Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Rln1	relaxin 1	5.4
Rnf144a	ring finger protein 144A	5.4
Nod1	nucleotide-binding oligomerization domain containing 1	5.4
Heph	hephaestin	5.4
Usp31	ubiquitin specific peptidase 31	5.4
Dcps	decapping enzyme, scavenger	5.4
Stk35	serine/threonine kinase 35	5.3
Gbas	glioblastoma amplified sequence	5.3
Folr1	folate receptor 1 (adult)	5.3
Arfip1	ADP-ribosylation factor interacting protein 1	5.3
Slc16a1	solute carrier family 16, member 1	5.3
RGD1560909	similar to DNA segment, Chr 1, Brigham & Womens Genetics 0212 expressed	5.3
Lect1	leukocyte cell derived chemotaxin 1	5.3
Sbk1	SH3-binding domain kinase 1	5.3
LOC100360582	5',3'-nucleotidase, cytosolic	5.3
Ambp	alpha-1-microglobulin/bikunin precursor	5.3
Srpx	sushi-repeat-containing protein, X-linked	5.3
Tmem144	transmembrane protein 144	5.3
Zbtb3	zinc finger and BTB domain containing 3	5.3
Erp27	endoplasmic reticulum protein 27	5.3
Tgm1	transglutaminase 1, K polypeptide	5.2
Cdkn2aip	CDKN2A interacting protein	5.2
Megf9	multiple EGF-like-domains 9	5.2
Gdf10	growth differentiation factor 10	5.2
Rasal2	RAS protein activator like 2	5.2
Nme4	non-metastatic cells 4, protein expressed in	5.2
Fam83h	family with sequence similarity 83, member H	5.2
Ccdc86	coiled-coil domain containing 86	5.2
Prl8a5	prolactin family 8, subfamily a, member 5	5.2
Arnt	aryl hydrocarbon receptor nuclear translocator	5.2
Slc24a3	solute carrier family 24, member 3	5.1
Bhlhe22	basic helix-loop-helix family, member e22	5.1
Trim72	tripartite motif-containing 72	5.1
Ube2f	ubiquitin-conjugating enzyme E2F (putative)	5.1
Tmem151a	transmembrane protein 151A	5.1
Slc1a3	solute carrier family 1, member 3	5.1
Tff3	trefoil factor 3, intestinal	5.1
Mgrn1	mahogunin, ring finger 1	5.1
Slc7a5	solute carrier family 7, member 5	5.1
Spata2	spermatogenesis associated 2	5.0
Atg10	autophagy-related 10 (S. cerevisiae)	5.0
Pdzk1	PDZ domain containing 1	5.0
Rxra	retinoid X receptor alpha	5.0
Zfp94	zinc finger protein 94	5.0
Tmem209	transmembrane protein 209	5.0
Spopl	speckle-type POZ protein-like	5.0
B4galt1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	5.0
Hmmr	hyaluronan mediated motility receptor (RHAMM)	5.0
Slc7a3	solute carrier family 7, member 3	4.9
Tpx2	TPX2, microtubule-associated, homolog (Xenopus laevis)	4.9

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Serpinb8	serpin peptidase inhibitor, clade B (ovalbumin), member 8	4.9
Cpne5	copine V	4.9
Dnajc5	DnaJ (Hsp40) homolog, subfamily C, member 5	4.9
RGD1564482	RGD1564482	4.9
Chrne	cholinergic receptor, nicotinic, epsilon	4.9
Tifa	TRAF-interacting protein with forkhead-associated domain	4.9
Arhgap29	Rho GTPase activating protein 29	4.9
Fert2	fer (fms/fps related) protein kinase, testis specific 2	4.9
Max	MYC associated factor X	4.8
Fam122a	family with sequence similarity 122A	4.8
Cenpf	centromere protein F	4.8
Etv4	ets variant 4	4.8
Atp8b1	ATPase, Class I, type 8B, member 1	4.8
Ccnl2	cyclin L2	4.8
Raly	RNA binding protein, autoantigenic	4.8
Dnajb4	DnaJ (Hsp40) homolog, subfamily B, member 4	4.8
Recql4	RecQ protein-like 4	4.8
Magt1	magnesium transporter 1	4.8
Nnat	neuronatin	4.8
Nkd1	naked cuticle homolog 1 (Drosophila)	4.8
Irak4	interleukin-1 receptor-associated kinase 4	4.8
Scn1a	sodium channel, voltage-gated, type I, alpha	4.8
Ptch1	patched 1	4.7
Casc5	cancer susceptibility candidate 5	4.7
Adamts1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	4.7
Kbtbd11	kelch repeat and BTB (POZ) domain containing 11	4.7
RGD1311863	similar to RIKEN cDNA 2410127L17	4.7
Ribc1	RIB43A domain with coiled-coils 1	4.7
Ghdc	GH3 domain containing	4.7
Hspa12a	heat shock protein 12A	4.7
Hsdl2	hydroxysteroid dehydrogenase like 2	4.7
Rcbtb2	RCC1 and BTB domain containing protein 2	4.7
Trmt11	tRNA methyltransferase 11 homolog (S. cerevisiae)	4.6
Myo10	myosin X	4.6
Ankrd6	ankyrin repeat domain 6	4.6
T2	brachyury 2	4.6
Zbtb10	zinc finger and BTB domain containing 10	4.6
Ftsjd1	FtsJ methyltransferase domain containing 1	4.6
Lgals4	lectin, galactoside-binding, soluble, 4	4.6
Galnt7	GalNAc-T7	4.6
Slc25a37	solute carrier family 25, member 37	4.6
Sstr1	somatostatin receptor 1	4.6
Gpm6b	glycoprotein m6b	4.6
Dcp1a	DCP1 decapping enzyme homolog A (S. cerevisiae)	4.6
Asz1	ankyrin repeat, SAM and basic leucine zipper domain containing 1	4.6
Tmem86a	transmembrane protein 86A	4.6
Ugt1a6	UDP glucuronosyltransferase 1 family, polypeptide A6	4.5
Prss36	protease, serine, 36	4.5
Tial1	Tia1 cytotoxic granule-associated RNA binding protein-like 1	4.5
Defb27	defensin beta 27	4.5

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Tbkbp1	TBK1 binding protein 1	4.4
Fam176a	family with sequence similarity 176, member A	4.4
Mylk3	myosin light chain kinase 3	4.4
C1qtnf1	C1q and tumor necrosis factor related protein 1	4.4
Sbno2	strawberry notch homolog 2 (Drosophila)	4.4
Fsip1	fibrous sheath interacting protein 1	4.4
Chaf1b	chromatin assembly factor 1, subunit B (p60)	4.4
MGC95152	similar to B230212L03Rik protein	4.4
Wdr72	WD repeat domain 72	4.4
Polq	polymerase (DNA directed), theta	4.3
Ugt1a9	UDP glucuronosyltransferase 1 family, polypeptide A9	4.3
Mtf2	metal response element binding transcription factor 2	4.3
Wwox	WW domain-containing oxidoreductase	4.3
Ugt1a8	UDP glycosyltransferase 1 family, polypeptide A8	4.3
Ugt1a7c	UDP glucuronosyltransferase 1 family, polypeptide A7C	4.3
Ugt1a5	UDP glucuronosyltransferase 1 family, polypeptide A5	4.3
Ugt1a3	UDP glycosyltransferase 1 family, polypeptide A3	4.3
Ugt1a2	UDP glucuronosyltransferase 1 family, polypeptide A2	4.3
Ugt1a1	UDP glucuronosyltransferase 1 family, polypeptide A1	4.3
Sgms2	sphingomyelin synthase 2	4.3
Prkar2b	protein kinase, cAMP dependent regulatory, type II beta	4.3
Decr2	2,4-dienoyl CoA reductase 2, peroxisomal	4.3
Fam83d	family with sequence similarity 83, member D	4.3
Sult1a1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	4.3
Kifc1	kinesin family member C1	4.2
Opa1	optic atrophy 1 homolog (human)	4.2
Rab11fip2	RAB11 family interacting protein 2 (class I)	4.2
Gtse1	G-2 and S-phase expressed 1	4.2
Slc27a6	solute carrier family 27 (fatty acid transporter), member 6	4.2
Cep55	centrosomal protein 55	4.2
Agmo	alkylglycerol monooxygenase	4.2
Slc25a30	solute carrier family 25, member 30	4.2
Lcn2	lipocalin 2	4.2
Nalcn	sodium leak channel, non-selective	4.2
Robo2	roundabout homolog 2 (Drosophila)	4.2
Asrgl1	asparaginase like 1	4.2
Lepr	leptin receptor	4.2
Mbtps2	membrane-bound transcription factor peptidase, site 2	4.1
Pllp	plasmolipin	4.1
Slc22a20	solute carrier family 22 (organic anion transporter), member 20	4.1
Extl3	exostoses (multiple)-like 3	4.1
Pygo1	pygopus 1	4.1
Lefty1	left right determination factor 1	4.1
Map4k2	mitogen activated protein kinase kinase kinase kinase 2	4.1
rnf141	ring finger protein 141	4.1
Ocrl	oculocerebrorenal syndrome of Lowe	4.1
Mfap5	microfibrillar associated protein 5	4.1
Crk	v-crk sarcoma virus CT10 oncogene homolog (avian)	4.1
Cmtm8	CKLF-like MARVEL transmembrane domain containing 8	4.0
Ddx25	DEAD (Asp-Glu-Ala-Asp) box polypeptide 25	4.0

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Kcnh2	potassium voltage-gated channel, subfamily H (eag-related), member 2	4.0
Fndc3b	fibronectin type III domain containing 3B	4.0
Fxr1	fragile X mental retardation, autosomal homolog 1	4.0
Dkk1	dickkopf homolog 1 (Xenopus laevis)	4.0
Nphp3	nephronophthisis 3 (adolescent)	4.0
Srsf10	serine/arginine-rich splicing factor 10	4.0
Ttbk2	tau tubulin kinase 2	4.0
Homez	homeobox and leucine zipper encoding	4.0
Stard5	StAR-related lipid transfer (START) domain containing 5	4.0
Cxadr	coxsackie virus and adenovirus receptor	4.0
Ano4	anoctamin 4	4.0
Slc6a2	solute carrier family 6, member 2	4.0
Ube2cbp	ubiquitin-conjugating enzyme E2C binding protein	4.0
Mitf	microphthalmia-associated transcription factor	3.9
Erc1	ELKS/RAB6-interacting/CAST family member 1	3.9
Pik3cd	phosphoinositide-3-kinase, catalytic, delta polypeptide	3.9
Tbc1d7	TBC1 domain family, member 7	3.9
Akr1e2	aldo-keto reductase family 1, member E2	3.9
Rab3d	RAB3D, member RAS oncogene family	3.9
Cenpm	centromere protein M	3.9
Chchd5	coiled-coil-helix-coiled-coil-helix domain containing 5	3.9
Prrx2	paired related homeobox 2	3.8
Slmo1	slowmo homolog 1 (Drosophila)	3.8
Eml2	echinoderm microtubule associated protein like 2	3.8
Sh3bp1	SH3-domain binding protein 1	3.8
Btrc	beta-transducin repeat containing	3.8
Phlpp1	PH domain and leucine rich repeat protein phosphatase 1	3.8
Rpp38	ribonuclease P/MRP 38 subunit (human)	3.8
Tnks	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase	3.8
Reep6	receptor accessory protein 6	3.8
Fblim1	filamin binding LIM protein 1	3.8
Fam25a	family with sequence similarity 25, member A	3.7
Sema4g	Semaphorin 4G	3.7
Ppp1r3a	protein phosphatase 1, regulatory subunit 3A	3.7
Traf3ip3	TRAF3 interacting protein 3	3.7
Rnf17	ring finger protein 17	3.7
Steap1	six transmembrane epithelial antigen of the prostate 1	3.7
Ikbip	IKBKB interacting protein	3.7
Mpp2	membrane protein, palmitoylated 2 (MAGUK p55 subfamily member 2)	3.7
Pde12	phosphodiesterase 12	3.7
Lxn	latexin	3.7
Alox12	arachidonate 12-lipoxygenase	3.7
Nt5c3	5'-nucleotidase, cytosolic III	3.6
Gnb5	guanine nucleotide binding protein (G protein), beta 5	3.6
Jph3	junctophilin 3	3.6
Ttc7b	tetratricopeptide repeat domain 7B	3.6
D2hgdh	D-2-hydroxyglutarate dehydrogenase	3.6
Cdkn2c	cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	3.6
Cachd1	cache domain containing 1	3.6
Kbtbd5	kelch repeat and BTB (POZ) domain containing 5	3.6

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Pex7	peroxisomal biogenesis factor 7	3.6
Tomm34	translocase of outer mitochondrial membrane 34	3.6
Arse	arylsulfatase E (chondrodysplasia punctata 1)	3.6
Fubp1	far upstream element (FUSE) binding protein 1	3.6
RGD1563159	RGD1563159	3.6
Npw	neuropeptide W	3.6
Mia	melanoma inhibitory activity	3.6
Mcee	methylmalonyl CoA epimerase	3.5
RGD1563325	similar to hypothetical protein MGC17943	3.5
Slc26a4	solute carrier family 26, member 4	3.5
Fbxo28	F-box protein 28	3.5
Ccdc102a	coiled-coil domain containing 102A	3.5
Rtn4ip1	reticulon 4 interacting protein 1	3.5
Lrrc4	leucine rich repeat containing 4	3.5
RGD1305537	similar to RIKEN cDNA 3110001I22	3.5
Tprg1	tumor protein p63 regulated 1	3.5
Kcnn2	potassium intermediate/small conductance calcium-activated channel, N2	3.5
Rgl3	ral guanine nucleotide dissociation stimulator-like 3	3.5
Sim2	single-minded homolog 2 (Drosophila)	3.5
Usp46	ubiquitin specific peptidase 46	3.5
Ehd3	EH-domain containing 3	3.5
Cubn	cubilin (intrinsic factor-cobalamin receptor)	3.4
Cers1	ceramide synthase 1	3.4
Gdf1	growth differentiation factor 1	3.4
Piwil2	piwi-like 2 (Drosophila)	3.4
Rabif	RAB interacting factor	3.4
Hyal3	hyaluronoglucosaminidase 3	3.4
Rab30	RAB30, member RAS oncogene family	3.4
Sytl1	synaptotagmin-like 1	3.4
Gpc2	glypican 2	3.4
Zmat4	zinc finger, matrin type 4	3.3
Ttc25	tetratricopeptide repeat domain 25	3.3
Il22	interleukin 22	3.3
Mid1ip1	MID1 interacting protein 1 (gastrulation specific G12 homolog (zebrafish))	3.3
Mutyh	mutY homolog (E. coli)	3.3
Flnc	filamin C, gamma	3.3
Tshz3	teashirt zinc finger homeobox 3	3.3
Pdxp	pyridoxal (pyridoxine, vitamin B6) phosphatase	3.3
Acsl3	acyl-CoA synthetase long-chain family member 3	3.3
Lpin1	lipin 1	3.2
Zc3hav1	zinc finger CCCH type, antiviral 1	3.2
Bfsp1	beaded filament structural protein 1	3.2
Fermt3	fermitin family member 3	3.2
Trim13	tripartite motif-containing 13	3.2
Magix	MAGI family member, X-linked	3.2
Cyp2d4	cytochrome P450, family 2, subfamily d, polypeptide 4	3.2
Abcb7	ATP-binding cassette, subfamily B (MDR/TAP), member 7	3.2
Pigy	phosphatidylinositol glycan anchor biosynthesis, class Y	3.2
Ppm1h	protein phosphatase 1H (PP2C domain containing)	3.2
Tm7sf2	transmembrane 7 superfamily member 2	3.2

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Wnt3	wingless-type MMTV integration site family, member 3	3.2
Cp	ceruloplasmin	3.2
St5	suppression of tumorigenicity 5	3.2
Myo5a	myosin VA	3.1
Ptpla	protein tyrosine phosphatase-like (proline instead of catalytic arginine), member a	3.1
Smo	smoothened, frizzled family receptor	3.1
Nog	noggin	3.1
Mmp3	matrix metallopeptidase 3	3.1
Trim37	tripartite motif-containing 37	3.1
Lactb2	lactamase, beta 2	3.1
Slc5a12	solute carrier family 5 (sodium/glucose cotransporter), member 12	3.0
RGD1310553	similar to expressed sequence AI597479	3.0
Tmem38b	transmembrane protein 38B	3.0
Trim14	tripartite motif-containing 14	2.9
Spata1	spermatogenesis associated 1	2.9
RGD1561149	similar to mKIAA1522 protein	2.9
Tmem79	transmembrane protein 79	2.9
Ctnnd1	catenin (cadherin associated protein), delta 1	2.9
Dnaja4	DnaJ (Hsp40) homolog, subfamily A, member 4	2.9
Rhbdd2	rhomboid domain containing 2	2.9
Nudt21	nudix (nucleoside diphosphate linked moiety X)-type motif 21	2.9
Pdk3	pyruvate dehydrogenase kinase, isozyme 3	2.9
Arhgap4	Rho GTPase activating protein 4	2.9
Stk38l	serine/threonine kinase 38 like	2.9
Hsf4	heat shock transcription factor 4	2.9
Mark4	MAP/microtubule affinity-regulating kinase 4	2.9
Fto	fat mass and obesity associated	2.8
Vps72	vacuolar protein sorting 72 homolog (S. cerevisiae)	2.8
Pcsk6	proprotein convertase subtilisin/kexin type 6	2.8
Ube2l6	ubiquitin-conjugating enzyme E2L 6	2.8
LOC361346	similar to chromosome 18 open reading frame 54	2.8
Mterfd1	MTERF domain containing 1	2.8
Gpn2	GPN-loop GTPase 2	2.8
LOC100362431	tetratricopeptide repeat domain 30B	2.8
Arsg	arylsulfatase G	2.8
RGD1308428	similar to RIKEN cDNA 4931406P16	2.8
Zfp655	zinc finger protein 655	2.7
Trhr	thyrotropin releasing hormone receptor	2.7
Ccdc61	coiled-coil domain containing 61	2.7
Azi1	5-azacytidine induced 1	2.7
Dnmt3b	DNA (cytosine-5-)-methyltransferase 3 beta	2.7
RGD1563941	similar to hypothetical protein FLJ20010	2.7
Nradd	neurotrophin receptor associated death domain	2.7
Mapk1ip1l	mitogen-activated protein kinase 1 interacting protein 1-like	2.7
Col9a2	collagen, type IX, alpha 2	2.7
Col9a1	collagen, type IX, alpha 1	2.7
Spin1	spindlin 1	2.7
Cib2	calcium and integrin binding family member 2	2.7
C1qtnf3	C1q and tumor necrosis factor related protein 3	2.6
Epyc	epiphycan	2.6

Supplementary Table S2 *(continued)*

Gene Symbol	Description	Fold Change (log2)
Tmem169	transmembrane protein 169	2.6
Stradb	STE20-related kinase adaptor beta	2.6
Fkbp7	FK506 binding protein 7	2.6
Rps6ka1	ribosomal protein S6 kinase polypeptide 1	2.6
Tctex1d2	Tctex1 domain containing 2	2.6
Plekhh3	pleckstrin homology domain containing, family H (with MyTH4 domain) member 3	2.6
Gins4	GINS complex subunit 4 (Sld5 homolog)	2.6
Wdr19	WD repeat domain 19	2.6
Trub1	TruB pseudouridine (psi) synthase homolog 1 (E. coli)	2.6
Fahd1	fumarylacetoacetate hydrolase domain containing 1	2.6
Slc34a3	solute carrier family 34 (sodium phosphate), member 3	2.6
Edem3	ER degradation enhancer, mannosidase alpha-like 3	2.6
Slc12a3	solute carrier family 12 (sodium/chloride transporters), member 3	2.5
Cblc	Cas-Br-M (murine) ecotropic retroviral transforming sequence c	2.5
LOC499643	similar to hypothetical protein FLJ25371	2.5
Mug2	murinoglobulin 2	2.5
Isg20	interferon stimulated exonuclease gene 20	2.5
Lum	lumican	2.5
Zpbp2	zona pellucida binding protein 2	2.5
Cpne8	copine VIII	2.5
Pir	pirin (iron-binding nuclear protein)	2.5
Zfp7	zinc finger protein 7	2.4
Pcsk1n	proprotein convertase subtilisin/kexin type 1 inhibitor	2.4
Sec23ip	SEC23 interacting protein	2.4
Rab4b	RAB4B, member RAS oncogene family	2.4
Tomm40	translocase of outer mitochondrial membrane 40 homolog (yeast)	2.4
Tapbp	TAP binding protein	2.4
Pi15	peptidase inhibitor 15	2.4
Hacl1	2-hydroxyacyl-CoA lyase 1	2.4
Usp15	ubiquitin specific peptidase 15	2.4
G3bp2	GTPase activating protein (SH3 domain) binding protein 2	2.3
Zdhhc2	zinc finger, DHHC-type containing 2	2.3
Rhobtb3	Rho-related BTB domain containing 3	2.3
Fgd1	FYVE, RhoGEF and PH domain containing 1	2.3
Gpx7	glutathione peroxidase 7	2.3
RGD1305939	hypothetical LOC300074	2.3
Egfl7	EGF-like-domain, multiple 7	2.2
Slc3a1	solute carrier family 3, member 1	2.2
Man1a2	mannosidase, alpha, class 1A, member 2	2.2
Klhl36	kelch-like 36 (Drosophila)	2.2
Prrc1	proline-rich coiled-coil 1	2.2
Cep97	centrosomal protein 97	2.2
Anks1a	ankyrin repeat and sterile alpha motif domain containing 1A	2.2
Fam35a	family with sequence similarity 35, member A	2.2
Ece2	endothelin-converting enzyme 2	2.1
Slc8a3	solute carrier family 8 (sodium/calcium exchanger), member 3	2.1
Fbln5	fibulin 5	2.1
LOC690918	hypothetical protein LOC690918	2.0

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ORIGINAL ARTICLE

Prevalence of low back pain as the primary pain site and factors associated with low health-related quality of life in a large Japanese population: a pain-associated cross-sectional epidemiological survey

Koji Yamada[1], Ko Matsudaira[2], Katsushi Takeshita[1], Hiroyuki Oka[3], Nobuhiro Hara[1], and Yasuo Takagi[4]

[1]*Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan,* [2]*Clinical Research Center for Occupational Musculoskeletal Disorders, Kanto Rosai Hospital, Kanagawa, Japan,* [3]*Department of Joint Disease Research, 22nd Century Medical and Research Center, The University of Tokyo, Tokyo, Japan, and* [4]*Graduate School of Health Management, Keio University, Kanagawa, Japan*

Abstract

Objectives. This study aimed to estimate the prevalence, magnitude, and direction of the associations among disability, pain intensity, number of pain sites, and health-related quality of life (HRQoL) in patients reporting low back pain (LBP) as their primary pain.

Methods. In January 2009, an Internet survey was performed for randomly selected adults aged 20–79 years who were registered as Internet research volunteers. Of 20 044 respondents, individuals with LBP as the primary pain were analyzed for associations among disability, number of pain sites, and HRQoL. Factors associated with low HRQoL were examined using multiple logistic regression modeling.

Results. Of the 20 044 respondents, 25.2 % ($n = 5060$) reported LBP and 13.5 % ($n = 2696$) reported LBP as their primary pain. Among those with LBP as the primary pain, HRQoL decreased with increase in disability and number of pain sites. In multivariate analyses, disability [adjusted odds ratio (aOR), 2.93–4.58], number of pain sites (aOR, 1.42–6.12), pain intensity ≥7 (aOR, 1.88), and age ≥60 years (aOR, 1.55) were associated with low HRQoL.

Conclusions. Approximately 13.5 % of patients reported LBP as their primary pain. Disability with absence from social activity and ≥7 pain sites were strongly associated with low HRQoL.

Keywords

Disability, EQ-5D, Low back pain, Multisite pain, Sick leave

History

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Introduction

Low back pain (LBP) is a common [1], costly [2], and, at times, disabling [3] condition that can lead to disability and sick leave from work or school. Pain at this site often fluctuates over time with frequent recurrences or exacerbations [4, 5]. The prevalence of LBP has been reported to range from 12–33 % [4] due to the methodologic heterogeneity across LBP prevalence studies [6, 7]. LBP is the most frequent and most expensive cause of work-related disability [8] and can affect health-related quality of life (HRQoL). LBP is a part of musculoskeletal pain [9, 10], but only one-sixth to one-third of individuals who suffer from LBP have LBP as their only pain source. Most LBP respondents also have pain at other sites [10]; this pain could be the primary reason for their disability. Moreover, a positive correlation was reported between the number of pain sites and functional problems in a large clinical study [9]. However, the prevalence and the impact of working disability and number of pain sites on HRQoL in those who have LBP as the primary pain have not been well examined.

Correspondence to: Koji Yamada, Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Tel: +81-3-3815-5411. Fax: +81-3-3818-4082. E-mail: forpatients2008@gmail.com

Therefore, the aim of this study was to estimate the prevalence, magnitude, and direction of the associations among disability, pain intensity, number of pain sites, and HRQoL in those reporting LBP as their primary pain in the pain-associated cross-sectional epidemiological (PACE) survey, which covers a large Japanese population.

Materials and methods

Subjects

The PACE survey was a cross-sectional Internet survey designed to evaluate the prevalence and characteristics of musculoskeletal pain in a large Japanese population. The study was performed over 10–18 January, 2009. Respondents were recruited at random from 1 477 585 research volunteers who were registered with an Internet survey company (Rakuten Research Inc., Tokyo, Japan), consistent with the Japanese demographic composition [11]. An invitation to participate in the research was sent through an e-mail containing a link to the survey. Double registration was prevented by checking the e-mail address and disabling the link to the questionnaire once the responder completed the survey. Forms were configured to automatically reject incomplete questionnaires. An additional credit point for Internet shopping was given as a financial incentive to the responders. On 18 January, 2009, the survey was closed when the number of respondents reached 20 063; thus,

the response rate is not relevant in this survey. Individuals whose reported age was <20 years or >79 years were excluded; thus, 20 044 participants were retained. This study was approved by Keio University's institutional review board.

Measures

The questionnaire included questions regarding musculoskeletal pain in the previous month and various individual factors. The respondents were asked about the characteristics of their musculoskeletal pain, such as the pain site(s), pain intensity at each site, site of the primary pain, duration of the primary pain, and disability due to the primary pain. Pain intensity was scored with a numeric rating scale (NRS) comprising 11 points (0 = no pain, 10 = worst pain imaginable). Disability was classified into three categories using a modified graded chronic pain scale (GCPS) [12], based on disability for social activity, such as work, school, and housework. Those with LBP and no disability were classified as modified GCPS grade 1, those with LBP and disability for social activity as modified GCPS grade 2, and those with LBP and disability leading to absence from social activity as modified GCPS grade 3. Respondents were asked about their demographic characteristics, including age, sex, occupational status, and HRQoL. HRQoL was measured using the Japanese EQ-5D instrument [13].

Definition of LBP

LBP was defined as pain experienced (over the previous month) below the costal margin and above the inferior gluteal folds, as described on the full-body manikin (Fig. 1, site 13), excluding those with pain around the anus (Fig. 1, site 21). Chronic LBP was defined as pain lasting ≥3 months.

EQ-5D

The EQ-5D instrument is a standardized general system for describing and valuing HRQoL [14]. It has good reliability and validity, and comprises five dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) that are rated on three levels (1 = no problem, 2 = some problem, 3 = extreme problem); thus, it generates 243 theoretically possible health states (11111 = full health, 33333 = most extreme state).

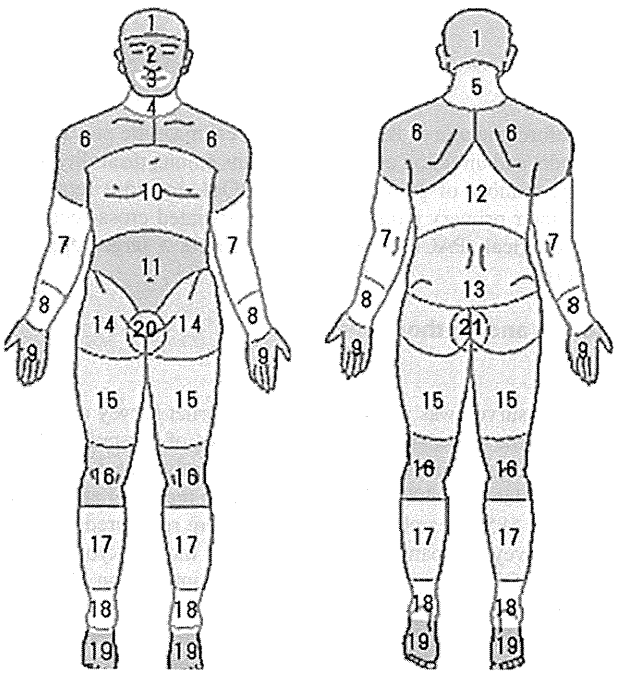

Fig. 1 The full-body manikin used in the pain-associated cross-sectional epidemiological (PACE) survey. Low back pain was defined as pain experienced below the costal margin and above the inferior gluteal folds, described as site number 13, excluding those with pain around the anus (site number 21)

Statistical analysis

First, the 1-month prevalence was calculated for those who had any LBP, LBP as the primary pain, and LBP as the only pain source (localized LBP). Further analyses were performed for those reporting LBP as their primary pain site using SPSS version 18 (IBM Corp., Armonk, N.Y., USA). Spearman's rho correlation coefficient was used to assess the correlations among HRQoL (EQ-5D score), disability, number of pain sites (other than LBP), and pain intensity (NRS score). For logistic regression analysis, the lowest 20 % of the EQ-5D scores in the total study population of the PACE survey was used as the dependent variable. A two-sided 5 % significance level was used in all statistical tests.

Results

LBP prevalence

Of the 20 044 respondents, 9746 (48.6 %) were men, and the overall mean score on the EQ-5D was 0.850 [standard error (SE), 0.001] with a ceiling effect of 45.7 % (9165 respondents; Table 1). The 1-month prevalence of LBP was 25.2 % (5060 respondents), of which only approximately half (2696 respondents; 13.5 % of all respondents) reported LBP as their primary pain and about one-seventh (706 respondents; 3.5 % of all respondents) reported LBP as their only pain source.

HRQoL in those with LBP as the primary pain

Further analyses were conducted for those with LBP as their primary pain. Of the 2696 respondents who reported LBP as the primary pain, 53.8 % (n = 1,424) were men, 78.1 % (n = 2,106) had chronic pain, 55.3 % (n = 1,491) reported LBP and no disability (modified GCPS grade 1), and 44.7 % (n = 1,205) reported disability for social activity with or without absence from social

Table 1. Characteristics of the total study population (n = 20,044)

Characteristic	n (%)
Age group (years)	
20–29	1,981 (9.9)
30–39	3,903 (19.5)
40–49	3,923 (19.6)
50–59	4,328 (21.6)
60–69	4,126 (20.6)
70–79	1,783 (8.9)
Mean ± SD	49.0 ± 14.2
Sex	
Male	9,746 (48.6)
Occupational status	
Worker	10,597 (52.9)
Housework and/or retired	7,655 (38.2)
Other (including student)	1,792 (8.9)
LBP prevalence	
Any LBP[a]	5,060 (25.2)
LBP as primary pain[b]	2,696 (13.5)
Localized LBP[c]	706 (3.5)
EQ5D score, mean ± SE	0.850 ± 0.001
Ceiling effect	9,165 (45.7)

LBP Low back pain, *SE* standard error
[a]Prevalence of respondents with LBP
[b]Prevalence of respondents with LBP as the primary pain site
[c]Prevalence of respondents with LBP as the only pain source

Table 2. Overall and by sex characteristics of respondents with LBP as the primary pain

Characteristic	Overall, *n* (%; *n* = 2696)	Men, *n* (%; *n* = 1424)	Women, *n* (%; *n* = 1272)
Age group (years)			
20–29	196 (7.3)	80 (5.6)	116 (9.1)
30–39	476 (17.7)	229 (16.1)	247 (19.4)
40–49	597 (22.1)	298 (20.9)	299 (23.5)
50–59	596 (22.1)	287 (20.2)	309 (24.3)
60–69	537 (19.9)	295 (20.7)	242 (19.0)
70–79	294 (10.9)	235 (16.5)	59 (4.6)
Mean ± SD	50.2 ± 13.8	52.4 ± 14.3	47.8 ± 12.9
Occupational status			
Worker	1,459 (54.1)	916 (64.3)	543 (42.7)
Housework and/or retired	1,013 (37.6)	395 (27.7)	618 (48.6)
Other (including student)	224 (8.3)	113 (7.9)	111 (8.7)
Duration of LBP			
Acute (<3 months)	526 (19.5)	281 (19.7)	245 (19.3)
Chronic (>3 months)	2,106 (78.1)	1,123 (78.9)	983 (77.3)
Unknown/refused to answer	64 (2.4)	20 (1.4)	44 (3.5)
Disability			
Grade 1[a]	1,491 (55.3)	808 (56.7)	683 (53.7)
Grade 2[b]	876 (32.5)	445 (31.3)	431 (33.9)
Grade 3[c]	329 (12.2)	171 (12.0)	158 (12.4)
NRS score (mean ± SE)	5.0 ± 0.0	4.8 ± 0.1	5.2 ± 0.1
Number of pain sites other than LBP (mean ± SE)	1.8 ± 0.0	1.6 ± 0.0	2.1 ± 0.1
EQ5D score (mean ± SE)	0.776 ± 0.003[d]	0.779 ± 0.004	0.772 ± 0.004

LBP Low back pain, *NRS* numeric rating scale, *SE* standard error
[a]LBP without disability for social activity, such as work, school, and housework
[b]LBP with disability for social activity, such as work, school, and housework
[c]LBP with disability leading to absence from social activity, such as work, school, and housework
[d]EQ5D score was significantly lower than that of the total study population (unpaired *t* test, $P < 0.01$)

activity (Table 2). The mean EQ-5D score was 0.776 (SE, 0.003), which was significantly lower than that of the total study population (unpaired *t* test, $P < 0.01$).

Next, the associations among HRQoL, number of pain sites, and pain intensity according to disability were analyzed (Table 3). We found that HRQoL decreased (Spearman's rank correlation coefficient, −0.371; $P < 0.01$) while pain intensity increased (Spearman's rank correlation coefficient, 0.418; $P < 0.01$) with higher disability. An increase in the number of pain sites was seen only between grade 1 and grade 2 disabilities (Table 3). Based on further evaluation of HRQoL stratified by age, sex, and disability, mean EQ-5D scores generally were lower in those with higher age and higher disability, and in women (Table 4).

Further analyses were conducted to evaluate the association among each variable stratified by the number of pain sites (Table 5). The number of respondents with LBP as a part of multisite pain was approximately 6.2 times larger than the number of those with localized LBP. In this analysis, HRQoL showed a negative correlation with the number of pain sites (Spearman's rank correlation coefficient, −0.256; $P < 0.01$). HRQoL was highest when the pain was localized, and lowest when the number of pain sites was ≥ 7. The proportion of those with disability for social activity (modified GCPS grades 2 and 3) and pain intensity also showed a positive correlation with the number of pain sites (Spearman's rank correlation coefficient, 0.184 and 0.359, respectively; both $P < 0.01$).

Factors associated with low HRQoL

In multivariate analyses adjusted by modified GCPS, number of pain sites, sex, age, and pain intensity, all the variables except sex were positively associated with low HRQoL (Table 6). The odds were higher as both disability and number of pain sites increased. Disability with absence from social activity and number of pain sites ≥ 7 had a strong relationship with low HRQoL. Similar trends were observed in both men and women; however, the impacts of absence from social activity and number of pain sites ≥ 7 were stronger in women than in men.

Discussion

In the present study, the 1-month prevalence of LBP was 25.2 % (5060 respondents), which is similar to that reported by Suzukamo and colleagues [15], who noted 30.6 % as the 1-month prevalence in Japan. Interestingly, of the 5060 respondents, only approximately half (2696 respondents; 13.5 % of all respondents) reported LBP as their primary pain, with the majority reporting chronicity. Recently, LBP has been recognized as a part of widespread musculoskeletal pain. Natvig and colleagues [10] reported that only

Table 3. Mean number of pain sites other than LBP, EQ5D score, and NRS score based on the disability of respondents with LBP as their primary pain

Disability (modified GCPS)	*n*	EQ5D score[d] (mean ± SE)	No. of pain sites other than LBP (mean ± SE)	NRS score[e] (mean ± SE)
Grade 1[a]	1,491	0.817 ± 0.003	1.5 ± 0.0	4.2 ± 0.0
Grade 2[b]	876	0.736 ± 0.004	2.3 ± 0.1	5.8 ± 0.1
Grade 3[c]	329	0.694 ± 0.009	2.3 ± 0.1	6.5 ± 0.1

GCPS Graded chronic pain scale, *LBP* low back pain, *NRS* numeric rating scale, *SE* standard error
[a]LBP without disability for social activity, such as work, school, and housework
[b]LBP with disability for social activity, such as work, school, and housework
[c]LBP with disability leading to absence from social activity, such as work, school, and housework
[d]EQ5D score showed a negative correlation with higher disability (Spearman's rank correlation coefficient, –0.371; $P < 0.01$)
[e]NRS score showed a positive correlation with higher disability (Spearman's rank correlation coefficient, 0.418; $P < 0.01$)

Table 4. Mean EQ5D score based on age, sex, and disability of respondents with LBP as the primary pain

Disability		Total (Grades 1 + 2 + 3)			Grade 1[a]			Grade 2[b]			Grade 3[c]		
Sex	Age (years)	*n*	Mean	SE	*n*	Mean	q	*n*	Mean	SE	*n*	Mean	SE
All	20–29	196	0.797	0.009	110	0.822	0.011	69	0.774	0.015	17	0.732	0.043
	30–39	476	0.785	0.006	236	0.828	0.008	173	0.756	0.009	67	0.706	0.021
	40–49	597	0.789	0.005	311	0.830	0.007	213	0.757	0.009	73	0.712	0.017
	50–59	596	0.777	0.006	360	0.817	0.006	172	0.727	0.010	64	0.686	0.021
	60–69	537	0.770	0.006	320	0.814	0.007	155	0.714	0.010	62	0.683	0.021
	70–79	294	0.729	0.008	154	0.782	0.009	94	0.676	0.010	46	0.659	0.026
	Total	2,696	0.776	0.003	1,491	0.817	0.003	876	0.736	0.004	329	0.694	0.009
Male	20–29	80	0.812	0.015	51	0.822	0.017	24	0.781	0.031	5	0.850	0.062
	30–39	229	0.794	0.009	114	0.837	0.011	80	0.772	0.013	35	0.702	0.033
	40–49	298	0.796	0.008	159	0.828	0.009	109	0.757	0.013	30	0.764	0.027
	50–59	287	0.781	0.008	172	0.820	0.009	81	0.725	0.014	34	0.718	0.024
	60–69	295	0.778	0.008	180	0.817	0.009	80	0.722	0.013	35	0.701	0.022
	70–79	235	0.734	0.008	132	0.781	0.009	71	0.666	0.011	32	0.689	0.034
	Total	1,424	0.779	0.004	808	0.817	0.004	445	0.734	0.006	171	0.718	0.013
Female	20–29	116	0.787	0.012	59	0.822	0.015	45	0.770	0.017	12	0.682	0.050
	30–39	247	0.777	0.008	122	0.820	0.011	93	0.743	0.012	32	0.710	0.024
	40–49	299	0.783	0.008	152	0.832	0.010	104	0.756	0.011	43	0.676	0.021
	50–59	309	0.773	0.008	188	0.814	0.008	91	0.730	0.014	30	0.650	0.034
	60–69	242	0.760	0.010	140	0.809	0.011	75	0.706	0.015	27	0.659	0.040
	70–79	59	0.708	0.020	22	0.787	0.034	23	0.704	0.020	14	0.590	0.035
	Total	1272	0.772	0.004	683	0.818	0.005	431	0.738	0.006	158	0.668	0.013

LBP Low back pain, *SE* standard error
[a]LBP without disability for social activity, such as work, school, and housework
[b]LBP with disability for social activity, such as work, school, and housework
[c]LBP with disability leading to absence from social activity, such as work, school, and housework

25 % of 893 participants who reported LBP during the previous week had localized LBP. In our study, the number of those with LBP as a part of multisite pain was about 6.2 times larger than the number of those with localized LBP. Previous studies [9, 10] have reported that many LBP respondents have pain elsewhere, which could be the primary reason for their disability. Therefore, we focused on LBP respondents reporting LBP as their primary pain for further analyses in this study.

In the present study, the mean EQ-5D score of those with LBP as their primary pain was 0.776 (SE, 0.003), which was significantly lower than that of the total study population [0.850 (SE, 0.001); $P < 0.01$], and slightly lower than the average score of patients with stage 5 chronic kidney disease (CKD) in Japan (0.798; 95 % CI, 0.757–0.839) [16]. Since stage 5 CKD represents established kidney failure, the similar HRQoL obtained in the present study indicates that the HRQoL of those who suffer from LBP could be as low as, or even lower than, those who are candidates for hemodialysis.

Generally, lower HRQoL is reported with higher disability in LBP patients [8, 17, 18]. Kovacs and colleagues revealed a negative correlation between the Rolland Morris Disability Questionnaire and the EQ-5D in LBP [8, 18]. In the present study, we used the GCPS [12], a well validated scale for assessing LBP disability, with minor revision. The revision was made to focus on disability and absence from social activity because the impacts of these disabilities on HRQoL have not been well examined. In our study, there was a negative correlation between disability and HRQoL, as in previous studies [8, 17, 18]. The differences in the mean EQ-5D scores between those with and those without disability and absence were 0.08 and 0.04, respectively. Interestingly, the differences were similar to the minimal clinically important difference reported in previous studies (0.033–0.074) [19, 20]. Collectively, these data suggest that the presence of disability for social activity and its severity regarding absence might have a significant meaning for those who suffer from LBP. Therefore, improvement of these disabilities might represent a clinically important difference, which needs further investigation.

Table 5. Proportion of LBP with disability, and mean EQ5D and NRS scores based on number of pain sites other than LBP in respondents with LBP as the primary pain

Number of pain sites other than LBP	*n*	EQ5D score[a] (mean ± SE)	LBP with working disability[b] (%)	NRS score[c] (mean ± SE)
0	706	0.813 ± 0.005	35.7	4.1 ± 0.1
1–3	1,582	0.776 ± 0.003	44.0	5.1 ± 0.1
4–6	325	0.729 ± 0.007	59.7	6.1 ± 0.1
≥7	83	0.644 ± 0.014	75.9	7.1 ± 0.2
Total	2,696	0.776 ± 0.002	44.7	5.0 ± 0.0

LBP Low back pain, *NRS* numeric rating scale, *SE* standard error
[a]EQ5D score showed a negative correlation with the number of pain sites other than LBP (Spearman's rank correlation coefficient, −0.256; $P < 0.01$)
[b]Proportion of those with working disability (modified graded chronic pain scale grade 2 or 3 disability) showed a positive correlation with the number of pain sites other than LBP (Spearman's rank correlation coefficient, 0.184; $P < 0.01$)
[c]NRS score showed a positive correlation with the number of pain sites other than LBP (Spearman's rank correlation coefficient, 0.359; $P < 0.01$)

In our study, HRQoL decreased as the number of pain sites increased, thus showing a negative correlation, whereas the proportion of disability and pain intensity increased as the pain sites increased. Kamaleri and colleagues [9] revealed that single-site pain did not have a large impact on physical fitness, feelings, or daily and social activities, and that functional problems increased markedly, in an almost linear manner, with increase in number of pain sites. From another study, the widest variation in health-related functioning, such as the items on the short form-36, was observed by the number of pain sites, with lower function seen with increase in number of pain sites [21]. LBP patients also have lower general health, poorer function, and poorer long-term work disability when their LBP is accompanied by multisite pain [10, 22, 23]. Our findings are consistent with those of previous reports, showing a similar relationship among pain intensity, disability, HRQoL, and number of pain sites in LBP responders. The reason why the majority of those with LBP as their primary pain also reported multisite pain could be the generalized hyperalgesia known to exist in

Table 6. Logistic regression analysis (dependent variable = lowest 20 % of EQ5D scores in total study population)

	Total[a]				Male[b]				Female[b]			
		95 % CI				95 % CI				95 % CI		
Variable	Adjusted odds	Lower	Upper	*P* value	Adjusted odds	Lower	Upper	*P* value	Adjusted odds	Lower	Upper	*P* value
Modified GCPS												
Grade 1	1.000				1.000				1.000			
Grade 2	2.930	2.393	3.589	<0.001	3.151	2.377	4.177	<0.001	2.750	2.052	3.686	<0.001
Grade 3	4.580	3.488	6.013	0.001	3.789	2.603	5.517	<0.001	5.642	3.780	8.420	<0.001
No. of pain sites other than LBP												
0	1.000				1.000				1.000			
1–3	1.420	1.128	1.786	0.003	1.173	0.873	1.576	0.290	1.850	1.275	2.685	0.001
4–6	2.367	1.733	3.232	<0.001	2.146	1.365	3.375	0.001	2.856	1.816	4.492	<0.001
≧7	6.124	3.541	10.589	<0.001	4.579	2.010	10.432	<0.001	8.426	3.970	17.882	<0.001
Sex												
F/M	1.044	0.868	1.256	0.644								
Age (years)												
<60	1.000				1.000					1.000		
≧60	1.545	1.271	1.879	<0.001	1.598	1.234	2.068	<0.001	1.485	1.097	2.011	0.010
NRS score												
<7	1.000				1.000					1.000		
≧7	1.883	1.541	2.300	<0.001	2.129	1.608	2.820	<0.001	1.650	1.238	2.200	0.001

CI Confidence interval, *F* female, *GCPS* graded chronic pain scale, *LBP* low back pain, *M* male, *NRS* numeric rating scale
[a]Multivariate analysis adjusted by modified GCPS, number of pain sites other than LBP, sex, age, and NRS score
[b]Multivariate analysis adjusted by modified GCPS, number of pain sites other than LBP, age, and NRS score

LBP patients [24]. Compared with healthy control subjects, LBP patients exhibit significantly lower pressure pain thresholds at all sites [25, 26]. The continuous nociceptive input might initiate central sensitization [27], which could develop widespread pain in those with LBP as their primary pain [24, 27].

In multivariate analyses, after adjusting for all the variables, modified GCPS grade, number of pain sites, age ≥60 years, and pain intensity were found to be associated with low HRQoL. Among these variables, disability with absence from social activity and ≥7 pain sites showed a stronger association than pain intensity (NRS score ≥7) and age ≥60 years. A similar tendency was seen in both men and women, highlighting the importance of multisite pain and disability in those who suffer from LBP. Although our study had limitations (due to its cross-sectional design), we believe the strong relationships seen in our study are noteworthy. Based on our results, occupational management [28, 29] focusing on returning to work, and management of multisite pain might have a more significant effect on HRQoL improvement than the management of pain itself in those who suffer from LBP. Further study is necessary to evaluate the effects of such management.

The strengths of our study include the large size of the population sample used to estimate the prevalence of those with LBP as their primary pain, and the magnitude of the associations among disability, pain intensity, number of pain sites, and HRQoL without any missing data. Some results support the validity of the PACE survey. First, the mean EQ-5D score of the PACE survey was similar to that found in a well-designed general population study (0.835) [30]. Second, the ceiling effect of the EQ-5D seen in the total study population also was similar to that reported in previous studies (42.5–47.0 %) [30–32]. Third, the percentage of those with LBP was similar to that reported previously in Japan [15]. Fourth, the percentage of workers in the total study population (52.8 %) was similar to that announced by the Japanese Ministry of Internal Affairs and Communications in 2009 (56.9 %) [11].

Some limitations in our study are notable, however. First, the selection bias due to the nature of an Internet survey needs to be addressed [33]. Although the study was conducted nationwide, using one of the largest domestic Internet survey companies, the volunteers from whom our sample was drawn were over-representative of people living in large cities, compared with the general population. Since LBP prevalence has geographic differences, with higher rates in urban populations than rural populations [34], caution is needed when interpreting the results of this study. Second, those who participate as Internet research volunteers may differ from the general population, and even from general Internet users. These potential differences could have affected the prevalence of LBP. Third, regarding the type of questionnaire, although a previous study reported that a Web-based questionnaire had adequate reliability compared with the paper-and-pencil version, even for older rural women [35], the mode of administration could affect the nature and rate of response [36]. Fourth, because this was a cross-sectional study, inferences cannot be drawn about causality.

In an Internet-based survey conducted in the United States, more than 27 000 individuals responded with a high response rate (75.7 %). The authors used a nationally representative Web-enabled panel of households that were recruited using a combination of random-digit dialing, landline-telephone recruiting, and address-based sampling [37]. Recruited households that did not have Internet access were provided free access via WebTV. Unlike other Internet-based surveys, the Internet-enabled panel used in the study was not limited to individuals with Internet access, and the sampling methodology was designed to ensure that the demographic characteristics of the panel were similar to those of the United States population. The methods used in this United States study maintain the representativeness of the study, while utilizing the advantages of Internet-based surveys for collecting a large amount of data. Such methodologic improvement might be necessary in our future studies.

Conclusion

Only approximately half of the LBP respondents reported LBP as their primary pain; among them, HRQoL decreased with higher disability and an increase in the number of pain sites. The presence of ≥7 pain sites and disability resulting in absence from social activity were strongly associated with low HRQoL. Occupational management focusing on return to work and management of multisite pain may have a more significant effect on HRQoL improvement than the management of pain itself in individuals with LBP.

Further research should focus on the effectiveness of such management in LBP respondents.

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Conflict of interest

None.

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ORIGINAL ARTICLE

Association of dietary intake with joint space narrowing and osteophytosis at the knee in Japanese men and women: the ROAD study

Shigeyuki Muraki[1], Toru Akune[1], Yoshio En-yo[2], Munehito Yoshida[2], Sakae Tanaka[3], Hiroshi Kawaguchi[3], Kozo Nakamura[4], Hiroyuki Oka[5], and Noriko Yoshimura[5]

[1]*Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan,* [2]*Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan,* [3]*Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan,* [4]*Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan, and* [5]*Department of Joint Disease Research, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*

Abstract

Objective. The objective of the present study is to identify dietary nutrients associated with joint space narrowing (JSN) and osteophytosis at the knee in a population-based cohort of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

Methods. From the baseline survey of the ROAD study, 827 participants (305 men and 522 women) in a rural cohort were analyzed. Dietary nutrient intakes for the last month were assessed by a self-administered brief diet history questionnaire. Minimum joint space width (mJSW) and osteophyte area (OPA) in the medial compartment of the knee were measured using a knee osteoarthritis (OA) computer-aided diagnostic system.

Results. In men, there were no associations of dietary nutrient intakes with mJSW or OPA. In women, vitamins K, B1, B2, B6, and C were associated with mJSW after adjustment for age, body mass index, and total energy ($p < 0.05$). Vitamins E, K, B1, B2, niacin, and B6 were significantly associated with OPA ($p < 0.05$) in women. Vitamins K, B and C may have a protective role against knee OA in women and might lead to disease-modifying treatments.

Conclusions. The present study revealed that low dietary intake of vitamins K, B, and C are associated with JSN and osteophytosis in women.

Keywords

Osteoarthritis, Knee, Diet, Cohort studies, Epidemiology

History

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Introduction

Knee osteoarthritis (OA), characterized by pathological features including joint space narrowing (JSN) and osteophytosis, is a major public health issue causing chronic pain and disability in the elderly in most developed countries [1]. The prevalence of radiographic knee OA is high in Japan [2], with 25,300,000 subjects aged 40 years and older estimated to experience radiographic knee OA [3]. According to the recent National Livelihood Survey of the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living [4]. Despite the urgent need for strategies for the prevention and treatment of this condition, there have been few established risk factors for knee OA except for age, female sex, obesity, previous injury, and occupational activities [5].

Current recommendations for OA include a combination of nonpharmacological interventions and pharmacological treatments [6]. However, considering that nonsteroidal anti-inflammatory drugs (NSAIDs), which may have serious adverse effects with long-term use, remain among the most widely prescribed drugs for OA [7], there is a need for safe and effective alternative strategies for prevention and treatment of this disease. Such strategies could come from dietary nutrition, because dietary factors are modifiable.

There have been several epidemiologic studies on the relationship between nutritional factors and OA [8–15]. Our previous study showed that dietary vitamin K intake was associated with the prevalence of knee OA [14], but disease was defined according to a categorical grade such as the Kellgren–Lawrence (KL) grade [16]. In the Framingham Study, the association of nutrition with JSN and osteophytosis was separately analyzed [8, 9, 12, 13] in Caucasians, but they were also defined by categorical grades. Categorical methods are statistically less powerful than continuous methods. Thus, the association between nutrition and knee OA might have been underestimated in previous studies.

To overcome these problems, joint space width or osteophyte area should be evaluated using a fully automatic system. To the best of our knowledge, there have been no population-based studies to separately measure joint space width or osteophyte area to clarify the association of dietary nutrient intake with JSN and osteophytosis. In the present study, we measured medial minimum joint space width (mJSW) and osteophyte area (OPA) at the knee in the large-scale population-based cohort study called Research on Osteoarthritis/osteoporosis Against Disability (ROAD). The

Correspondence to: Shigeyuki Muraki, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: +81-3-58009178. Fax: +81-3-58009179. E-mail: murakis-ort@h.u-tokyo.ac.jp

purpose of the present study is to clarify which nutritional factors were associated with JSN and osteophytosis.

Materials and methods

Subjects

The ROAD study is a nationwide prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OA and osteoporosis are the representative bone and joint diseases, respectively). It consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [2, 3, 17]; a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 subjects (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.3 years), who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [18]. The participation rate was 75.6 %. Participants in mountainous and coastal regions were also recruited from the resident registration lists, and the participation rates in these two areas were 56.7 and 31.7 %, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

From the baseline data of 855 subjects aged ≥40 years in the mountainous cohort, we excluded 3 individuals who had undergone knee surgeries. In addition we excluded 18 individuals who had lateral knee OA, defined as being present when a knee had KL grade ≥2 and lateral JSN score ≥1 on a 0–3 scale according to the Osteoarthritis Research Society International (OARSI) atlas [19]. We also excluded 4 who did not complete questionnaires regarding dietary nutrition, and 3 whose radiographic conditions were insufficient for measuring JSN and osteophyte area. Thus, a total of 827 participants (305 men and 522 women) were analyzed in the present study.

Dietary assessment

For the dietary survey, we used a self-administered brief diet history questionnaire (BDHQ) and investigated dietary nutrient intakes for the previous month. A questionnaire was given to each participant with detailed explanation to fill out at home, and was reviewed by well-trained interviewers when the participants visited the clinic. The BDHQ is a 4-page, structured questionnaire that inquires about the consumption frequency of 56 food and beverage items, with specified serving sizes described in terms of a natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. The BDHQ was developed based on a comprehensive (16-page) version of a validated self-administered diet history questionnaire [20], and is now widely used for dietary survey in Japan [14, 21]. Estimates of dietary intake for the 56 food and beverage items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was based on the Standard Tables of Food Composition in Japan. In the present study, dietary intake levels of total energy and 15 nutrient factors (animal protein, vegetable protein, animal fat, vegetable fat, carbohydrate, vitamin B1, 2, 6, and 12, niacin, vitamins C, D, E, K, and salt) were analyzed.

Radiographic assessment

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to make the patella centralized over the lower end of the femur, we used fluoroscopic guidance with an anterior–posterior X-ray beam. The images were downloaded into digital imaging and communication in medicine (DICOM) format files. mJSW (mm) in the medial compartment and OPA (mm^2) at the medial tibia were measured by the KOACAD system, and the knee with lower mJSW was defined as the designated knee of each participant. The KOACAD system has been described in detail elsewhere [22–24], and is summarized here only briefly. The KOACAD system can quantify the major features of knee OA on standard radiographs and allows objective, accurate, simple, and easy assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure mJSW in the medial and lateral compartments and OPA at the medial tibia using digitized knee radiographs. Initially, correction for radiographic magnification was performed based on the image size of a rectangular metal plate. Next, to determine the region of interest (ROI), the center of the tibiofemoral joint was determined as follows: A vertical neighborhood difference filter that vertically scanned digital images to detect the margins of the tibial and femoral condyles was applied to identify points with high absolute values for differences of scale. Then, the center of all points was calculated and defined as the center of the tibiofemoral joint. Finally, a 480 × 200 pixel rectangle around the center was defined as the ROI. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space by vertical filtering with a 3 × 3 square neighborhood difference filter. Both ends of the upper rim were determined using a Canny filter to remove the noise associated with lines, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the two outlines was designated as the lower rim of the joint space (Fig. 1a). A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line was designated as the inside rim. Medial and lateral joint space areas were determined as areas surrounded by the upper, lower, inside, and outside rims as defined above. Medial and lateral mJSWs were further determined as the minimum vertical distances in the respective joint space area (Fig. 1b). To measure the OPA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent over the smoothly extended outline was designated as the OPA (Fig. 1c). We examined the reproducibility of mJSW and OPA measured on radiographs taken at 2-week intervals for 20 individuals; the reproducibility of both mJSW and OPA were high [intraclass correlation coefficient (ICC) = 0.86 and 0.99, respectively] [22]. In addition, we measured mJSW and OPA by KOACAD more than twice on 1979 radiographs, and confirmed that all parameters were unchanged independent of observer or time measured (all ICC = 1.0) [22]. We have previously published reference values of joint space width and osteophyte area by gender and age strata in Japan using the KOACAD system [25].

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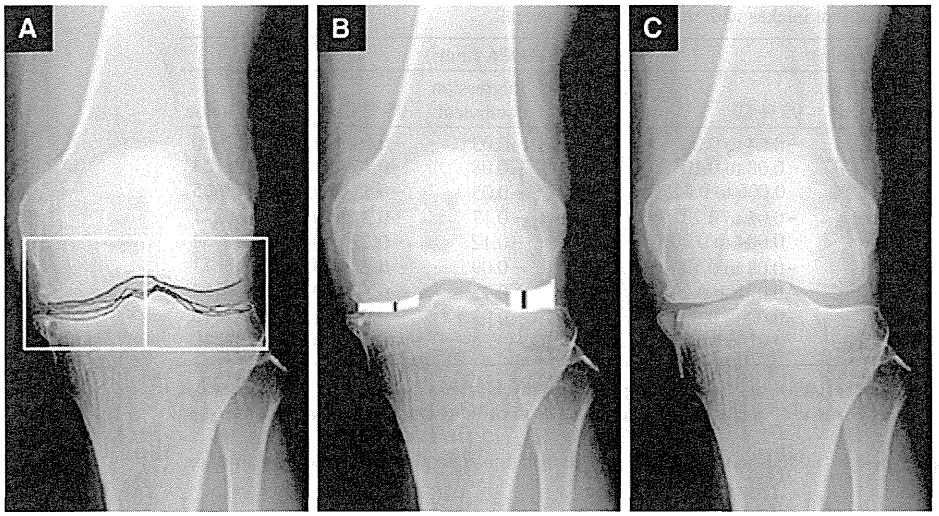

Fig 1. Schema of image processing by KOACAD (cited from Ref. [28]). (a) Outlines of anterior and posterior margins of the tibial plateau. The *middle line* between the two outlines is defined as the lower rim of the joint space. (b) Medial and lateral minimum joint space widths were defined as the minimum vertical distances in the joint space area. (c) Osteophyte area (*red area*) that is medially prominent over the smoothly extended outline of the tibia

Statistical analysis

Differences in age, height, weight, and body mass index (BMI) were examined by nonpaired Student's *t* test. mJSW, OPA, total energy, and dietary nutrient intakes between men and women were examined by Wilcoxon rank-sum test. The distribution of mJSW, OPA, total energy, and dietary nutrient intakes were not normal, thus we applied log transformation to these variables, and multiple regression analysis after adjustment for age, BMI, gender, and total energy was used to determine the association of dietary nutrient intakes with mJSW and OPA in the overall population. Furthermore, multiple regression analysis after adjustment for age, BMI, and total energy was used to determine the association of dietary nutrient intakes with mJSW and OPA in men and women. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC). *p*-Value <0.05 was considered significant.

Results

Characteristics of 827 participants are presented in Table 1. There were no significant differences in BMI between men and women. mJSW was significantly wider in men than women, and OPA was significantly smaller in men than women. Total energy and almost all of dietary nutrient intakes except for vitamins K and C were significantly higher in men than women ($p < 0.01$), whereas vitamin C intake was significantly lower in men than women ($p < 0.0001$) (Table 2). Vitamin K intake was not significantly different between men and women ($p = 0.07$).

Table 1. Characteristics of participants

	Overall	Men	Women	*p* Value
No. of participants	827	305	522	
Age (years)	69.2 ± 9.3	69.6 ± 8.7	68.9 ± 9.6	0.29
Height (cm)	163.0 ± 9.2	161.3 ± 6.7	148.1 ± 6.6	<0.0001
Weight (kg)	54.0 ± 10.2	60.0 ± 10.2	50.5 ± 8.5	<0.0001
BMI (kg/m^2)	23.0 ± 3.2	23.0 ± 3.0	23.0 ± 3.4	0.86
mJSW (mm)	2.43 ± 1.11	2.91 ± 1.01	2.15 ± 1.07	<0.0001
OPA (mm^2)	3.72 ± 8.33	1.72 ± 4.20	4.88 ± 9.79	<0.0001

Data are mean ± standard deviation (SD). Nonpaired Student's *t* test was used to compare age, height, and BMI between men and women. Wilcoxon rank-sum test was used to compare mJSW and OPA between men and women

BMI body mass index, *mJSW* minimum joint space width, *OPA* osteophyte area

We next analyzed the association of dietary nutrient intakes with mJSW and OPA. Overall, after adjustment for age, BMI, gender, and total energy, mJSW was not associated with vitamins D, E, B1 or niacin, but was significantly associated with vitamins K ($R = 0.344$, $p = 0.03$), B2 ($R = 0.343$, $p = 0.04$), and C ($R = 0.345$, $p = 0.02$) (Table 3). OPA was not significantly associated with vitamins D, E, K, B12, C or niacin, but was significantly associated with vitamins B1 ($R = 0.421$, $p = 0.03$), B2 ($R = 0.421$, $p = 0.03$), and B6 ($R = 0.422$, $p = 0.02$) (Table 3). When analyzed in men and women separately, in men, multiple regression analysis after adjustment for age, BMI, and total energy showed that mJSW and OPA were not significantly associated with any nutritional factors (Table 4). In contrast, in women, mJSW was significantly associated with vitamins K ($R = 0.283$, $p = 0.01$), B1 ($R = 0.271$, $p = 0.04$), B2 ($R = 0.270$, $p = 0.04$), B6 ($R = 0.273$, $p = 0.01$), and C ($R = 0.281$, $p = 0.01$) (Table 5), while OPA was significantly associated with vitamins E ($R = 0.426$, $p = 0.04$), K ($R = 0.427$, $p = 0.03$), B1 ($R = 0.436$,

Table 2. Dietary nutrient intakes in men and women

	Overall	Men	Women
Total energy, MJ/day	7.6 (6.3–9.3)	9.5 (8.1–12.1)	6.9* (6.0–7.9)
Dietary nutrients			
Vitamin D, μg/day	17.7 (11.5–25.8)	20.7 (13.3–30.5)	16.4* (10.7–24.2)
Vitamin E, mgα-TE/day	6.9 (5.4–8.8)	7.4 (5.6–9.6)	6.7* (5.3–8.3)
Vitamin K, μg/day	211.0 (146.6–287.9)	224.4 (150.2–313.5)	202.9 (145.3–281.0)
Vitamin B1, mg/day	0.71 (0.58–0.86)	0.79 (0.64–0.97)	0.67* (0.56–0.80)
Vitamin B2, mg/day	0.97 (0.76–1.19)	1.07 (0.82–1.34)	0.92* (0.73–1.12)
Niacin, mgNE/day	14.9 (11.6–19.2)	17.9 (13.9–22.7)	13.6* (10.4–17.1)
Vitamin B6, mg/day	1.1 (0.9–1.4)	1.3 (1.0–1.6)	1.03* (0.86–1.26)
Vitamin B12, μg/day	9.8 (6.8–13.5)	11.0 (7.7–15.8)	8.8* (6.3–12.0)
Vitamin C, mg/day	101.7 (78.3–133.4)	94.0 (71.7–122.0)	108.1* (82.6–137.3)

Values are median (interquartile range)

TE tocopherol equivalent, *NE* niacin equivalent

*$p < 0.01$ versus men by Wilcoxon rank-sum test

Table 3. Association of dietary nutrient intakes with mJSW and OPA overall

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p*-Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	0.006	−0.04 to 0.06	0.8044	−0.03	−0.09 to 0.02	0.2000
Vitamin E, mgα-TE/day	0.01	−0.08 to 0.10	0.7613	−0.08	−0.17 to 0.02	0.1114
Vitamin K, μg/day	0.06	0.006 to 0.11*	0.0309	−0.05	−0.11 to 0.004	0.0665
Vitamin B1, mg/day	0.09	−0.05 to 0.23	0.2058	−0.17	−0.32 to 0.02*	0.0271
Vitamin B2, mg/day	0.10	0.004 to 0.20*	0.0418	−0.12	−0.22 to 0.01*	0.0254
Niacin, mgNE/day	0.02	−0.08 to 0.13	0.6422	−0.09	−0.20 to 0.01	0.0877
Vitamin B6, mg/day	0.12	−0.001 to 0.24	0.0526	−0.15	−0.28 to 0.03*	0.0164
Vitamin B12, μg/day	0.04	−0.02 to 0.09	0.2066	−0.03	−0.09 to 0.02	0.2515
Vitamin C, mg/day	0.09	0.01 to 0.16*	0.0179	−0.04	−0.12 to 0.03	0.2640

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, gender, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

$p = 0.002$), B2 ($R = 0.435$, $p = 0.003$), niacin ($R = 0.428$, $p = 0.02$), and B6 ($R = 0.433$, $p = 0.01$) (Table 5).

Discussion

This is the first population-based cohort study of the relationship between dietary nutrient intakes and JSN and osteophytosis separately in Japanese men and women. In the overall population, vitamins K, B2, and C were significantly associated with mJSW, while vitamins B1, B2, and B6 were significantly associated with OPA. When analyzed in men and women separately, we observed that there were no associations of dietary nutrient intakes with mJSW or OPA in men. In contrast, in women, vitamins K, B1, B2, and B6 were associated with both mJSW and OPA. Vitamin C was associated with mJSW, but not with OPA. Previous studies have already shown that vitamins K and C were associated with knee OA; however, the knee OA was defined by KL grade or other categorical methods in almost all studies [8–15]. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, JSN and osteophyte formation are not assessed separately, thus one cannot clarify whether osteophytosis and JSN have distinct risk factors. In addition, a recent cross-sectional study showed that osteophytosis was unrelated to JSN on plain radiographs [26]. Furthermore, our study on an experimental mouse model for OA identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression [27, 28]. In addition, there were distinct effects on quality of life (QOL) for JSN and osteophytosis [26]. Such accumulating evidence indicates that JSN and osteophytosis may have distinct etiologic mechanisms and their progression may be neither constant nor proportional. Thus, to examine factors associated with knee OA, these two OA features should be separately assessed. Furthermore, because categorical methods are statistically less powerful than continuous methods, the association between nutrition and knee OA might have been underestimated in previous studies. This study is the first to report that vitamins K, B1, B2, and B6 are significantly associated with both mJSW and OPA, and that vitamin C is significantly associated with mJSW in women. The association of dietary factors with knee OA may be weaker than for gender or obesity, but they are easily modifiable; therefore, these results may contribute to prevent incidence or progression of knee OA, although it is not completely clear what modifications of vitamin intake would be required to achieve clinically meaningful change in mJSW and OPA.

Vitamin K includes vitamin K1, or phylloquinone, which is contained in green leafy vegetables, and vitamin K2, or menaquinone, which is synthesized by bacteria and abundantly contained in a traditional Japanese fermented soybean food called *natto* [29]. Our previous study showed that dietary vitamin K intake was inversely associated with prevalence of knee OA defined by KL grade [14]. However, because of the different etiology that

Table 4. Association of dietary nutrient intakes with mJSW and OPA in men

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p* Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	−0.02	−0.10 to 0.06	0.5804	0.04	−0.03 to 0.11	0.2710
Vitamin E, mgα-TE/day	−0.01	−0.14 to 0.11	0.8501	0.03	−0.09 to 0.14	0.6567
Vitamin K, μg/day	0.02	−0.06 to 0.09	0.6626	−0.01	−0.08 to 0.06	0.7939
Vitamin B1, mg/day	−0.01	−0.21 to 0.19	0.8995	0.08	−0.11 to 0.26	0.4275
Vitamin B2, mg/day	0.07	−0.08 to 0.22	0.3515	0.05	−0.09 to 0.19	0.4772
Niacin, mgNE/day	−0.03	−0.18 to 0.12	0.7149	0.06	−0.08 to 0.20	0.4127
Vitamin B6, mg/day	0.04	−0.13 to 0.22	0.6214	−0.005	−0.17 to 0.16	0.9554
Vitamin B12, μg/day	−0.004	−0.09 to 0.09	0.9345	0.06	−0.03 to 0.14	0.1816
Vitamin C, mg/day	0.03	−0.03 to 0.14	0.5079	0.01	−0.08 to 0.11	0.8113

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

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Table 5. Association of dietary nutrient intakes with mJSW and OPA in women

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p* Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	0.03	−0.03 to 0.09	0.3550	−0.07	−0.14 to 0.004	0.0631
Vitamin E, mgα-TE/day	0.05	−0.08 to 0.18	0.4234	−0.15	−0.29 to −0.008*	0.0383
Vitamin K, μg/day	0.11	0.03 to 0.19*	0.0062	−0.10	−0.18 to −0.009*	0.0302
Vitamin B1, mg/day	0.21	0.01 to 0.41*	0.0366	−0.35	−0.56 to −0.13*	0.0020
Vitamin B2, mg/day	0.13	0.006 to 0.26*	0.0411	−0.22	−0.37 to −0.08*	0.0025
Niacin, mgNE/day	0.08	−0.06 to 0.21	0.2819	−0.18	−0.33 to −0.03*	0.0195
Vitamin B6, mg/day	0.18	0.02 to 0.34*	0.0261	−0.25	−0.42 to −0.07*	0.0053
Vitamin B12, μg/day	0.07	−0.005 to 0.14	0.0679	−0.07	−0.16 to 0.006	0.0699
Vitamin C, mg/day	0.13	0.04 to 0.23*	0.0077	−0.09	−0.20 to 0.02	0.1139

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

may exist between JSN and osteophytosis, these two OA features should be assessed separately to examine factors associated with knee OA. However, the association of these two features with vitamin K cannot be separately analyzed by KL grade. The Framingham Study showed that plasma levels of phylloquinone were inversely associated with osteophytosis in the knee [12], but no population-based study has determined the association of dietary vitamin K intake with mJSW width and OPA separately. In the present study, vitamin K was associated with both JSN and osteophytosis in women, although the results for vitamin K were of borderline significance after adjusting for additional potential confounders, particularly regarding OPA. Several basic studies have shown that vitamin K plays an important role in cartilage metabolism, as an inhibitor of extracellular matrix calcification as well as a promoter of cell survival and proliferation [30–38]. In addition, warfarin, a vitamin K-antagonist anticoagulant, is known to cause warfarin embryopathy characterized by abnormal calcification and decreased growth of cartilage [37, 38]. Habitual low dietary vitamin K intake may exert an inhibitory effect on the vitamin K-dependent MGP and Gas6 functions and modulate the pathogenesis of OA by influencing the process of osteophytosis and cartilage destruction.

Several previous studies have shown that vitamin C intake was inversely associated with knee OA [9, 15], but no population-based study has analyzed the association of vitamin C intake with mJSW and OPA at the same time. In the present study, vitamin C was associated with narrower mJSW in women, but not with OPA. This finding may indicate that vitamin C intake is more strongly associated with JSN than with osteophytosis in women. Damage caused by free radicals has long been thought to be pathogenic, and free radicals play an important role in the progression of many chronic diseases, including OA [9, 11, 39–42]. Vitamin C is an antioxidant, which may partly explain the effect of vitamin C on JSN. This may lead to the logical possibility of using vitamin C supplementation for primary prevention or as a therapeutic intervention for OA.

There have been no studies regarding the association of dietary vitamin B intake with knee OA. In the present study, we found that vitamins B1, B2, and B6 were significantly associated with mJSW in women. Vitamin B is closely involved in the metabolism of homocysteine [43], which has recently been seen to play a role in osteoporosis-related bone damage, and may be linked to its involvement in collagen formation. Homocysteine inhibits the synthesis of insoluble collagen fibrils in vitro by interfering with normal cross-linking [44]. From the perspective of cartilage homeostasis, these changes in matrix organization interfere with chondrocyte-mediated mineralization, potentially altering the function and properties of calcified cartilage [45]. This may be due to homocysteine-mediated inhibition of lysil oxidase, which catalyzes the cross-linking of collagen molecules, a function necessary for its mineralization in bone tissue [46].

In the present study, we found gender differences regarding the association of dietary nutrient intakes with mJSW and OPA. In women, vitamins B and K were significantly associated with both mJSW and OPA, and vitamin C was significantly associated with mJSW, whereas in men, no dietary factors were significantly associated with mJSW or OPA. This difference may be partly explained by muscle strength in men. Because men are known to have greater muscle strength than women at all ages, and muscle strength has a protective effect on knee OA [47–49], it might be that the greater muscle strength obscures the effects of dietary nutrient intakes on knees in men.

There are several limitations to the present study. First, this was a cross-sectional study of baseline data, and thus no causal relationship can be determined. Second, in the present study, we used self-reported measures for dietary assessments; these measurements are prone to bias and measurement error. In addition, the dietary survey in this study investigated dietary habits only for the previous month, which did not necessarily reflect a long habit of several years, despite the fact that OA is a slowly progressing chronic disease. This dietary survey also investigated whether participants had changed their dietary habits. Those who answered "yes" accounted for 9.6 %, whereas 90.4 % of participants answered that they had not changed their dietary habits. Although it is likely that dietary habits in middle-aged and elderly people are usually quite different from those in children and young adults, there is a possibility that most participants in this study had not changed their dietary habits for several years or for a longer time, which may have affected the disease process of OA. Furthermore, the dietary survey in the present study was conducted from autumn to winter although there are four seasons in Japan and diets may vary with the season. Therefore, the present study could suffer from some bias for the effect of season on the nutritional quality of diets. Third, nutritional factors cannot be assumed to be joint location specific, and osteophytes may even be more pronounced in the contralateral tibiofemoral compartment [50]; however, at present, the KOACAD system can only measure medial osteophytes at the tibia. We are now developing a KOACAD system to measure osteophytes at other sites; thus, we may be able to clarify the association between osteophytes at other sites and QOL in the near future. Finally, we clarified the association of vitamins B, C, and K with mJSW and OPA, but did not determine what changes in intake of these vitamins would be needed to achieve clinically meaningful change in mJSW and OPA, because we

have not yet clarified what changes in mJSW and OPA are clinically meaningful. In addition, this is a cross-sectional study, thus causal relationships of vitamins B, C, and K with mJSW and OPA cannot be clarified.

In conclusion, the present cross-sectional study using a population-based cohort revealed that low dietary intakes of vitamins K, B1, B2, and B6 are associated with both JSN and osteophytosis in women. Vitamin C intake was associated with JSN in women, but not with osteophytosis. Further studies, along with longitudinal data from the ROAD study, will elucidate the environmental background of OA and help clarify clinical evidence regarding the development of disease-modifying treatments.

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Conflict of interest

None.

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