nested case-controlled study of African-American and white youths showed nonlinear associations between POPs (35 PCB congeners, nine organochlorine pesticides, ten polychlorinated diphenyl ether congeners and one polybrominated biphenyl conger) and the prevalence of diabetes defined by the prescription of hypoglycemic medication or an FPG level ≥ 126 mg/dL at two or more blood tests [15]. A cross-sectional study in Belgium found significantly negative associations between PCB 170, 180, and the PCB total and insulin resistance [16]. Therefore, the effect of low levels of POPs apparently varied among studies, and further investigation is needed to determine whether POP exposure may be a risk factor for diabetes.

In the present study, 13 PCB congeners that are regarded as commonly present among Japanese adults were measured [17], and the associations with diabetes were assessed in middle-aged obese Japanese people without apparent exposure to POPs.

Subjects and Methods

Study population

This study was performed among the participants of the Saku Control Obesity Program (SCOP), the details of which have been described previously [18]. Briefly, the program consisted of a randomized intervention trial using cognitive-behavioral treatment at the Saku Health Dock Center. People who had undergone health checkups at the center were registered in the database, and 976 members aged 40 to 64 years who were free of type 1 diabetes or severe diseases such as stroke, cardiovascular disease, advanced cancer or significant renal or hepatic dysfunction and had a body mass index (BMI) in the upper five percentile (28.3 or above at their last medical checkup) were invited. A total of 235 people agreed to participate in the SCOP, and anthropometric measurements, various biomarkers and questionnaires regarding dietary habits, lifestyle, past and present medical history, and family history were obtained at baseline and during a follow-up examination. The participants were randomly assigned to two groups; group A, who participated in a lifestyle intervention program during year 1, and group B, who participated in the same intervention program during year 2. All the procedures were reviewed and approved by the ethical committees of the National Institute of Health and Nutrition and Saku Central Hospital, and written informed consent was obtained from all the participants.

Blood sampling and PCB congener-specific analysis

One hundred seventeen people participated in group A, and each participant provided a whole blood sample at baseline examination. The blood samples were obtained by venipuncture after fasting, and 2 mL of the sample was used for the PCB analysis. The PCB congeners that were measured were PCB 74, 99, 118, 138, 146, 153, 156, 163/164, 170, 180 and 182/187. These congeners reportedly account for 75% of the total amount of detected PCBs among healthy Japanese adults [17]. The PCB congeners were analyzed using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) at Otsuka Pharmaceutical Co. Ltd. (Tokushima, Japan) using a method described in detail elsewhere [17].

The obtained PCB concentrations were measured in units of pg/g blood; however, PCB concentrations are often expressed in terms of lipid weight because of the lipophilic nature of POPs and the invariability of lipid-adjusted PCB values, regardless of fluctuations in serum lipid levels [19, 20]. To correct for the serum total lipid level and obtain the lipid-adjusted PCB value (ng/g lipid), the measured PCB concentration in pg/g blood was divided by the total lipid value, as calculated using the short formula proposed by Phillips *et al.* [19, 20] as follows:

$$\text{Total lipids} = (2.27 \times \text{total cholesterol}) + \text{triglycerides} + 62.3 \text{ (mg/dL)}$$

The resulting value was then multiplied by 10^2 to adjust the unit.

Evaluation of diabetes

Diabetes was diagnosed based on blood test results, prescribed medication, and the medical history. Subjects with an HbA1c level $\geq$ 6.9% or a prescription for a hypoglycemic medicine were regarded as the 'definite diabetes' group. In addition, a broader definition was also considered and consisted of the combination of a FPG level and HbA1c measurements indicative of diabetes [21], since conducting a 75-g OGTT in all the participants was not practical for the detection of undiagnosed diabetes. Accordingly, subjects with an FPG level $\geq$ 126 mg/dL, an HbA1c level $\geq$ 6.5%, a prescription for hypoglycemic medicine, or a history of physician-diagnosed diabetes were defined as the 'all diabetes' group. The value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS)(%) + 0.4%, considering the relational expression of HbA1c (JDS)(%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) [22].

Statistical analyses

The association between exposure variables and the prevalence of diabetes was estimated using odd ratios, 95% confidence intervals, and p values obtained from multiple logistic regression analyses. Three models were applied to analyze the associations between the prevalence of diabetes and the serum PCB concentrations. In the first model, the directly measured wet weight concentration (pg/g blood) of PCBs was applied with age (continuous variable), sex (dichotomous variable) and BMI (continuous variable) as potential confounders. Next, the serum total lipid value was added as an adjustment. In the third model, the lipid-adjusted PCB concentration (ng/g lipid), age, sex and BMI were included in the model.

All analyses were performed using Stata SE 10.1 (StataCorp LP, TX, USA), and p values less than 0.05 were considered statistically significant.

Results

The basic characteristics of the participants are summarized in Table 1. Among the 117 group A members, 59 (50.4%) were male and 58 (49.6%) were female. Fifteen (12.8%) were classified in the definite diabetes group, and 32 (27.4%) were classified in the all diabetes group. No significant differences in the mean values of data for the diabetes and non-diabetes groups were observed except for the HbA1c and FPG levels.

Table 2 summarizes the blood PCB congener levels among the participants. All the congeners were skewed to the right. Mean of their concentration was higher among older age group people for all of the PCB congeners. PCBs that were common within the participants were PCB 153, 180, 138 and 118, and this tendency was similar in other studies measuring these congeners among the population [17, 23].

The results of the multiple logistic regression analyses with definite diabetes as the dependent variable are shown in Table 3. PCB 146 and 180 had a statistically significant positive association with definite diabetes, and PCB 163/164 and 170 had a significantly negative association with definite diabetes when the PCB congeners were adjusted for sex, age and BMI. An additional adjustment for total lipids did not change the significance of these associations. When the analyses were

Table 1 Characteristics of participants.

	Definite DM	Not definite DM	All DM	Not all DM
Number	15	102	32	85
Sex (male/female)	7/8	52/50	17/15	42/43
Age (years)	55.5 ± 6.7	54.0 ± 6.6	55.4 ± 6.0	53.8 ± 6.8
BMI	30.9 ± 3.0	30.3 ± 2.7	30.5 ± 2.7	30.3 ± 2.7
Waist circumference (cm)	101.8 ± 7.7	101.7 ± 7.3	101.4 ± 7.1	101.8 ± 7.5
Abdominal fat (cm^2)	149.4 ± 65.2	136.7 ± 45.1	142.4 ± 51.9	136.8 ± 46.7
HbA1c (%)	8.2 ± 1.9	5.9 ± 0.4	7.3 ± 1.5	5.7 ± 0.3
FPG (mg/dL)	159.7 ± 51.3	103.4 ± 11.4	136.5 ± 42.2	100.9 ± 9.0
Total cholesterol (mg/dL)	207.7 ± 24.4	208.8 ± 34.1	202.8 ± 26.4	210.8 ± 35.0
Triglycerides (mg/dL)	176.7 ± 104.6	145.8 ± 78.5	154.6 ± 80.7	147.9 ± 83.4
HDL cholesterol (mg/dL)	53.9 ± 13.1	52.0 ± 11.9	50.9 ± 12.9	52.8 ± 11.7
LDL cholesterol (mg/dL)	118.5 ± 24.9	128.3 ± 30.9	121.0 ± 25.6	129.3 ± 31.7
Total lipid (mg/dL)	710.4 ± 129.7	682.0 ± 123.5	677.4 ± 110.4	688.8 ± 129.4
Urinary acid (mg/dL)	5.7 ± 1.3	6.0 ± 1.4	5.8 ± 1.2	6.0 ± 1.4
Systolic blood pressure (mmHg)	136.7 ± 12.4	131.6 ± 16.0	134.8 ± 14.6	131.3 ± 16.0
Diastolic blood pressure (mmHg)	80.9 ± 8.5	81.0 ± 13.5	82.9 ± 13.0	80.2 ± 12.9

Definite DM: subjects with an HbA1c level ≥ 6.9% or a prescription for hypoglycemic medicine. All DM: subjects with an FPG level ≥ 126 mg/dL, and HbA1c level ≥ 6.5%, a prescription for hypoglycemic medicine, or a history of diabetes. Data are the mean ± standard deviation. Total lipid was estimated from the measured total cholesterol and triglyceride levels.

Table 2 Concentrations of PCB congeners.

Age group (Number)		< 50 (27)	50-59 (62)	>= 60 (28)	All ages (117)		
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Median	Range
PCB 74	pg/g blood	22.4 ± 16.0	33.3 ± 15.9	51.3 ± 25.5	35.1 ± 21.1	28.7	9.4 - 120.8
	ng/g lipid	3.3 ± 2.1	5.0 ± 2.5	7.7 ± 4.5	5.3 ± 3.4	4.4	1.4 - 23.3
PCB 99	pg/g blood	19.2 ± 11.3	24.9 ± 11.2	32.6 ± 21.4	25.4 ± 14.9	21.6	4.7 - 123.7
	ng/g lipid	2.8 ± 1.4	3.7 ± 1.8	5.0 ± 4.1	3.8 ± 2.6	3.4	0.5 - 23.8
PCB 118	pg/g blood	47.9 ± 32.1	59.1 ± 30.4	87.9 ± 52.1	63.4 ± 39.5	54.0	16.1 - 293.8
	ng/g lipid	7.1 ± 4.2	8.8 ± 4.4	13.5 ± 10.0	9.6 ± 6.5	7.9	1.8 - 56.6
PCB 138	pg/g blood	63.3 ± 38.2	77.9 ± 31.9	104.2 ± 68.2	80.9 ± 46.4	73.7	23.2 - 405.6
	ng/g lipid	9.2 ± 4.6	11.7 ± 5.2	16.0 ± 13.3	12.2 ± 8.1	11.0	3.3 - 78.2
PCB 146	pg/g blood	18.8 ± 10.2	23.7 ± 10.6	33.1 ± 22.0	24.8 ± 14.8	21.5	6.0 - 131.8
	ng/g lipid	2.7 ± 1.2	3.6 ± 1.8	5.1 ± 4.3	3.7 ± 2.6	3.3	1.0 - 25.4
PCB 153	pg/g blood	129.6 ± 74.8	168.1 ± 74.1	230.5 ± 158.9	174.1 ± 106.1	154.2	50.9 - 947.5
	ng/g lipid	18.8 ± 9.0	25.4 ± 12.2	35.5 ± 31.0	26.3 ± 18.8	23.2	7.4 - 182.7
PCB 156	pg/g blood	14.0 ± 7.0	17.9 ± 7.6	23.6 ± 13.1	18.3 ± 9.6	16.1	6.2 - 73.3
	ng/g lipid	2.0 ± 0.9	2.7 ± 1.2	3.5 ± 2.4	2.7 ± 1.6	2.5	0.9 - 14.1
PCB 163/164	pg/g blood	30.6 ± 15.5	39.3 ± 17.0	54.0 ± 32.9	40.8 ± 22.9	36.0	10.3 - 200.3
	ng/g lipid	4.5 ± 2.0	5.9 ± 2.8	8.2 ± 6.4	6.1 ± 4.1	5.5	1.6 - 38.6
PCB 170	pg/g blood	16.6 ± 7.6	22.0 ± 8.4	29.3 ± 19.9	22.5 ± 12.7	19.7	7.8 - 110.9
	ng/g lipid	2.4 ± 1.0	3.3 ± 1.3	4.4 ± 3.7	3.4 ± 2.2	3.0	1.1 - 21.4
PCB 180	pg/g blood	63.2 ± 30.1	83.0 ± 30.2	111.7 ± 76.1	85.3 ± 48.1	75.7	28.5 - 446.3
	ng/g lipid	9.2 ± 3.9	12.5 ± 5.1	16.9 ± 14.5	12.8 ± 8.5	11.3	3.9 - 86.0
PCB 182/187	pg/g blood	33.0 ± 20.3	42.3 ± 19.6	58.6 ± 40.5	44.1 ± 27.5	39.3	11.3 - 243.3
	ng/g lipid	4.7 ± 2.5	6.4 ± 3.4	9.0 ± 7.9	6.6 ± 4.9	6.1	1.5 - 46.9
Total PCB	pg/g blood	458.7 ± 249.2	591.3 ± 230.2	817.0 ± 513.9	614.7 ± 345.1	535.5	181.5 - 3097.3
	ng/g lipid	66.8 ± 30.3	89.1 ± 37.8	125.0 ± 100.0	92.5 ± 60.8	82.7	26.9 - 597.1

SD: standard deviation.

Table 3 Risk of definite diabetes according to PCBs.

	No adjustment for lipid [a]		Adjusted for total lipids [b]		Lipid-adjusted PCBs [c]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
PCB 74	0.92	(0.79-1.07)	0.91	(0.79-1.06)	0.67	(0.25-1.83)
PCB 99	1.09	(0.84-1.41)	1.05	(0.79-1.38)	2.02	(0.36-11.18)
PCB 118	1.00	(0.91-1.09)	1.00	(0.92-1.09)	0.97	(0.52-1.82)
PCB 138	1.02	(0.89-1.16)	1.03	(0.90-1.17)	0.93	(0.39-2.24)
PCB 146	2.36	(1.06-5.24)	2.46	(1.09-5.59)	137	(0.80-23650)
PCB 153	0.93	(0.85-1.01)	0.94	(0.86-1.02)	0.64	(0.37-1.11)
PCB 156	1.60	(0.92-2.77)	1.52	(0.86-2.67)	20.2	(0.57-713)
PCB 163/164	0.60	(0.39-0.91)	0.59	(0.38-0.91)	0.03	(0.002-0.46)
PCB 170	0.45	(0.25-0.79)	0.42	(0.23-0.78)	0.01	(0.0003-0.42)
PCB 180	1.35	(1.10-1.67)	1.39	(1.10-1.76)	5.32	(1.46-19.32)
PCB 182/187	0.95	(0.70-1.28)	0.88	(0.62-1.26)	1.21	(0.15-10.03)

[a] Adjusted for sex, age and BMI. [b] Adjusted for sex, age, BMI and total lipid. Adjusted for sex, age and BMI using lipid-adjusted PCBs. Data are odds ratio (95% confidence interval).

Table 4 Risk of all diabetes according to PCBs.

	No adjustment for lipid [a]		Adjusted for total lipids [b]		Lipid-adjusted PCBs [c]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
PCB 74	1.02	(0.94-1.10)	1.02	(0.94-1.10)	1.16	(0.68-1.98)
PCB 99	1.08	(0.92-1.27)	1.10	(0.94-1.30)	1.70	(0.60-4.80)
PCB 118	0.97	(0.91-1.02)	0.97	(0.91-1.02)	0.79	(0.54-1.15)
PCB 138	1.01	(0.93-1.10)	1.02	(0.93-1.11)	1.17	(0.67-2.06)
PCB 146	1.56	(1.05-2.31)	1.59	(1.08-2.35)	29.2	(1.89-451)
PCB 153	0.96	(0.91-1.01)	0.95	(0.90-1.00)	0.73	(0.51-1.07)
PCB 156	0.93	(0.68-1.27)	0.99	(0.71-1.37)	0.94	(0.12-7.62)
PCB 163/164	0.80	(0.65-0.98)	0.77	(0.62-0.95)	0.14	(0.03-0.58)
PCB 170	0.85	(0.67-1.07)	0.86	(0.69-1.08)	0.40	(0.09-1.91)
PCB 180	1.10	(1.10-1.20)	1.09	(1.01-1.19)	1.76	(1.01-3.08)
PCB 182/187	1.00	(0.85-1.17)	1.05	(0.88-1.25)	1.15	(0.36-3.64)

[a] Adjusted for sex, age and BMI. [b] Adjusted for sex, age, BMI and total lipid. [c] Adjusted for sex, age and BMI using lipid-adjusted PCBs. Data are odds ratio (95% confidence interval).

performed using the lipid-adjusted PCB concentrations, the significance of the positive relation between PCB 146 and definite diabetes was attenuated, but the positive association with PCB 180 and the negative association with PCB 163/164 and 170 remained.

On the other hand, broadening the definition of diabetes to include all diabetic participants attenuated the association between the PCB levels and the risk of diabetes (Table 4). PCB 146 and 180 continued to have positive associations with definite diabetes, but the significance of the negative association with PCB 170 was lost and only PCB 163/164 maintained a significant negative association. Adding total lipids as a potential confounder or using the lipid-adjusted PCB values did not change the significant associations with PCB 146, 180 and 163/164.

Discussion

Statistically significant associations between the PCB congener concentrations and the prevalence of diabetes were observed among middle-aged Japanese obese adults. PCB 180 was positively and PCB 163/164 was negatively associated with both the definite diabetes and the all diabetes groups, regardless of adjustments for possible confounding factors. A positive association between PCB 146 and diabetes was observed except in the analysis using lipid-adjusted PCB concentrations in the definite diabetes group, and a negative association for PCB 170 was observed in the definite diabetes group.

To date, information about the relationship between specific PCB congeners and diabetes is limited. Many

epidemiological studies have focused on TCDD, which is known to cause dermal toxicity, neurotoxicity, immunotoxicity and carcinogenicity, as well as PCB 153, which is thought to be correlated with the total amount of PCBs and may be useful as an indicator substance of multifarious PCBs [24]. Recent studies have measured more PCB congeners in detail; however, analyses were performed using the accumulated TEQs [13] or the total/subtotal sum of PCB congeners [14, 25], and differences in the specific effects of PCB congeners have rarely been reported.

Knowledge from experimental studies is also insufficient. The biological pathway is thought to include interactions among aryl hydrocarbon receptor (AhR) [26], peroxisome proliferator-activated receptor (PPAR) [27], and type 4 glucose transporter (GLUT4) [28], but these findings have mainly been obtained for TCDD, and the biological functions of PCB 146, 163/164, 170 and 180 are not known in detail.

Although the results of previous studies have not exactly supported the findings of the present study, the influence of PCBs on diabetes through indirect mechanisms can be considered. Many cross-sectional studies have shown that PCBs correlate positively with BMI, which may increase insulin resistance and the risk of diabetes. A positive relation was observed between BMI and serum level of PCB 180 [29] and the sum of PCB 118, 138, 153 and 180 [30]. Other studies investigated that total PCB concentration of 101 congeners and the concentrations of PCB 74, 99, 153 and 206 were inversely associated with the serum testosterone levels in men [31], and lower testosterone levels are correlated with higher insulin resistance [32] and a higher risk of diabetes [33]. In addition, testosterone replacement for hypogonadal men with diabetes reduced their insulin resistance and improved their control of diabetes [34]. Therefore, PCBs may be partly responsible for the development of diabetes by lowering the testosterone level and increasing insulin resistance, even though PCB 146, 163/164, 170 or 180 was not associated with BMI in the present study.

On the other hand, there were studies showing inverse relationship between PCBs and insulin resistance. There were cross-sectional studies reporting that the serum levels of PCB 118, 138, 153 and 180 [35], PCB 153, 170, 180 and the sum of these PCB congeners and PCB 138 were inversely associated with obesity, while the concentrations of PCB 170, 180 and the sum of the PCBs were correlated negatively with insulin resistance [16].

These findings suggest that PCBs may be positively or negatively associated with insulin resistance and diabetes. As the PCB 170 concentration was especially low among obese people [16], PCB 170 may have a stronger weight reduction effect, compared with the other congeners. The participants of the present study were extremely obese subjects in the Japanese population; therefore, the effect of obesity might have been pronounced.

The strength of the present study is that diabetes was ascertained using a blood test, as a certain proportion of undiagnosed diabetes exists among the general population. In fact, among the participants of this study, there were only nine self-reported physician-diagnosed cases of diabetes, but blood sample measurements enabled the identification of six undiagnosed cases of diabetes using the definite diabetes criteria and 23 cases using the all diabetes criteria.

Nevertheless, the present study also has several limitations. First, because of its cross-sectional design, the cause-effect relation could not be explained. Although the elimination rate of TCDD has been suggested to be unrelated to the presence of diabetes among US veterans [36], implying that the difference in blood TCDD levels occurred before the development of diabetes, the difference in elimination rates among PCB congeners is not well known.

Environmental exposure to PCBs is more complicated than occupational or accidental exposures. Food and inhalation are the main routes of intake, and metabolism and excretion are related to elimination; however, such factors have not been fully explored. Meat, dairy products and fish are the major sources of PCBs, and the consumption of certain types of fish is correlated with certain types of PCBs [25, 37]; however, appropriate data that would enable adjustments to the analyses were not available for the present study population. The possibility that the negative association between PCB congeners and the prevalence of diabetes was due to the protective effect of n-3 polyunsaturated fatty acids contained in fatty fish cannot be denied, considering that the blood levels of dioxins and PCBs are well correlated with fish consumption [38]. The number of parities and lifetime lactation may influence the elimination of PCBs [39], but this information was also not considered. Further studies that include such missing data may clarify the robustness of the present findings.

In conclusion, PCB 180 had a positive associa-

tion and PCB 163/164 had a negative association with the prevalence of diabetes among middle-aged, obese Japanese subjects after adjustments for age, sex, BMI, and total lipids. PCB 146 and 170 may have positive and negative associations, respectively, with the prevalence of diabetes. Further consideration, including the intake and elimination of PCB congeners, may strengthen these findings.

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HEALTH & ENVIRONMENT

Japan for Sustainability in Health through a New Movement of Food and Nutrition Education 'Shokuiku'

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ABSTRACT

Background and objective : **Japan's remarkable longevity is a definite accomplishment as a nation which fully benefited from all local sources of their healthy diet. However, obesity and other non-communicable diseases will be a big threat to the Japan's aging population in the near future. Hence, one extreme reaction has been resistance to the economic development in the name of protecting and sustainability of public health nutrition so-called *Shokuiku*. The objective of the literature review is to provide an overview of the nutrition transition in Japan and how the concept of sustainable development in health has been broadened to the continuity of people's well being including food and nutrition education *Shokuiku* as a prioritized area.**

Methods: **A review of literature on current nutrition and health problems and its relationship with the sustainability in health studies related to Japanese people were summarized.**

Results: **Studies showed the transition of nutrition occurred and how changing of lifestyles such as smoking, falling rate of physical activity, increased stress and anxiety due to rapid urbanization and nutrition paradigm gave threat to sustainability in health in present and future generation. However, to fulfill Health Japan 21 vision, Basic Law on *Shokuiku* regarding food and nutrition. This law is considered sustainable due to encouragement of respect for diverse traditional food culture which is healthy, appreciation of food production in harmony with environment, revitalization of rural communities with locally grown products and improvement of food security. On the other hand, this nutrition education comply the term of *sustainable* meaning the center of the needs of future generation including environmental issues, whereas *development* capture the needs of current generation.**

Conclusion: **In short, *Shokuiku* cover the sustainability in nutrition education for a long term and fulfill the needs of present population without neglecting the ability of future generation in meeting their needs. *Shoku* means diet and *iku* stand for education is an initiation in health promotion, and should be conceptualized and well-defined for everyone in achieving sustainability in health for future Japan.**

KEY WORDS

sustainable development, food and nutrition education, Shokuiku

CURRENT NUTRITION AND HEALTH ROBLEMS IN JAPAN

The Japanese enjoy the world's longest lifespan and healthy lives. Japan's aging society is becoming a demographic dilemm[1] contributing to a skyrocketing of health care costs and its high dependency ratio[2]. And yet, Japan's longevity is a definite accomplishment as a nation fully benefiting from all local sources of their healthy diet in surprising ways. There are two threats to the success of Japan's health system, the frontline is a rapid increase of aging population, followed by remarkable acceleration structural-reform from of agricultural to industrial-based economy[3]. The transition to a post-Fordist economy (new economy) driven by rapid socioeconomic progress[4] may

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