Journal of Epidemiology 27 (2017) S9–S21

Contents lists available at ScienceDirect

Journal of Epidemiology

journal homepage: http://www.journals.elsevier.com/journal-of-epidemiology/

Original Article

Cross-sectional analysis of BioBank Japan clinical data: A large cohort of 200,000 patients with 47 common diseases

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ARTICLE INFO

Article history:
Received 22 October 2016
Accepted 15 December 2016
Available online 9 February 2017

Keywords:
BioBank Japan Project
Biobank
Common disease
Clinical information
Family history

ABSTRACT

Background: To implement personalized medicine, we established a large-scale patient cohort, BioBank Japan, in 2003. BioBank Japan contains DNA, serum, and clinical information derived from approximately 200,000 patients with 47 diseases. Serum and clinical information were collected annually until 2012.
Methods: We analyzed clinical information of participants at enrollment, including age, sex, body mass index, hypertension, and smoking and drinking status, across 47 diseases, and compared the results with the Japanese database on Patient Survey and National Health and Nutrition Survey. We conducted multivariate logistic regression analysis, adjusting for sex and age, to assess the association between family history and disease development.
Results: Distribution of age at enrollment reflected the typical age of disease onset. Analysis of the clinical information revealed strong associations between smoking and chronic obstructive pulmonary disease, drinking and esophageal cancer, high body mass index and metabolic disease, and hypertension and cardiovascular disease. Logistic regression analysis showed that individuals with a family history of keloid exhibited a higher odds ratio than those without a family history, highlighting the strong impact of host genetic factor(s) on disease onset.

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Peer review under responsibility of the Japan Epidemiological Association.
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http://dx.doi.org/10.1016/j.je.2016.12.003

Conclusions: Cross-sectional analysis of the clinical information of participants at enrollment revealed characteristics of the present cohort. Analysis of family history revealed the impact of host genetic factors on each disease. BioBank Japan, by publicly distributing DNA, serum, and clinical information, could be a fundamental infrastructure for the implementation of personalized medicine.

Introduction

BioBank Japan (BBJ) was established with the cooperation of 12 medical institutes, consisting of over 60 hospitals, as a leading project of the Ministry of Education, Culture, Sports, Science and Technology in 2003.[1,2] As a disease-oriented biobank, BBJ collected DNA and serum samples from approximately 200,000 patients with 47 diseases. BBJ annually updates clinical information, which is another essential element of biobanks.[3] The clinical information associated with the biospecimens was utilized in previous studies to select or stratify the participant group. Samples and their clinical information were used for over 200 studies.[4] However, so far, a comprehensive analysis of the clinical information of the BBJ cohorts has not been conducted. Here, we analyzed clinical

Table 1
Baseline characteristics of participants with 47 diseases in the present cohort.

47 Diseases	Number of Subjects	Mean (SD) age at registration (y)				% of male subjects	% of male patients (Patient survey)
		Male		Female			
Whole cohort	**199,982**	**62.66**	**14.66**	**61.55**	**16.02**	**53.05**	**N/A**
Lung cancer	3779	67.64	9.54	66.07	9.81	64.25	50.51
Esophageal cancer	1291	65.66	8.06	65.56	10.44	86.29	84.00
Gastric cancer	6322	67.01	9.90	65.18	11.77	73.39	66.27
Colorectal cancer	6759	67.10	9.95	66.42	10.86	62.76	55.54
Liver cancer	1924	67.37	8.47	69.97	8.15	75.68	68.18
Pancreatic cancer	392	66.02	9.80	66.21	11.02	64.54	50.85
Gallbladder/cholangiocarcinoma	392	67.71	9.22	68.75	9.05	62.50	51.02
Prostate cancer	5066	72.60	7.46	N/A		100.00	100.00
Breast cancer	6336	63.74	11.21	57.67	11.98	0.73	1.33
Uterine cervical cancer	1218	N/A		51.83	13.33	0.00	0.00
Uterine corpus cancer	1026	N/A		58.93	10.65	0.00	0.00
Ovarian cancer	888	N/A		56.39	11.91	0.00	0.00
Hematological cancer	1307	60.99	15.08	60.26	16.65	54.32	53.97
Cerebral infarction	16,534	68.82	9.90	71.68	10.60	62.27	44.37
Cerebral aneurysm	2710	60.52	11.51	62.84	10.78	35.24	N/A
Epilepsy	2303	46.56	21.75	43.31	21.98	57.27	54.42
Bronchial asthma	8700	51.89	23.11	53.54	20.68	49.32	51.51
Pulmonary tuberculosis	863	62.14	16.82	62.43	19.34	71.38	64.10
Chronic obstructive pulmonary disease	2774	72.33	8.57	72.71	9.82	86.81	68.28
Interstitial lung disease/pulmonary fibrosis	808	68.74	11.41	68.11	11.97	58.04	55.32
Myocardial infarction	13,272	65.92	10.37	71.19	9.90	80.98	64.32
Unstable angina	4330	66.76	9.71	71.26	9.15	73.70	55.20
Stable angina	14,807	67.86	9.81	71.05	9.71	69.39	55.20
Arrhythmia	15,912	67.03	11.67	69.27	12.52	64.38	52.24
Heart failure	7610	66.01	12.63	71.46	12.72	61.81	38.18
Peripheral arterial diseases	2683	70.84	9.02	71.70	9.97	78.12	61.97
Chronic hepatitis B	1346	54.57	13.21	55.62	14.97	62.63	62.50
Chronic hepatitis C	5819	63.37	11.84	64.64	11.92	53.70	52.92
Liver cirrhosis	2519	62.74	11.50	65.38	14.17	62.29	49.52
Nephrotic syndrome	1056	47.45	22.88	48.23	21.74	60.32	58.06
Urolithiasis	6307	53.02	13.72	56.90	14.42	75.60	67.42
Osteoporosis	6743	72.28	12.89	73.77	9.57	7.59	7.23
Diabetes mellitus	39,697	63.31	11.33	65.80	12.00	63.23	52.74
Dyslipidemia	43,812	62.15	11.97	66.26	10.79	50.76	33.55
Graves' disease	2323	49.86	14.23	49.04	15.75	27.85	22.22
Rheumatoid arthritis	4139	64.05	12.12	62.39	12.29	20.25	18.87
Hay fever	5658	46.39	17.63	44.94	15.84	42.93	46.74
Drug eruption	585	60.53	16.17	54.82	17.46	45.81	N/A
Atopic dermatitis	2938	29.98	14.85	29.74	13.54	53.13	51.61
Keloid	809	48.53	19.97	43.31	19.60	38.94	N/A
Uterine fibroid	5904	N/A		44.69	9.49	0.00	0.00
Endometriosis	1843	N/A		38.93	8.22	0.00	0.00
Febrile seizure	333	4.16	3.57	4.35	5.09	60.96	N/A
Glaucoma	4755	66.87	12.43	70.03	10.95	46.79	41.98
Cataract	20,002	70.43	10.31	72.91	9.52	44.81	36.83
Periodontitis	3898	58.20	15.92	56.59	16.00	43.69	41.03
Amyotrophic lateral sclerosis	782	60.86	10.21	61.03	10.76	64.32	N/A

information including age, sex, body mass index (BMI), hypertension, smoking, and drinking status across 47 diseases, and compared the results with the Japanese database. In addition, we assessed the association between target diseases and positive family history.

Materials and methods

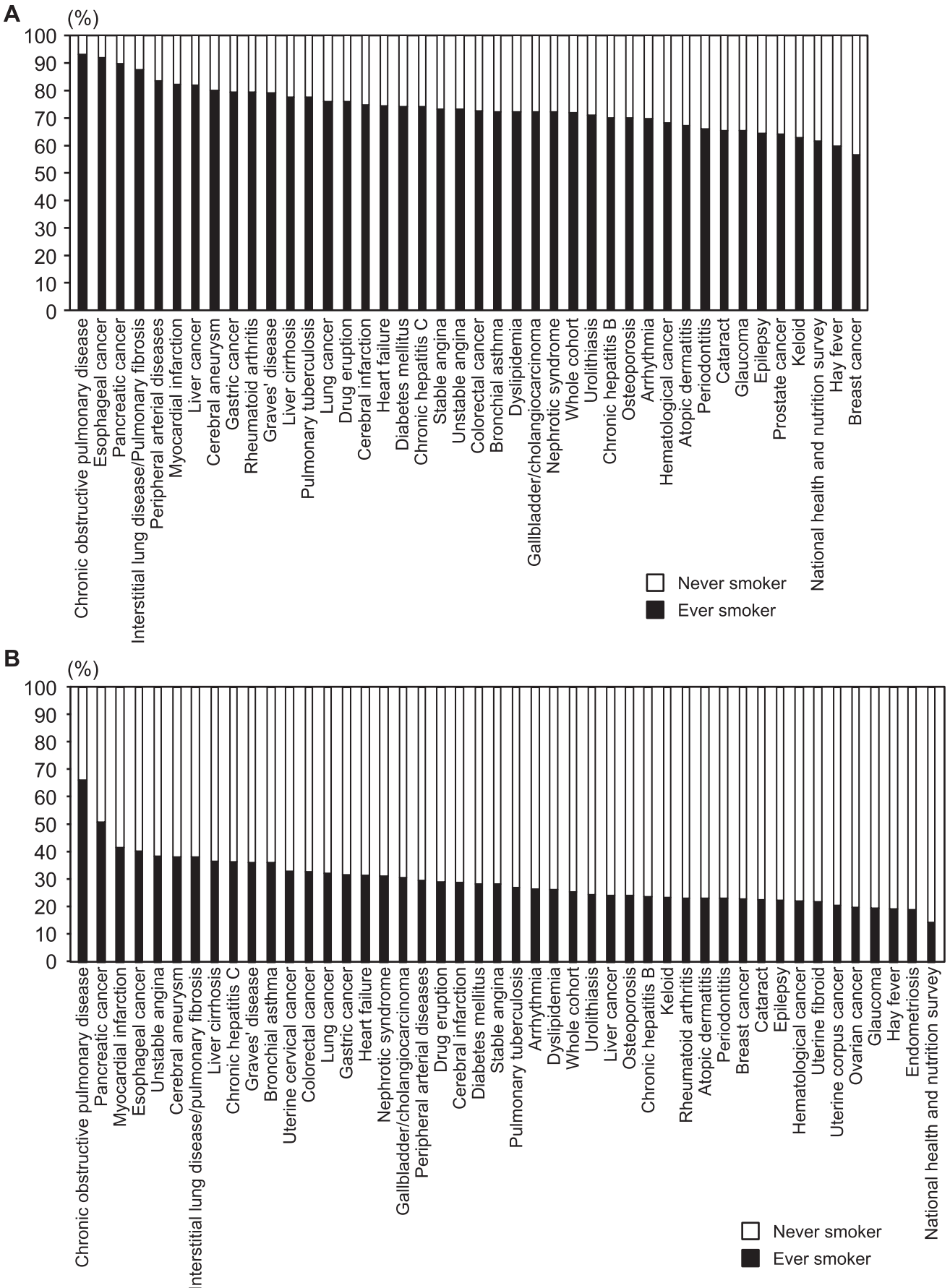
Study design

In the present cohort, we focused on 47 common diseases (Table 1). Patients diagnosed with any one of the 47 diseases were recruited from 66 hospitals affiliated with 12 medical institutes between fiscal year of 2003 and 2007. The detailed protocol of the recruitment process has been described elsewhere.[2] Written informed consent was obtained from all participants. The study protocol was reviewed and approved by the Ethics Committees of all participating institutions, including the Institute of Medical Science, the University of Tokyo, and the Center for Integrative Medical Sciences, RIKEN.

We included patients who had been diagnosed with the diseases by physicians at the cooperating hospitals (eTable 1). As this project registered not only patients with newly developed diseases but also patients who were diagnosed and treated before starting the project, some participants were enrolled several years after disease onset or diagnosis.[2] We excluded patients who had

Table 2
Baseline smoking status of participants with 47 diseases in the present cohort.

47 Diseases	Smoking status							
	Male subjects				Female subjects			
	Never smoker	Ex-smoker	Current smoker	Smoker with unknown status	Never smoker	Ex-smoker	Current smoker	Smoker with unknown status
Whole cohort	**25.02**	**43.75**	**27.78**	**3.45**	**78.76**	**9.37**	**10.45**	**1.42**
Lung cancer	11.73	71.45	14.05	2.78	73.39	21.75	3.89	0.97
Esophageal cancer	10.92	64.88	18.74	5.46	56.57	30.86	9.14	3.43
Gastric cancer	18.53	55.01	22.72	3.74	76.16	15.33	7.36	1.15
Colorectal cancer	22.87	49.81	23.78	3.55	79.54	12.14	6.94	1.38
Liver cancer	20.39	45.13	26.84	7.64	77.29	10.48	9.17	3.06
Pancreatic cancer	15.60	55.60	28.00	0.80	66.91	16.55	14.39	2.16
Gallbladder/ cholangiocarcinoma	26.34	48.15	21.40	4.12	80.69	10.34	6.90	2.07
Prostate cancer	31.88	46.54	17.19	4.39	N/A			
Breast cancer	42.22	42.22	15.56	0.00	78.24	13.04	7.63	1.08
Uterine cervical cancer	N/A				63.60	14.36	19.09	2.96
Uterine corpus cancer	N/A				80.80	9.35	8.16	1.69
Ovarian cancer	N/A				80.09	9.55	8.85	1.51
Hematologic cancer	27.99	45.60	20.20	6.20	81.41	10.15	6.02	2.41
Cerebral infarction	24.86	47.69	24.36	3.10	82.97	8.96	6.77	1.30
Cerebral aneurysm	19.06	48.99	27.80	4.15	69.68	15.69	12.59	2.04
Epilepsy	36.12	28.21	31.45	4.22	76.19	7.52	14.79	1.50
Bronchial asthma	26.44	40.08	30.96	2.53	65.90	13.48	19.24	1.39
Pulmonary tuberculosis	19.31	50.17	29.04	1.49	78.84	10.79	8.30	2.07
Chronic obstructive pulmonary disease	7.31	64.68	25.81	2.20	35.77	39.44	22.54	2.25
Interstitial lung disease/pulmonary fibrosis	13.07	62.96	20.04	3.92	72.59	18.07	8.73	0.60
Myocardial infarction	17.96	56.98	21.56	3.50	70.36	17.62	10.56	1.45
Unstable angina	21.60	55.61	20.26	2.52	76.59	13.85	8.58	0.98
Stable angina	21.70	54.36	21.95	1.99	79.56	11.64	8.07	0.74
Arrhythmia	25.61	50.01	21.42	2.95	83.20	9.58	6.50	0.72
Heart failure	23.68	49.63	23.05	3.63	79.32	12.06	7.53	1.09
Peripheral arterial disease	10.39	52.66	31.74	5.22	64.67	20.91	12.65	1.76
Chronic hepatitis B	28.69	31.11	34.87	5.33	77.30	8.79	12.47	1.43
Chronic hepatitis C	22.32	38.40	34.49	4.79	74.75	9.21	13.71	2.33
Liver cirrhosis	19.74	34.05	40.65	5.56	73.94	10.80	13.25	2.00
Nephrotic syndrome	26.97	39.89	30.52	2.62	69.25	14.40	12.74	3.60
Urolithiasis	29.17	28.68	38.46	3.69	76.98	5.49	15.61	1.92
Osteoporosis	32.60	38.83	25.15	3.42	87.79	5.27	5.99	0.95
Diabetes mellitus	23.08	41.24	32.45	3.24	78.49	9.26	11.11	1.15
Dyslipidemia	24.42	43.83	27.52	4.23	81.61	8.26	8.80	1.33
Graves' disease	20.20	26.06	49.84	3.91	60.68	12.90	24.92	1.50
Rheumatoid arthritis	17.30	41.84	35.46	5.40	78.09	8.53	11.41	1.97
Hay fever	42.40	28.30	24.43	4.88	77.01	8.91	12.18	1.89
Drug eruption	25.00	42.58	29.69	2.73	72.37	9.54	16.45	1.64
Atopic dermatitis	48.12	13.75	36.53	1.60	70.64	7.06	20.91	1.39
Keloid	38.08	35.43	25.17	1.32	72.69	7.96	18.06	1.29
Uterine fibroid	N/A				73.66	9.34	14.68	2.31
Endometriosis	N/A				70.96	8.86	16.67	3.52
Febrile seizure	100.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
Glaucoma	30.31	42.49	24.10	3.10	87.76	5.98	4.87	1.39
Cataract	28.69	43.61	24.22	3.47	86.66	6.23	5.95	1.17
Periodontitis	35.55	27.76	36.06	0.63	78.78	6.10	14.63	0.49
Amyotrophic lateral sclerosis	37.10	17.97	41.94	3.00	84.67	2.30	13.03	0.00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Chronic obstructive pulmonary disease
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Peripheral arterial diseases
Myocardial infarction
Liver cancer
Cerebral aneurysm
Gastric cancer
Rheumatoid arthritis
Graves' disease
Liver cirrhosis
Pulmonary tuberculosis
Lung cancer
Drug eruption
Cerebral infarction
Heart failure
Diabetes mellitus
Chronic hepatitis C
Stable angina
Unstable angina
Colorectal cancer
Bronchial asthma
Dyslipidemia
Gallbladder/cholangiocarcinoma
Nephrotic syndrome
Whole cohort
Urolithiasis
Chronic hepatitis B
Osteoporosis
Arrhythmia
Hematological cancer
Atopic dermatitis
Periodontitis
Cataract
Glaucoma
Epilepsy
Prostate cancer
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Interstitial lung disease/pulmonary fibrosis
Liver cirrhosis
Chronic hepatitis C
Graves' disease
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Peripheral arterial diseases
Drug eruption
Cerebral infarction
Diabetes mellitus
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Dyslipidemia
Whole cohort
Urolithiasis
Liver cancer
Osteoporosis
Chronic hepatitis B
Keloid
Rheumatoid arthritis
Atopic dermatitis
Periodontitis
Breast cancer
Cataract
Epilepsy
Hematological cancer
Uterine fibroid
Uterine corpus cancer
Ovarian cancer
Glaucoma
Hay fever
Endometriosis
National health and nutrition survey
Never smoker
Ever smoker

Table 3
Baseline alcohol intake status of participants with 47 diseases in the present cohort.

47 Diseases	Alcohol intake							
	Male subjects				Female subjects			
	Never drinker	Ex-drinker	Current drinker	Drinker with unknown status	Never drinker	Ex-drinker	Current drinker	Drinker with unknown status
Whole cohort	**30.32**	**13.35**	**52.24**	**4.09**	**71.80**	**3.99**	**21.70**	**2.52**
Lung cancer	26.73	15.85	54.21	3.21	69.94	6.37	21.81	1.87
Esophageal cancer	8.29	25.59	61.38	4.74	47.43	16.00	32.00	4.57
Gastric cancer	25.19	18.96	51.49	4.36	73.12	7.57	17.62	1.69
Colorectal cancer	23.53	15.88	56.15	4.45	73.11	5.83	18.99	2.08
Liver cancer	23.90	34.83	33.01	8.27	76.59	10.94	9.41	3.06
Pancreatic cancer	25.70	29.72	42.97	1.61	65.22	10.14	23.91	0.72
Gallbladder/cholangiocarcinoma	30.58	27.27	38.43	3.72	84.83	2.07	13.10	0.00
Prostate cancer	29.33	13.05	51.47	6.16	N/A			
Breast cancer	28.89	11.11	60.00	0.00	63.67	5.21	29.02	2.10
Uterine cervical cancer	N/A				58.90	5.57	30.80	4.73
Uterine corpus cancer	N/A				71.02	3.59	22.51	2.89
Ovarian cancer	N/A				68.91	3.83	24.13	3.13
Hematologic cancer	29.05	12.28	50.72	7.95	72.76	5.69	18.10	3.45
Cerebral infarction	28.51	18.33	49.38	3.78	79.64	4.97	13.67	1.73
Cerebral aneurysm	23.72	15.81	55.34	5.13	66.86	6.69	24.05	2.40
Epilepsy	37.35	16.11	42.03	4.50	66.54	4.67	25.88	2.90
Bronchial asthma	34.16	9.44	53.53	2.87	69.26	3.83	25.29	1.62
Pulmonary tuberculosis	30.69	33.17	34.32	1.82	74.69	11.20	12.03	2.07
Chronic obstructive pulmonary disease	38.48	17.86	42.01	1.66	74.50	6.80	17.00	1.70
Interstitial lung disease	32.02	17.32	46.71	3.95	76.74	4.53	16.62	2.11
Myocardial infarction	41.68	13.70	41.29	3.32	79.48	5.42	13.48	1.62
Unstable angina	39.27	13.59	44.10	3.04	78.80	4.56	14.76	1.88
Stable angina	34.04	13.74	49.55	2.67	78.71	4.68	15.27	1.35
Arrhythmia	26.37	14.17	56.05	3.42	75.69	4.33	18.60	1.37
Heart failure	32.31	17.08	46.34	4.27	79.82	5.78	13.30	1.09
PAD	31.01	19.94	43.80	5.24	77.46	8.10	11.62	2.82
Chronic hepatitis B	27.18	18.08	47.45	7.28	68.43	5.70	24.03	1.83
Chronic hepatitis C	30.61	26.60	37.50	5.29	72.35	8.90	15.51	3.25
Liver cirrhosis	19.23	35.20	38.92	6.65	70.86	11.35	14.24	3.56
Nephrotic syndrome	39.70	14.42	41.95	3.93	67.59	6.37	23.82	2.22
Urolithiasis	32.49	5.44	56.80	5.27	72.96	2.72	22.00	2.32
Osteoporosis	39.63	14.43	42.89	3.05	82.07	2.47	13.70	1.76
Diabetes mellitus	31.47	15.17	49.88	3.49	79.10	5.29	14.02	1.59
Dyslipidemia	30.78	10.71	54.08	4.44	76.03	3.40	18.52	2.06
Graves' disease	38.24	8.82	48.37	4.58	66.73	5.02	25.93	2.32
Rheumatoid arthritis	35.47	13.79	44.95	5.79	75.46	4.11	17.89	2.54
Hay fever	31.18	4.31	58.22	6.29	59.31	2.80	32.50	5.40
Drug eruption	30.98	15.29	49.02	4.71	71.57	2.68	21.74	4.01
Atopic dermatitis	45.44	3.68	47.04	3.84	57.37	2.44	36.62	3.57
Keloid	39.33	7.33	50.67	2.67	63.71	1.51	33.69	1.08
Uterine fibroid	N/A				53.52	2.23	38.57	5.67
Endometriosis	N/A				55.51	2.26	34.56	7.66
Febrile seizure	100.00	0.00	0.00	0.00	66.67	0.00	33.33	0.00
Glaucoma	27.42	12.46	56.14	3.98	77.61	2.98	17.16	2.25
Cataract	31.05	14.42	50.58	3.95	81.00	2.95	14.49	1.57
Periodontitis	29.82	7.20	61.53	1.45	63.54	2.75	32.14	1.57
Amyotrophic lateral sclerosis	28.57	0.00	57.14	14.29	100.00	0.00	0.00	0.00

received a bone marrow transplant and those who were not of East Asian descent.

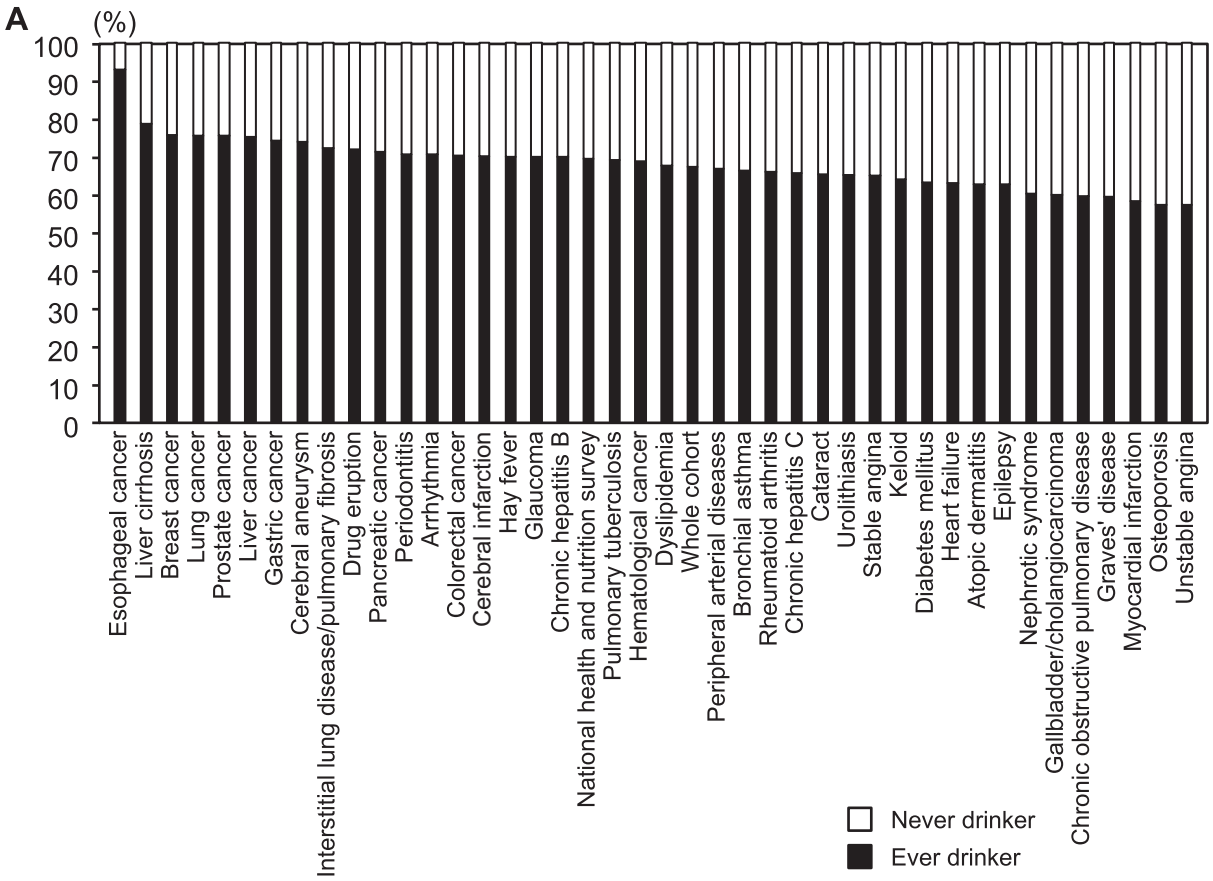
Clinical information

Clinical information including common clinical variables, disease-specific variables, prescriptions, and drug side-effect information, was collected from each participant. The detailed methods of the collection of clinical information has been described elsewhere.[2] The clinical database was updated every year until 2012. After a thorough review and data-cleansing of clinical variables,[2] clinical information of 199,982 participants with 47 diseases at enrollment was established on March 31 2015 and used in the current study.

Japanese database

The Ministry of Health, Labour and Welfare in Japan conducts a Patient Survey every three years and a National Health and Nutrition Survey every year. We obtained the results of the Patient Survey of 2005[5] and those of the National Health and Nutrition Survey of 2006.[6] Table 65 in the Patient Survey was used to

Fig. 1. Age-adjusted ratios of participants with a smoking history for each disease. The distributions of male (**A**) and female (**B**) participants with a smoking history in the BBJ cohort and in the National Health and Nutrition Survey (Japan, 2006) were compared. Age-adjustment was performed according to the age distribution of the National Health and Nutrition Survey (Japan, 2006).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Lung cancer
Prostate cancer
Liver cancer
Gastric cancer
Cerebral aneurysm
Interstitial lung disease/pulmonary fibrosis
Drug eruption
Pancreatic cancer
Periodontitis
Arrhythmia
Colorectal cancer
Cerebral infarction
Hay fever
Glaucoma
Chronic hepatitis B
National health and nutrition survey
Pulmonary tuberculosis
Hematological cancer
Dyslipidemia
Whole cohort
Peripheral arterial diseases
Bronchial asthma
Rheumatoid arthritis
Chronic hepatitis C
Cataract
Urolithiasis
Stable angina
Keloid
Diabetes mellitus
Heart failure
Atopic dermatitis
Epilepsy
Nephrotic syndrome
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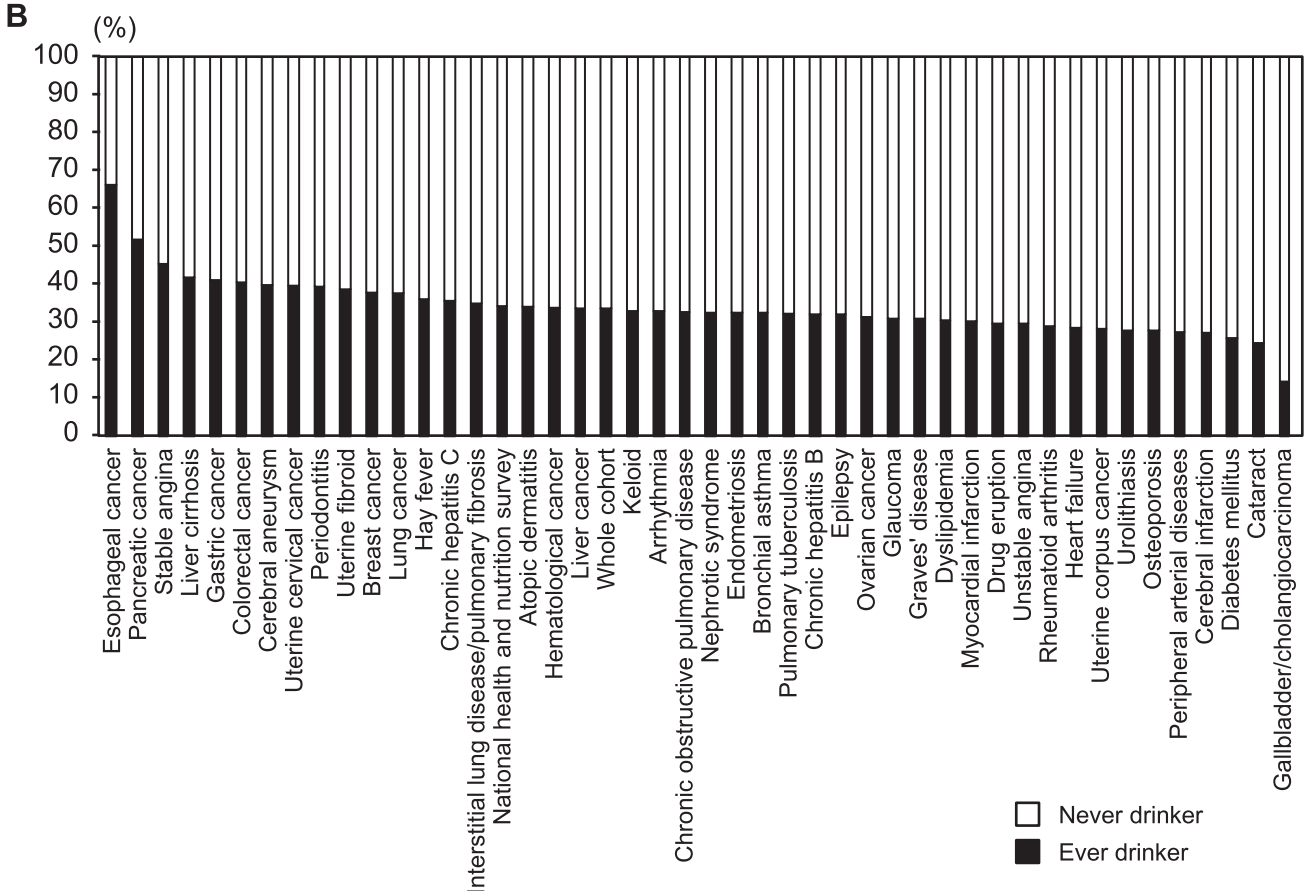
Chronic obstructive pulmonary disease
Graves' disease
Myocardial infarction
Osteoporosis
Unstable angina
Never drinker
Ever drinker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Urolithiasis
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Never drinker
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Table 4
Baseline BMI and hypertension of participants with 47 diseases in the present cohort.

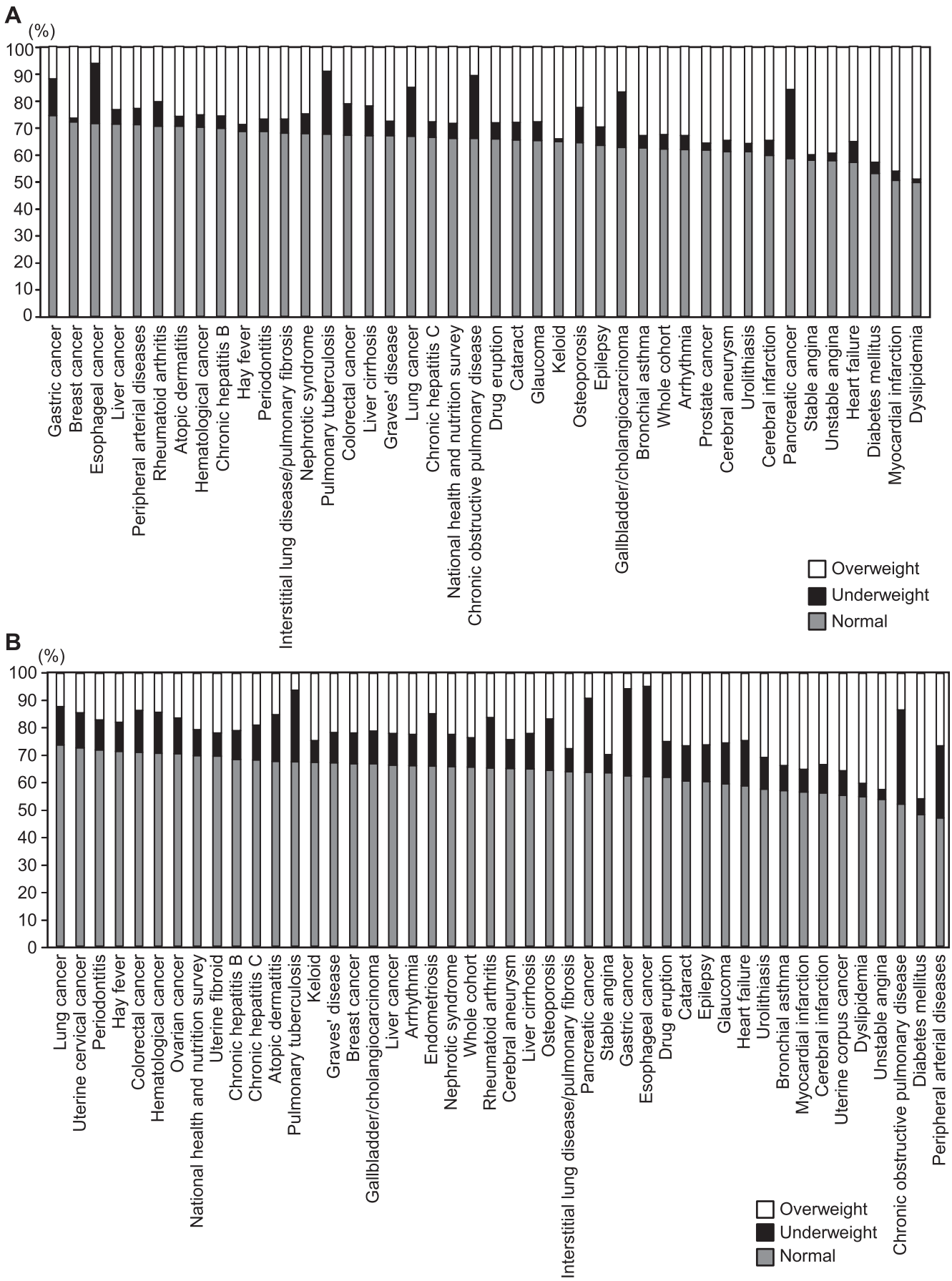
47 Diseases	BMI				%Hypertension	
	Male subjects		Female subjects		Male subjects	Female subjects
	Mean	(SD)	Mean	(SD)		
Whole cohort	**23.51**	**3.47**	**22.94**	**3.89**	**51.52**	**41.11**
Lung cancer	22.29	3.05	22.05	3.37	36.74	33.83
Esophageal cancer	20.53	2.96	19.77	3.25	27.29	24.86
Gastric cancer	21.25	3.04	20.34	3.26	30.91	24.26
Colorectal cancer	22.66	3.17	22.00	3.51	38.00	30.31
Liver cancer	22.68	3.27	22.82	3.96	44.64	45.51
Pancreatic cancer	20.44	3.19	19.90	3.03	30.83	29.50
Gallbladder/cholangiocarcinoma	21.46	3.29	22.20	3.89	33.47	31.29
Prostate cancer	23.28	2.86	N/A		38.00	N/A
Breast cancer	23.87	3.75	22.74	3.60	52.17	22.82
Cervical cancer	N/A		21.93	3.29	N/A	19.23
Uterine cancer	N/A		23.74	4.37	N/A	25.83
Ovarian cancer	N/A		22.04	3.38	N/A	19.21
Hematopoietic tumor	23.11	3.23	21.87	3.33	30.94	26.71
Cerebral infarction	23.53	3.19	23.39	3.86	67.12	65.34
Cerebral aneurysm	23.86	3.36	23.11	3.64	65.45	59.52
Epilepsy	23.47	3.84	22.70	4.19	36.36	25.64
Bronchial asthma	23.79	3.71	23.78	4.55	41.19	35.14
Pulmonary tuberculosis	20.82	3.28	20.26	3.26	32.31	37.80
Chronic obstructive pulmonary disease	21.30	3.37	20.33	4.08	46.05	44.66
Interstitial lung disease/pulmonary fibrosis	23.02	3.21	22.62	3.75	42.37	40.65
Myocardial infarction	24.04	3.23	23.40	3.74	73.11	77.01
Unstable angina	24.02	3.21	23.74	3.74	74.33	74.80
Stable angina	23.85	3.16	23.63	3.66	77.17	77.45
Arrhythmia	23.53	3.30	22.90	3.80	66.75	65.33
Heart failure	23.50	3.89	22.64	4.31	78.70	78.10
Peripheral arterial diseases	22.52	3.25	22.44	3.80	70.21	69.17
Chronic hepatitis B	23.32	3.11	22.55	3.51	40.67	33.60
Chronic hepatitis C	22.86	3.15	22.54	3.65	46.19	40.71
Liver cirrhosis	22.88	3.51	23.03	4.05	52.18	49.41
Nephrotic syndrome	23.00	3.34	22.50	3.94	62.32	50.68
Urolithiasis	24.43	3.39	23.59	4.16	37.27	35.61
Osteoporosis	21.96	3.52	22.26	3.62	49.22	44.46
Diabetes mellitus	24.03	3.72	24.57	4.41	60.32	62.82
Dyslipidemia	24.78	3.45	24.11	3.88	64.47	59.48
Graves' disease	23.55	3.63	22.35	3.61	41.03	32.00
Rheumatoid arthritis	22.49	3.29	21.85	3.69	40.57	33.56
Hay fever	23.66	3.17	22.06	3.51	24.70	14.77
Drug eruption	23.27	3.39	22.62	4.07	49.81	30.87
Atopic dermatitis	23.01	3.51	21.48	3.70	13.24	5.75
Keloid	23.95	3.29	22.71	4.11	27.60	18.82
Uterine fibroid	N/A		22.29	3.51	N/A	14.09
Endometriosis	N/A		21.43	3.25	N/A	7.93
Febrile seizure	28.73	0.00	21.26	4.80	N/A	N/A
Glaucoma	23.05	3.18	22.90	3.66	43.87	41.08
Cataract	23.08	3.15	23.05	3.85	49.53	45.68
Periodontitis	23.27	3.14	22.25	3.37	27.33	15.90
Amyotrophic lateral sclerosis	21.14	1.68	28.00	3.14	N/A	N/A

estimate Japanese patient numbers, stratified by sex and age for each disease. Distributions of BMI categories, hypertension prevalence, smoking history, and alcohol intake history in the general Japanese population were calculated from Tables 23, 49-2, 97, and 91 of the National Health and Nutrition Survey, respectively.

Analysis of clinical information

The distributions of BMI, hypertension prevalence, smoking history, and alcohol intake history in the BBJ cohort were adjusted for sex and age group for each table in the national public survey when we compared the distributions among the 47 diseases and Japanese database. BMI category and hypertension were defined according to World Health Organization (WHO) criteria as follows: BMI < 18.5 was defined as underweight, 18.5 ≤ BMI < 25 as normal, 25 ≤ BMI < 30 as overweight, and 30 ≤ BMI as obese[7]; hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or when participants were prescribed antihypertensive drugs. Multivariate logistic regression analyses were performed to assess the association between each target disease and positive family history associated with the target disease, adjusted for sex and age. SAS 9.4 software was used for the data analysis. A p-value of <0.05 was considered statistically significant.

Fig. 2. Age-adjusted ratio of participants with alcohol history in each disease. The distributions of male (**A**) and female (**B**) participants with a drinking history in the BBJ cohort and in the National Health and Nutrition Survey (Japan, 2006) were compared. Age-adjustment was performed according to the age distribution of the National Health and Nutrition Survey (Japan, 2006).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Bronchial asthma
Myocardial infarction
Cerebral infarction
Uterine corpus cancer
Dyslipidemia
Unstable angina
Chronic obstructive pulmonary disease
Diabetes mellitus
Peripheral arterial diseases
Overweight
Underweight
Normal

Results

Basic characteristics (Age and sex)

We characterized the BioBank Japan cohort at enrollment by analyzing common clinical variables of age and sex across the target diseases. Mean age at enrollment, across the entire cohort or for each disease, was comparable between both sexes, but varied among the diseases (Table 1). The highest mean age was observed in men with prostate cancer and in women with osteoporosis (72.60 and 73.77 years, respectively), while the youngest mean age was observed in men and women with febrile seizures (4.16 and 4.35 years, respectively), reflecting the typical age of onset of each disease. A greater number of men were registered in the BBJ cohort compared to women (53.05% vs. 46.95%), while sex ratios varied according to the diseases (Table 1).

To highlight sex and age characteristics of the BBJ cohort, we further compared the sex and age distribution for each disease with the Patient Survey. We included participants with 42 out of the 47 diseases for the comparison, as we obtained the relevant clinical data from the Patient Survey (eTable 2). Almost all diseases displayed equivalent age distributions, while lower proportions of participants <20 years of age were observed in three diseases (bronchial asthma, atopic dermatitis and hay fever), which are likely to occur in younger populations (eFigs. 1.1–1.5 and eTable 3). The proportion of male participants with dyslipidemia was considerably higher in the BBJ cohort (50.76%) than in the Patient Survey (33.55%), although both age distributions appeared equivalent. The low proportion of female patients with heart failure aged ≥80 years resulted in a lower proportion of female participants in the BBJ cohort. We also observed a low proportion of elderly female participants with cerebral infarction, chronic obstructive pulmonary disease (COPD), peripheral arterial diseases (PAD), unstable angina, stable angina, and myocardial infarction in the BBJ cohort. Varied distributions between the BBJ cohort and Patient Survey were observed in pulmonary tuberculosis and nephrotic syndrome.

Basic characteristics (Lifestyle and physical status)

We also evaluated life style including smoking and alcohol intake history, and physical status including BMI and blood pressure, at enrollment in the BBJ cohort. We included participants ≥20 years of age in this analysis because the frequency of smoking, alcohol intake, and hypertension among individuals under 20 years of age is quite low, and the criteria for underweight or obesity according to BMI in children and teenagers are different from those applied to adults.[8] Furthermore, we compared the BBJ cohort and the National Health and Nutrition Survey 2006 for physical and life style, after adjusting for sex and age, because sex- and age-distribution varied among diseases.

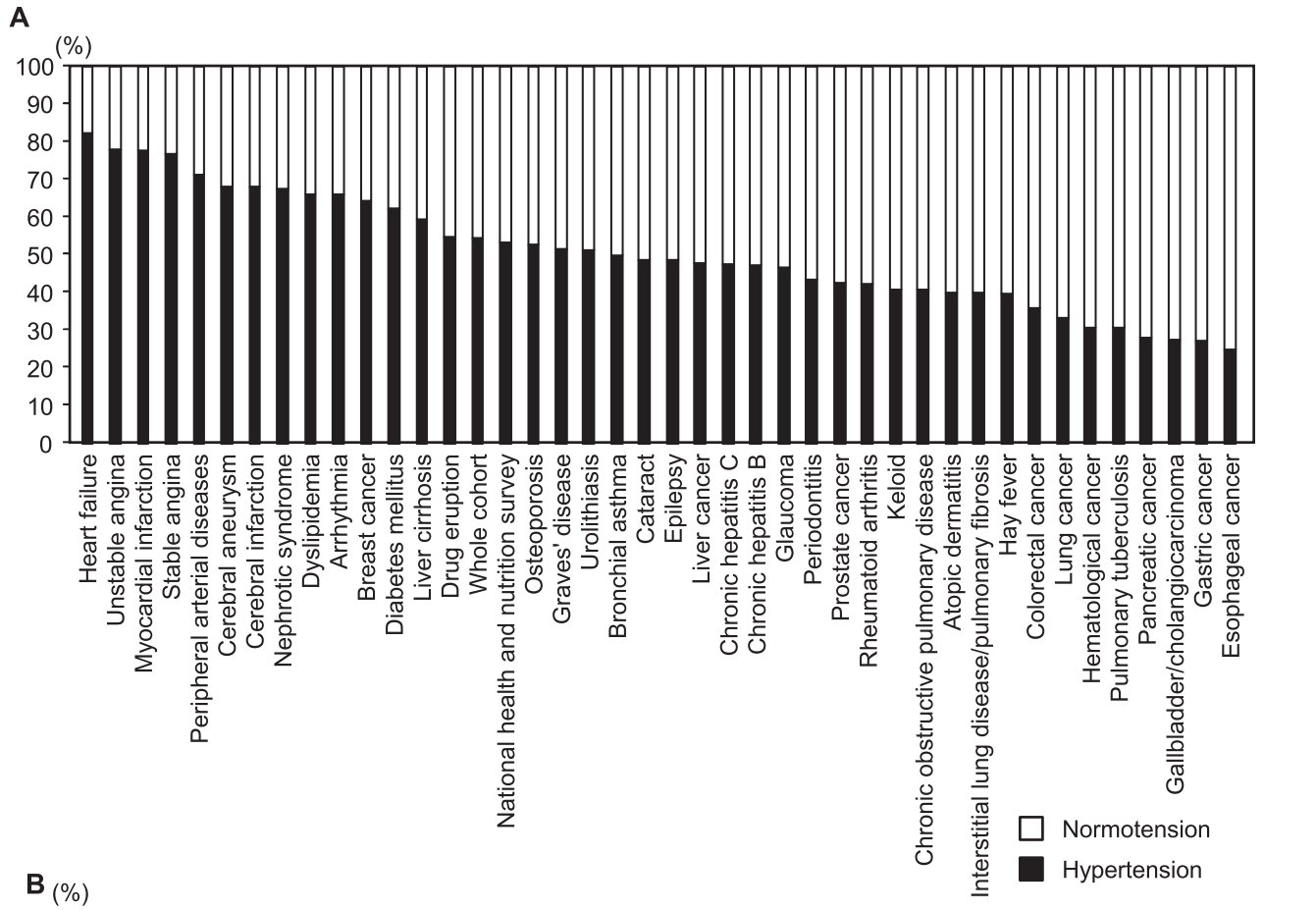
Smoking history at enrollment (including subjects both with and without information on current smoking status) was positive in 74.98% of male subjects and 21.24% of female subjects in the BBJ cohort, while current smokers accounted for 27.78% of male subjects and 10.45% of female subjects (Table 2). The highest frequency of positive smoking history in both sexes was observed in COPD, followed by PAD in male subjects, and esophageal cancer in female subjects (Table 2). The highest proportion of ex-smokers for both sexes was observed in participants with lung cancer, esophageal cancer and COPD (71.45%, 64.88% and 64.68% in male subjects, and 21.75%, 30.86% and 39.44% in female subjects, respectively), while the highest proportion of current smokers for both sexes was observed in participants with Graves' disease (49.84% in male subjects and 24.92% in female subjects) (Table 2). We then compared age-adjusted smoking history among the 47 diseases. The frequency of smokers was highest among participants with COPD, esophageal cancer, interstitial lung diseases/pulmonary fibrosis, pancreatic cancer, and cardiovascular diseases, in which smoking was shown to be a critical risk factor (Fig. 1 and eTable 4).

A positive alcohol history at enrollment (including those with and without current drinking status) was found in 69.68% of male subjects and 28.20% of female subjects (Table 3). The proportion of current drinkers in the whole cohort was much higher than that of ex-drinkers in both sexes: 52.24% and 13.35% of male subjects and 21.70% and 3.99% of female subjects were current and ex-drinkers, respectively. Among the 47 diseases, the proportion of ex-drinkers was relatively high among participants with liver cirrhosis (34.05% in male subjects and 10.80% in female subjects), liver cancer (34.83% and 10.94%), pulmonary tuberculosis (33.17% and 11.20%), esophageal cancer (25.59% and 16%), and pancreatic cancer (29.72% and 10.14%) (Table 3). Age-adjusted alcohol intake history showed that the frequency of drinkers in esophageal cancer was remarkably higher than that in other diseases for male and female subjects (Fig. 2 and eTable 5). To highlight the smoking and drinking status in the BBJ cohort, the frequency of smokers or drinkers, stratified by sex and age group, was compared between the BBJ and the National Health and Nutrition Survey. The BBJ cohort had a higher frequency of smokers among female subjects across all age groups and among elderly male subjects, particularly among those >60 years of age; the frequency of drinkers was almost equivalent between the BBJ and the National Health and Nutrition Survey for both sexes and across all age groups (eFig. 2A and B and eTables 6 and 7).

Mean BMI at enrollment in the BBJ cohort was 23.51 in male subjects and 22.94 in female subjects. Analysis of BMI in each disease revealed that underweight participants (BMI<18.5) had an increased association of various cancers, while overweight or obese participants (BMI ≥ 25) had an increased association of metabolic and cardiovascular diseases (Table 4, Fig. 3 and eTable 8). When comparing the National Health and Nutrition Survey and the BBJ, there was a greater proportion of participants with overweight or obesity in the BBJ, among male and female subjects and across all age-groups; conversely, similar distribution patterns were found when comparing the BBJ cohort and the Survey, by sex and age-group (eFig. 2C and eTables 6 and 7). In contrast, in the BBJ cohort, there were fewer underweight participants in their twenties (for both sexes) but more underweight participants >60 years (among male subjects) and >50 years (among female subjects) (eFig. 2D and eTables 6 and 7).

Nearly half of the participants of the BBJ cohort had hypertension (51.52% of male subjects and 41.11% of female subjects, Table 4) at enrollment. The frequency of hypertension in cardiovascular diseases, particularly in coronary diseases, was higher than that in other diseases, while the frequency of hypertension among cancer participants tended to be low (Table 4, Fig. 4 and eTable 9). The frequency of hypertension increased with age, similarly to the increase observed in the Survey. However, the frequency of hypertension among subjects <50 years of age was higher and subjects >60 years of age was lower in the BBJ cohort than in the Survey (eFig. 2E and eTables 6 and 7).

Fig. 3. Age-adjusted ratio of participants with overweight or underweight in each disease. The distributions of obese or underweight participants among male (**A**) and female (**B**) subjects in the BBJ cohort and in the National Health and Nutrition Survey (Japan, 2006) were compared. Age-adjustment was performed according to the age distribution of the National Health and Nutrition Survey (Japan, 2006). BMI ≥25 was defined as overweight and BMI less than 18.5 was defined as underweight.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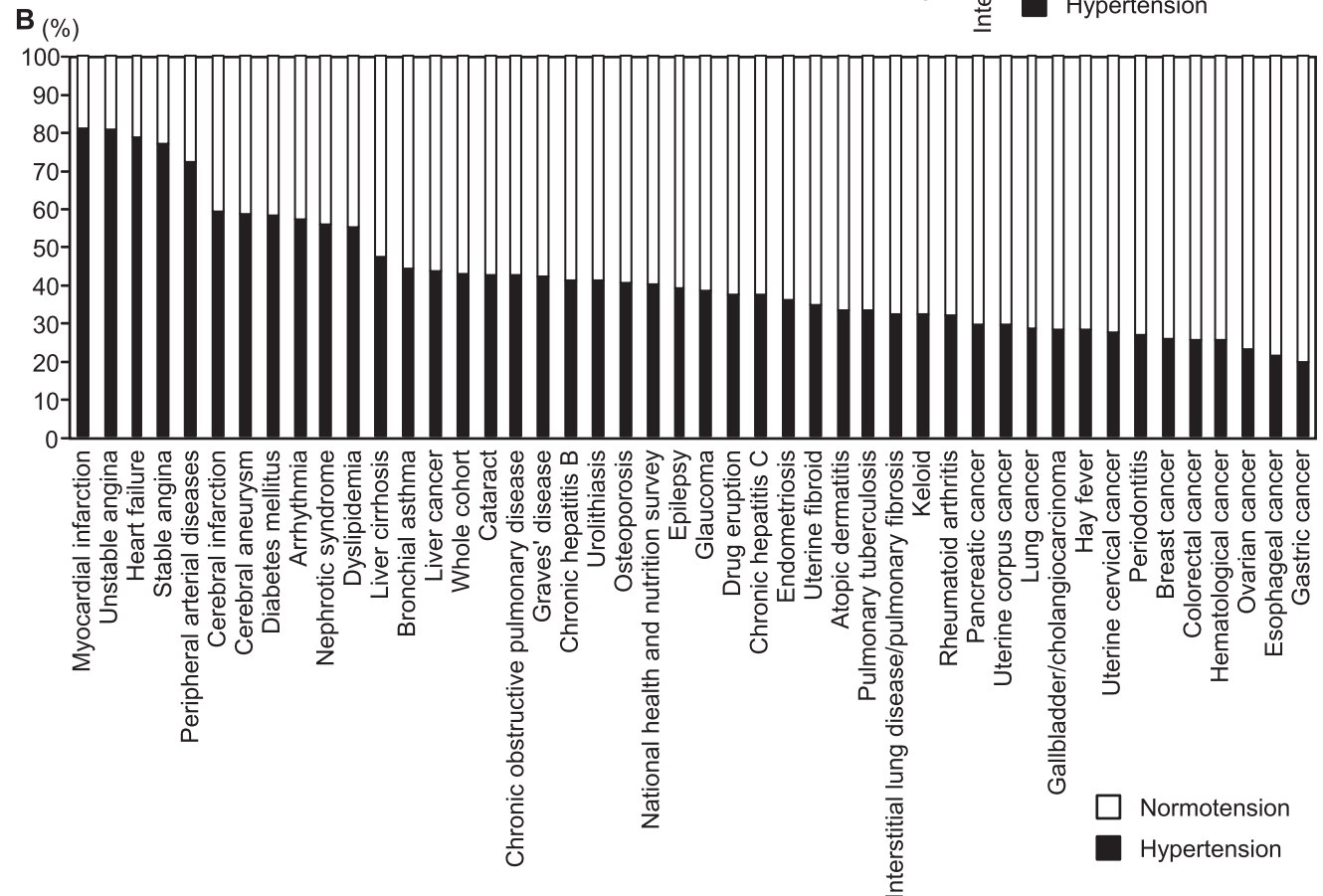
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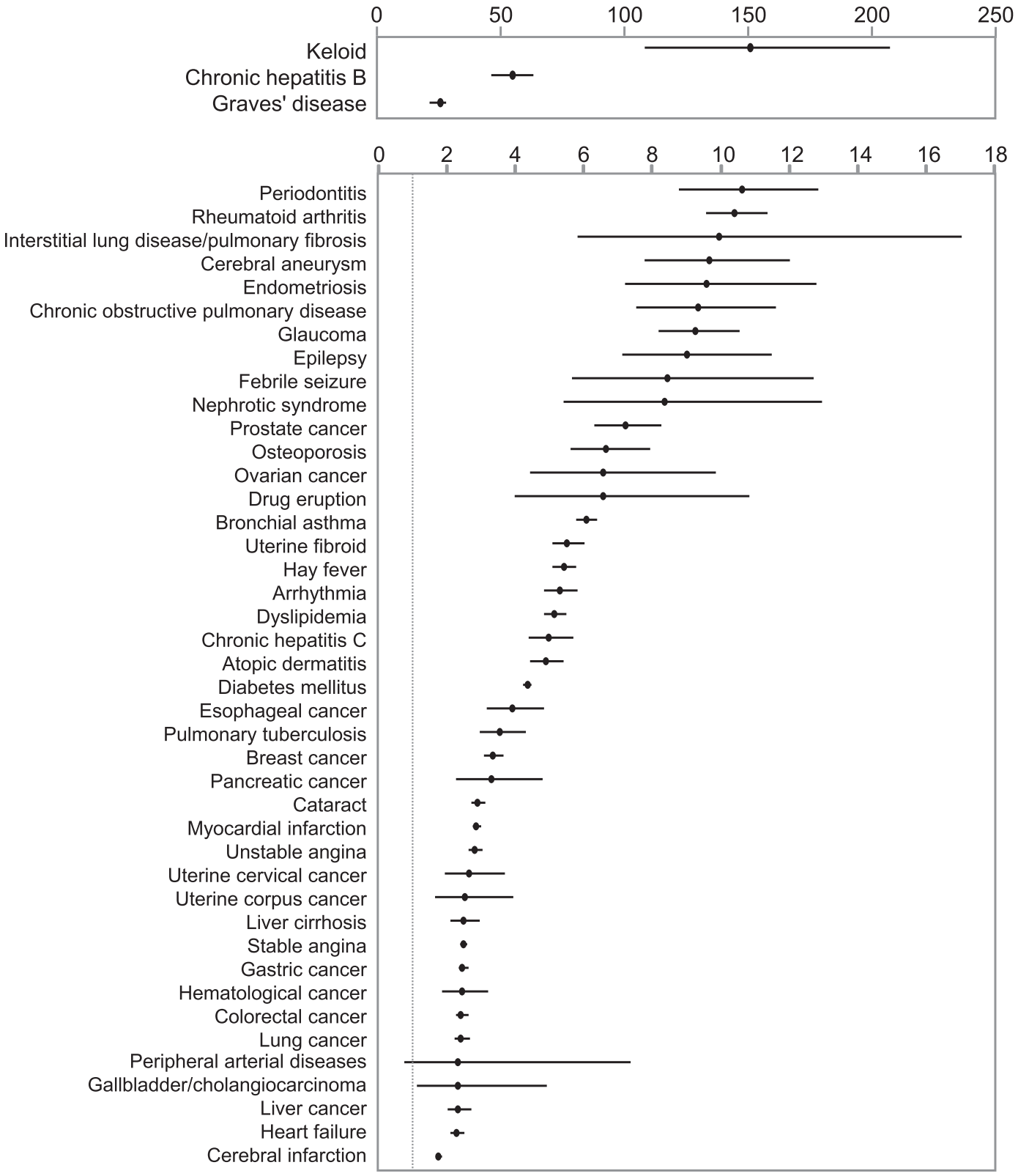

Fig. 5. Sex- and age-adjusted odds ratios in family history, related with the 47 diseases. Dots represent odds ratios and bars represent 95% CIs by logistic regression analysis. The list of family histories, associated with the 47 diseases, is set out in eTable 2.

Fig. 4. Age-adjusted ratio of participants with hypertension in each disease. The distributions of male (**A**) and female (**B**) participants with hypertension in the BBJ cohort and in the National Health and Nutrition Survey (Japan, 2006) were compared. Age-adjustment was performed according to the age distribution of the National Health and Nutrition Survey (Japan, 2006). Participants with a systolic blood pressure ≥135-mmHg, a diastolic blood pressure ≥90-mmHg, or participants prescribed antihypertensive medication, were diagnosed with hypertension.

Family history

Finally, we performed multivariate logistic-regression analysis using age and sex status as covariates to assess the association between positive family history and disease risk. We were able to obtain the questionnaire-based information regarding family history of 45 diseases out of the 47 diseases (eTable 10). For all the diseases, except for PAD, there was a significant association with a positive family history, with an odds ratio of >1.7 (Fig. 5 and eTable 11). Notably, the odds ratios for keloid, chronic hepatitis B, and Grave's disease were relatively high (149.417, 53.474, and 23.751, respectively) indicating the strong impact of genetic and familial factors on disease onset.

Discussion

We analyzed common clinical variables at enrollment, across the whole BBJ cohort, as well as for each target disease, and we compared these results with those of the Japanese database to highlight the characteristics of the BBJ cohort. Statistical analyses were not conducted in this study, as the large-scale cohort sample in the BBJ would yield relatively low-p-values, even when absolute differences were very small. The distribution of age, life style, and physical status, showed that the characteristics of each disease group could generally be explained.

It is an established fact that smoking and/or alcohol intake are risk factors for various diseases including cancer, cardiovascular disease, hepatic disease, and respiratory disease.[9,10] In fact, these diseases showed a higher frequency of participants with a positive smoking or drinking history at enrollment in the BBJ cohort (Figs. 1 and 2 and eTables 4 and 5). Although we cannot estimate the odds ratios of smoking and drinking status due to the lack of control data in the present cohort, age-adjusted distributions of the smoking and drinking histories of participants suggest that these lifestyle factors have a significant impact on disease onset.

Analysis of BMI at enrollment indicated that lower BMI was more prevalent among participants with malignant tumors, while higher BMI was common among participants with metabolic and cardiovascular disease (Fig. 3 and eTable 8). Obesity could be a risk factor for dyslipidemia, type 2 diabetes, coronary disease,[11] while cancer can induce weight loss. Therefore, we need to be cautious in the interpretation of the association between diseases and lifestyle or physical factors.

To highlight the characteristics of the BBJ cohort, we compared the age and sex distributions of the BBJ cohort with those of the Patient Survey for each disease, and the distributions of smoking and drinking history, BMI and hypertension in the BBJ cohort with those of the National Health and Nutrition Survey. It is difficult to discuss the discrepancy or consistency between the BBJ cohort and the Japanese database, because backgrounds of the subjects and methods to determine the numbers of patients or the distributions of life style and physical status were different. However, the comparisons between the BBJ cohort and the Japanese database gave us better insight about the characteristics of the BBJ cohort, contributing to utmost utilization of the biobank samples.

As one of our main aims was to identify genetic factors causing susceptibility to diseases, we analyzed the association between positive family history and disease onset to evaluate the impact of host genetic factors. It has been reported that a positive family history is an important risk factors for many common chronic diseases,[12–19] and keloid, chronic hepatitis B, and Graves' disease showed the highest odds ratios for a positive family history (Fig. 5). While it is important to consider the possibility that perinatal transmission, a major route of hepatitis B virus transmission,[20] resulted in the high odds ratio observed in chronic hepatitis B, several genome-wide association studies (GWAS), which identified some single nucleotide polymorphism loci significantly associated with these diseases in Japan,[21–32] support the finding that genetic factors are associated with these diseases. However, the odds ratios, calculated in the previous genomic studies, were not as high as in the present analysis, suggesting the possibility that further genomic analysis could identify novel genomic loci. In addition, the fact that common clinical variables were consistently identified across the 47 diseases enabled us to evaluate and compare the risk significance of the positive family history on the diseases and to perform further genomic or other “omics” analyses based on these results.

This study has some limitations. We could not eliminate the possibility of reporting bias, causing significantly higher odds ratio of positive family history in almost all target diseases, as the information on family history was mainly based on participants' interviews, although this was completed by certified medical coordinators. Another limitation of this analysis is that the reference population for each logistic analysis was not the disease-free general population but the participants with the other diseases in the cohort. Therefore, again, we need to take into account selection bias.[33]

In conclusion, we have established a large biobank cohort, consisting of approximately 200,000 patients with 47 diseases. Analysis of the clinical dataset and comparisons between the present cohort and the Japanese database largely revealed consistent trends in common clinical variables, particularly among participants aged ≥40 years, suggesting that the sampling is representative for the general patient population in Japan. Further analysis, combined with various high-throughput ‘omics’ technologies, using their DNA and serum samples, will aid us to identify novel genomic variants or biomarkers associated with disease progression or drug efficacy, contributing to the implementation of personalized medicine.

Conflicts of interest

None declared.

Acknowledgements

We express our gratitude to all the participants in the BioBank Japan Project. We thank all the medical coordinators of the cooperating hospitals for collecting samples and clinical information, as well as Yasushi Yamashita and staff members of the BioBank Japan Project for administrative support. We also thank Dr. Kumao Toyoshima for his overall supervision of the BioBank Japan Project. This study was supported by funding from the Tailor-Made Medical Treatment with the BBJ Project from Japan Agency for Medical Research and Development, AMED (since April 2015), and the Ministry of Education, Culture, Sports, Science, and Technology (from April 2003 to March 2015).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.12.003.

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