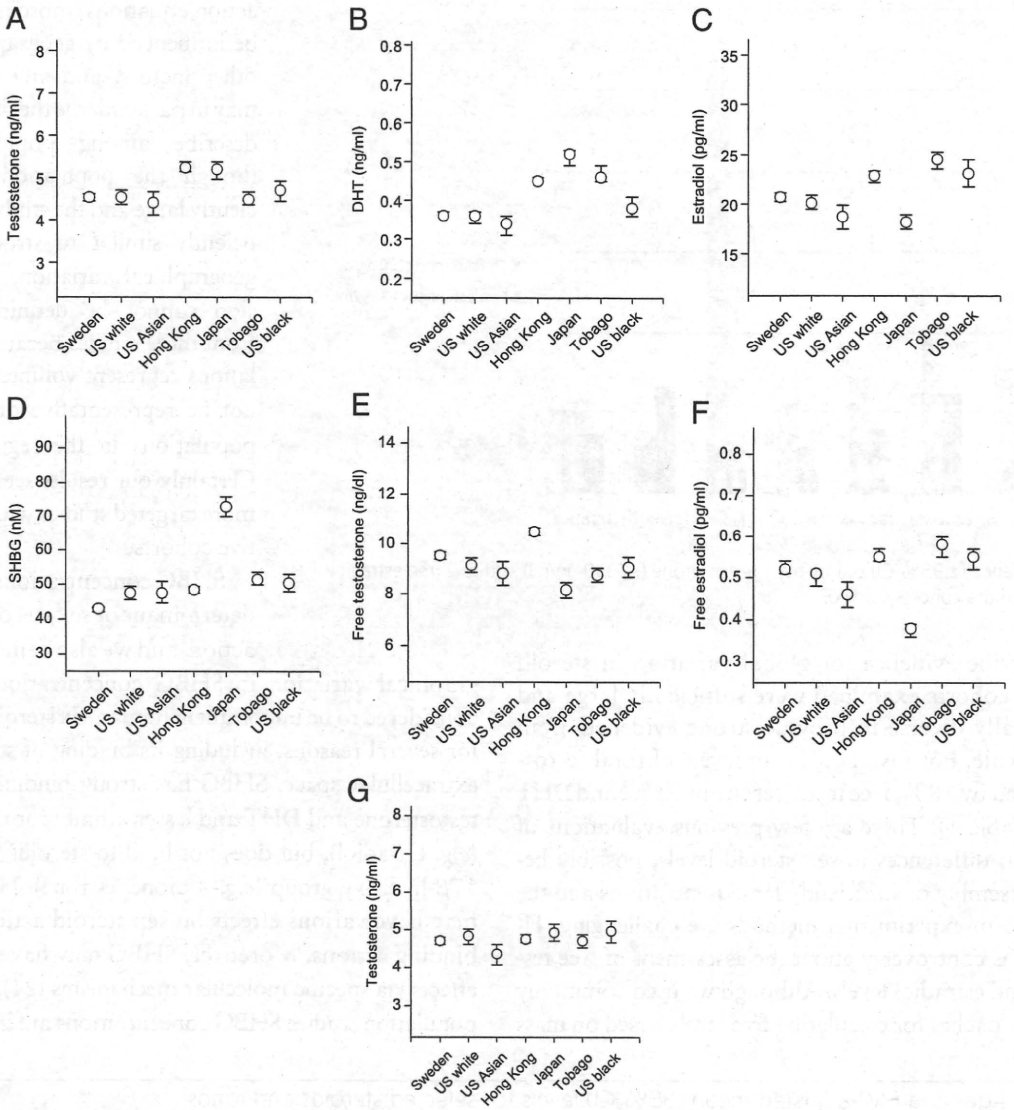

FIG. 2. Age-adjusted (A–F) and age- and BMI-adjusted (G) means (±95% CI) for selected steroids.

States and Tobago) had higher estrogen levels than Caucasians or Asians. Total and free estradiol levels were 10–16% higher and estrone levels 27–39% higher in Black men after age and BMI adjustments (Table 2). Moreover, in Blacks the ratios of total estradiol:total testosterone and estrone:androstenedione (4-dione) were increased compared with other groups (Table 2). Second, after age and BMI adjustments, Asian men (from the United States, Hong Kong, and Japan) had lower serum levels of glucuronidated androgen metabolites [androsterone-glucuronide (ADT-G), androstane-3α,17β-diol-3-glucuronide (3α-diol-3G), and androstane-3α,17β-diol-17-glucuronide (3α-diol-17G)] than did Blacks and Caucasians, and the ratios of these compounds to their precursors [DHT and androsterone (ADT)] were lower in Asian men (Table 2). Racial patterns in other compounds were not apparent.

Discussion

In this large, international study of older men, we found major variation between groups in the concentrations of sex steroids, in their precursors and metabolites, and in SHBG. Differences between populations transcend racial distinctions and thus strongly suggest that there are important geographical and environmental influences on sex steroid metabolism. However, in part, the variation was also the consequence of two fundamental racial differences in steroid metabolism-increased estrogen production by aromatase in Blacks and reduced androgen glucuronidation in Asians. As a result of overall population variation, there is considerable discrepancy between groups in the proportion of men who would be identified as hypogonadal or who would be considered at higher risk of fracture.

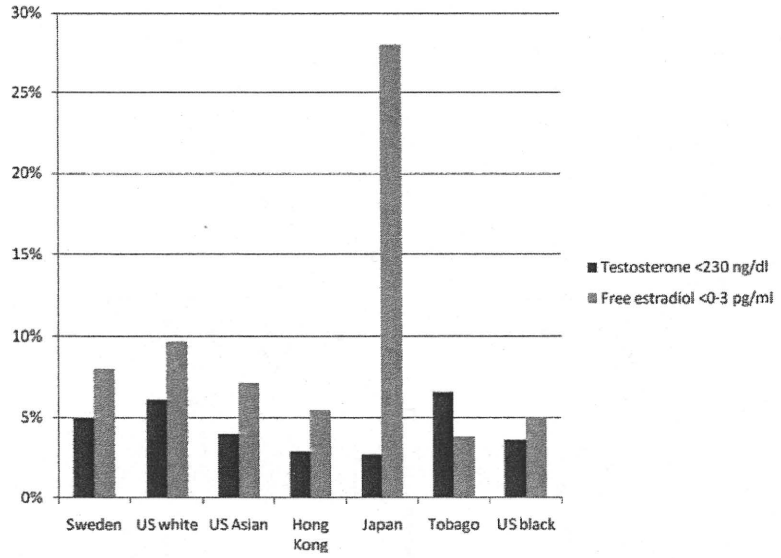

FIG. 3. Prevalence (±95% CI) of low total testosterone (<2.30 ng/ml) and low free estradiol (<0.3 pg/ml) in the cohorts studied.

We describe evidence for global variation in steroid levels. The cohorts examined were sufficiently large and geographically diverse to provide strong evidence of an effect of locale. For instance, mean levels of total testosterone varied by 18%, free testosterone by 25%, and DHT by 42% (Table 1). There are few previous evaluations of geographical differences in sex steroid levels, possibly because the assembly of sufficiently large populations and the use of uniform experimental methods are challenging. Finally, there is controversy about the assessment of free testosterone and estradiol levels. Although we used commonly applied approaches for calculating free levels based on mass action equations, those methods may be influenced by geography, race, or other factors, and any such factors may in part underlie the differences we describe among populations. Although the populations are sufficiently large and the study designs sufficiently similar to strongly suggest geographical variation, that conclusion cannot be definitively drawn from these studies because our populations represent volunteers that may not be representative of the general populations in the regions studied. Certainly our results set the stage for more targeted studies with representative cohorts.

SHBG concentrations are a major determinant of sex steroid levels and action, and we also demonstrate geographical variation in SHBG concentrations. SHBG is considered to be important in human sex steroid physiology for several reasons, including its binding of steroids in the extracellular space. SHBG has strong binding affinity for testosterone and DHT and lesser affinity for other steroids (*e.g.* estradiol), but does not bind to steroids that lack the 17β-hydroxy group (*e.g.* 4-dione, estrone). Hence, SHBG may have various effects on sex steroid actions via these binding actions. Moreover, SHBG may have direct tissue effects via specific molecular mechanisms (21), and in large population studies SHBG concentrations are independently

TABLE 2. Age- and BMI-adjusted mean (95% CI) levels for selected steroids and ratios

				P values for pairwise comparisons		
	White	Asian	Black	White-Asian	White-Black	Asian-Black
DHT (pg/ml)[a,b]	0.38 (0.37, 0.39)	0.39 (0.39, 0.40)	0.46 (0.44, 0.48)	0.03	<0.0001	<0.0001
DHT:T[a]	0.29 (0.29, 0.29)	0.28 (0.28, 0.29)	0.31 (0.31, 0.31)	<0.0001	<0.0001	<0.0001
E1 (pg/ml)	32.15 (31.58–32.83)	29.38 (28.84–29.81)	40.70 (39.44–41.86)	<0.0001	<0.0001	<0.0001
E2 (pg/ml)[a]	20.09 (19.69–20.49)	20.09 (19.69–20.49)	23.34 (22.42–24.29)	0.73	<0.0001	<0.0001
Free E2 (pg/ml)	0.49 (0.48–0.51)	0.48 (0.48–0.49)	0.54 (0.52–0.55)	0.03	<0.0001	<0.0001
E2:T	1.40 (1.38–1.41)	1.41 (1.40–1.42)	1.49 (1.46–1.51)	0.10	<0.0001	<0.0001
Free E2:free T	0.045 (0.043–0.046)	0.047 (0.046–0.048)	0.057 (0.055–0.060)	0.04	<0.0001	<0.0001
E1:4-dione[b]	10.58 (10.44–10.72)	11.11 (10.99–11.23)	13.01 (12.76–13.26)	<0.0001	<0.0001	<0.0001
ADT-G (ng/ml)[a]	26.11 (25.31–26.94)	19.91 (19.29–20.33)	27.79 (26.39–29.27)	<0.0001	0.06	<0.0001
3α-diol-3G (ng/ml)[a]	1.27 (1.23–1.32)	0.80 (0.77–0.82)	1.18 (1.12–1.25)	<0.0001	0.04	<0.0001
3α-diol-17G (ng/ml)[a]	2.39 (2.32–2.49)	1.86 (1.8–1.92)	2.39 (2.25–2.53)	<0.0001	0.93	<0.0001
3α-diol-3G:DHT	1.41 (1.37–1.44)	1.00 (0.97–1.03)	1.23 (1.17–1.29)	<0.0001	<0.0001	<0.0001
3α-diol-17G:DHT[a]	2.05 (2.01–2.09)	1.77 (1.73–1.80)	1.89 (1.82–1.96)	<0.0001	0.0005	0.001
ADT-G:ADT[a]	26.85 (25.87–27.83)	22.75 (21.87–23.64)	27.35 (25.55–29.15)	<0.0001	0.67	<0.0001

E1, Estrone; E2, estradiol; T, testosterone.

[a] BMI × group interaction included in model to allow BMI adjustment to be group-specific.

[b] Age × group interaction included in model to allow age adjustment to be group-specific.

associated with important outcomes (20–22). Levels were considerably higher in two rural areas of Japan. Similar results have been reported in Japanese women (22, 23). The significance of these findings is unclear, but high levels of SHBG in the Japanese were reflected in differences in testosterone and estradiol concentrations that could lead to alterations in androgenic and estrogenic action. Like sex steroids, SHBG may be affected by a wide variety of genetic as well as environmental factors including diet (7, 24, 25). Finally, there is controversy about the assessment of free sex steroid levels (15, 26). Although we used commonly applied approaches for calculating free levels based on mass action equations, those methods may be influenced by geography, race, or other factors, and any such factors may in part underlie the differences we describe among populations.

The causation of differences among our populations is not yet clear. Ecological influences including diet, environmental chemicals, climate, physical activity, smoking, and social status (24, 25, 27, 28) have been linked to effects on sex steroid physiology and could contribute to international variation. In addition, differences in the prevalence of reproductive disorders could contribute to our results. There were obvious differences in body mass index among the groups, and body composition is well known to influence sex steroid levels and physiology (29, 30). In fact, adjustment for body mass index in our analyses altered the population differences, but in large part they persisted, suggesting that body mass index is at best a partial explanation for group variations.

International variation in sex steroid levels could have obvious implications for the diagnosis and treatment of hypogonadism. Our results show that use of a conventional criterion for age-related androgen insufficiency (<230 ng/dl) (19) would yield noteworthy population differences in the prevalence of hypogonadism that would in turn result in differences in the number of men considered for replacement therapy. In addition, population differences in sex steroid levels may be similarly relevant to the international epidemiology of common conditions that affect older men, including inflammation, prostate disease, neoplasia, frailty, and osteoporosis. For instance, serum estradiol levels are useful in estimating fracture risk in older men (20, 31), at least in Caucasians, and we show that there appears to be substantial racial and geographical variation in the proportion of men considered at higher risk using this criterion. Variation in estrogen levels and evidence of increased aromatase activity have been linked to the risk of cardiovascular disease in older men and women (32). Finally, geographical and racial variation in sex steroid levels in older men may herald comparable variation in women, and if present during growth population variation could lead to developmental differences in sex steroid-dependent human phenotypes such as reproductive function, body composition, bone structure, and hair distribution.

Racial, presumably genetic, influences on sex steroid metabolism have long been sought. Some studies suggest the presence of higher estradiol levels in both Black men (33) (in a representative population in the United States) and women (34) but involved few participants and generally employed RIA methods that have limitations. Moreover, most comparisons involve subjects limited to one geographic area (28). Our findings considerably extend those reports and provide a global perspective. We demonstrate not only that Black men in the United States and Tobago have higher mean estradiol levels than populations of Caucasians and Asians but also provide evidence (higher estrone levels and reduced precursor/product ratios) that implicates increased aromatase activity as the likely explanation. These results may have important health implications. For instance, femoral cortical thickness and trabecular bone density are greater in older Black men (35), and Black men have lower hip fracture rates (36, 37), findings that are consistent with higher estrogen levels. In our study, considerably fewer Black men had free estradiol levels below a threshold level associated with increased fracture risk (20, 31).

We also show that androgen metabolism in Asian men is distinct. The levels of glucuronidated androgen metabolites (but not ADT) were clearly reduced in Asian men, as were the ratios of these compounds to their precursors, indicating that glucuronidation is likely affected. In support of these large population results, we previously reported that a proportion of Asians have a deletion in the uridine diphosphate-glucuronosyltransferase UGT2B17, consistent with lower rates of androgen glucuronidation. We and others have also shown that polymorphisms or copy number variation in the major enzymes responsible for glucuronidation of androgens (UGT2B15, UGT2B17, and UGT2B7) appear to have an impact on levels of glucuronidated androgens (38, 39), suggesting that these genes are interesting candidates to explain racial differences in glucuronidated androgen levels. Of potential physiological importance, serum androgen glucuronide levels may be more strongly related to total androgen activity than are measures of individual androgens. Of practical concern, a reduction in testosterone glucuronidation with high serum and low urine testosterone levels in Asians can result in misinterpretations of common monitors for androgen use in athletes (40). Other studies have explored Asian-Caucasian differences in reproductive function (27) but have been small and rarely involved disparate geographies.

The study has considerable strengths. It represents a unique international collaboration that brings together

well-characterized cohorts that were recruited and evaluated using similar methods. Large numbers of study participants provided adequate power to identify group differences, and we measured a large number of sex steroids, including potent androgens and estrogens as well as their precursors and metabolites. Importantly, all steroid measures were performed in a single laboratory employing rigorous quality control procedures, and the methods used avoid limitations of previous approaches. On the other hand, as mentioned above, the cohorts were recruited using very comparable strategies, and they are similar in many relevant respects, but they may not be completely representative of their broader populations. Our analyses are cross-sectional, and although the effects of sex steroids in older men are of considerable interest, we did not assess variation in women and younger people. The apparent racial differences we describe appear robust, but we classified race in broad racial categories and did not formally examine genetic admixture or racial subgroups. Moreover, whereas our results provide a new recognition of possible racial and geographical variation in sex steroid metabolism, we have not determined the mechanisms responsible. Finally, some variation may have been introduced by the approaches used for sample handling. For instance, whereas we attempted to standardize the methods for sample collection and storage, there were some minor differences that might have contributed to variation.

In summary, in a large, international study of older men we found evidence for substantial racial and geographical differences in the levels of major circulating androgens and estrogens, in their precursors and metabolites, and in SHBG. Such variation could result in diversity in important health outcomes, for instance in the proportion of older men with hypogonadism and in the risk of fracture attributable to estrogen deficiency. Understanding the causes of potential differences could yield new insights into racial and environmental influences on sex steroid regulation.

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Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22

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ABSTRACT

Objectives Osteoarthritis (OA) is the most prevalent form of arthritis and accounts for substantial morbidity and disability, particularly in older people. It is characterised by changes in joint structure, including degeneration of the articular cartilage, and its aetiology is multifactorial with a strong postulated genetic component.

Methods A meta-analysis was performed of four genome-wide association (GWA) studies of 2371 cases of knee OA and 35 909 controls in Caucasian populations. Replication of the top hits was attempted with data from 10 additional replication datasets.

Results With a cumulative sample size of 6709 cases and 44 439 controls, one genome-wide significant locus was identified on chromosome 7q22 for knee OA (rs4730250, $p=9.2\times10^{-9}$), thereby confirming its role as a susceptibility locus for OA.

Conclusion The associated signal is located within a large (500 kb) linkage disequilibrium block that contains six genes: *PRKAR2B* (protein kinase, cAMP-dependent, regulatory, type II, β), *HPB1* (HMG-box transcription factor 1), *COG5* (component of oligomeric golgi complex 5), *GPR22* (G protein-coupled receptor 22), *DUS4L* (dihydrouridine synthase 4-like) and *BCAP29* (B cell receptor-associated protein 29). Gene expression analyses of the (six) genes in primary cells derived from different joint tissues confirmed expression of all the genes in the joint environment.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent form of chronic joint disease and accounts for substantial morbidity and disability, particularly among older people. It is characterised by loss of joint homeostasis. The articular cartilage cannot maintain its integrity and is progressively damaged, the subchondral bone envelope is thickened changing loads in the bone-cartilage biomechanical unit, the synovium shows signs of inflammation and bony spurs (osteophytes) appear at the edges of the bone. Its aetiology is multifactorial with a significant genetic component as shown by twin and family studies.[1 2]

Many genetic variants have been considered as potential risk factors for OA, but most of the reported associations are inconclusive or not replicated. A recent large-scale meta-analysis found evidence that the *GDF5* locus on chromosome 20 was associated with the increased risk of knee OA in Caucasians.[3–6] Other genome-wide data have reported an association with the *DVWA* gene in Asians but not Caucasians[7] and a *PTGS2* variant that replicated but did not reach genome-wide significance (GWS).[8] Recently, a genome-wide association (GWA) study identified a locus on chromosome 7q22 which has an association with combined knee OA and/or hand OA phenotype.[9]

In this study we have synthesised available data from four GWA studies under the auspices of the

Translational Research in Europe Applied Technologies for Osteoarthritis (TreatOA) consortium (www.treatoa.eu). A total of 2371 cases of knee OA were available for this first stage of the analysis. The most significant signals were further investigated in additional samples of European descent and single nucleotide polymorphisms (SNPs) that reached GWS were further evaluated in Asian samples.

METHODS

Study design

A detailed description of all samples used in this study is provided in the online supplement. A three-stage design was used for the identification of any potential associations between sequence variants and knee OA in populations of European ancestry. We first synthesised the available data from four GWA studies (deCODE, Rotterdam Study, Framingham, Twins UK) using inverse variance fixed effects models. The variants that reached the 2×10^{-5} level of significance were selected for further replication. These SNPs were followed up in eight additional European cohorts (arcOGEN, Greek, Spanish, Finnish, Nottingham, Chingford study, GARP, Estonian and Swedish). The SNPs that replicated in the follow-up samples were genotyped in two additional European samples (deCODE (Icelandic) and Swedish). One cohort provided computer-generated replication from an ongoing GWA study (arcOGEN, 12 SNPs were directly genotyped and 6 were imputed) while de novo replication was performed in the other cohorts. Furthermore, the top hits were followed up in Asian populations (Chinese and Japanese samples). The effect sizes from the meta-analysis of the GWA studies and the effect sizes from the replication effort were all combined to provide an overall estimate. We also synthesised the effect estimates of the European and Asian samples to provide a global summary effect estimate.

Phenotype definitions

Study subjects with a radiographic Kellgren and Lawrence (K/L) grade ≥2[10] or total knee replacement were included as cases in the analysis. When clinical criteria were considered (Greek, Spanish and GARP study groups), the American College of Rheumatology classification criteria were used.[11] Subjects who had no known affected joints among those assessed acted as controls. For example, in a cohort that assesses knee, hip and hand OA, controls were participants with no affected hip or hand joints for the knee OA analysis. Population-based controls were used for the arcOGEN study.

Genotyping and imputation

Samples from the GWA studies were genotyped using the Infinium HumanHap300 (Illumina) for deCODE and Twins UK samples, HumanHap550v3 Genotyping BeadCHip (Illumina) for the Rotterdam Study and the Affymetrix GeneChip Human Mapping 500K for the Framingham cohort. The number of SNPs genotyped ranged from 314 075 to 500 510. Imputations were performed to increase the coverage. All the top SNPs studied had acceptable imputation quality. The genotyped and imputed SNPs that successfully passed the quality control criteria (n=2 335 627) were considered for the analyses. Detailed information on genotyping platform, quality control and imputation methods for each cohort are shown in table S1 in the online supplement.

The replication samples for the Greek, Spanish, Finnish, Chingford and GARP studies were genotyped using the MassArray iPlex Gold from Sequenom. Replication genotyping was carried out by a genotyping contractor (Kbiosciences Ltd, Hertfordshire, UK) using a competitive allele-specific PCR SNP genotyping system for the Nottingham and the Estonian cohort. The additional 622 Icelandic cases and the samples from the Swedish cohort were genotyped by deCODE genetics using the Centaurus (Nanogen) platform.[12] Detailed information on genotyping is provided in the online supplement.

Statistical analysis

Association analysis

Each team performed an association test per gender for knee OA under a per-allele model. The λ inflation factor was calculated per gender-specific effect size using the genomic control method[13] and the standard errors were corrected by the square root of the λ inflation factor was calculated per gender-specific effect size using the genomic control method[13] and the standard errors were corrected by the square root of the λ inflation factor ($SE_{corrected} = SE_{observed} \times \sqrt{\lambda}$). Robust standard errors were estimated to adjust for the family relationships (Framingham and GARP studies)). Robust standard errors were estimated to adjust for the family relationships (Framingham and GARP studies)

Meta-analysis

The effect size for each SNP (OR per copy of minor allele as per HapMap) was calculated using inverse variance fixed effects models,[14] synthesising all the sex-specific effect sizes and the corrected standard errors. Analyses combining men and women were also performed. In family studies the results from men and women combined were used to account for relatedness between women and men within families. Meta-analyses of the GWA studies were performed using the METAL software (www.sph.umich.edu/csq/abecasis/metal). Between-study heterogeneity was tested using the Cochran Q statistic, which is considered significant at $p<0.1$. The extent of inconsistency across studies was quantified using the I^2 metric which ranges from 0 to 100%.[15] Heterogeneity is considered low, moderate, high and very high for 0–24%, 25–49%, 50–74% and >75%, respectively.[16] We also computed the 95% CI for the I^2.[17] The calculation was repeated with random effects models for all SNPs that were further evaluated in replication datasets. Meta-analyses of the 18 top hits were performed using Stata Version 10.1.

Assessment of credibility

In order to assess the credibility of the top hit, we calculated the Bayes factor under a spike and smear prior to using as an alternative an average genetic effect corresponding to an OR of 1.2 and a conservative agnostic prior of 0.0001%.[18]

Functional analysis

Two methodological approaches were used to investigate the functional role of genes identified by GWA studies: (1) by assessing their expression in primary human joint cells (synovial fibroblasts, chondrocytes and meniscal cells) and its change in response to the proinflammatory cytokines tumour necrosis factor α and interleukin 1β as well as comparing their gene expression profiles during chondrocyte dedifferentiation (3D pellet cultures vs monolayer culture); and (2) by assessing their expression dynamics by whole mount in situ hybridisation using zebrafish (*Danio rerio*) embryos aged 6 h (shield), 10 h (bud), 13 h (5–9 somites) and 1, 2, 3 and 4 days to explore their role during embryogenesis.

RESULTS

Meta-analysis of GWA studies and replication of top findings

The descriptive characteristics of the GWA studies used for the meta-analyses are from Iceland (deCODE), the Netherlands (Rotterdam study), USA (Framingham) and the UK (Twins UK). The characteristics of these studies are shown in table 1 and in the online supplement. The four GWA datasets included a total of 2371 cases and 35 909 controls. A quantile-quantile plot comparing the meta-analysis association results of the four studies with those expected by chance showed an excess of SNP associations indicating a likely true association signal (figure 1). Data analysis showed the strongest association on chromosome 7q22 with a p value of 5.06×10^{-8} for rs4730250 localised in dihydrouridine synthase 4-like gene (*DUS4L*) (figure 2). Other associated signals in the 7q22 gene cluster were in high linkage disequilibrium (LD) ($r^2>0.8$) with the top signal (figure 2).

We selected for follow-up in replication samples all SNPs with a p value $<2\times10^{-5}$ in the meta-analysis association results. A total of 18 SNPs from 10 chromosomal loci satisfied this criterion (see table S2 in online supplement). However, as some of those SNPs were fully equivalent in the HapMap-CEU dataset, a total of 11 non-identical SNPs were tested for replication in 3326 cases and 7691 controls from eight European studies (see table 1 and online supplement). Two SNPs (rs4730250 and rs10953541), both located at 7q22, replicated nominally ($p<0.05$) in the combined analysis of the follow-up samples with p values of 6.3×10^{-4} and 8.3×10^{-3}, respectively. The two SNPs rs4730250 and rs10953541 were then further genotyped in two additional replication sets.

Both SNPs reached GWS in a meta-analysis of all European sample sets (GWA datasets and replication cohorts, table 2). A total of 6709 cases of knee OA cases and 44 439 controls were analysed. SNP rs4730250 was genome-wide significant with a per-allele summary OR of 1.17 (95% CI 1.11 to 1.24) and a p value of 9.2×10^{-9}. The minor allele frequency was 0.17 in the combined dataset. Low heterogeneity was observed ($I^2=15\%$, 95% CI 0% to 48%) which was not statistically significant ($p=0.26$ for Cochran Q statistic, figure 3). No gender-specific effects were seen. The summary estimates did not differ significantly in men and women ($p=0.74$, test of homogeneity, figure 3). Analysis of both sexes together in all cohorts did not alter the results (OR 1.17, 95% CI 1.07 to 1.27, $p=4.1\times10^{-8}$). The summary effect sizes of all loci under study are shown in table 2

Table 1 Characteristics of the studies included in the analysis

Team	Knee OA cases/ controls	Platform used	Age mean (range)	BMI mean (range)	Women (%)	Knee OA definition	Control definition
GWA studies							
deCODE	1033/32482	Infinium HapMap 300	69 (19–99)	26 (14–60)	58	TKR	Healthcare records
Framingham	419/1674	Affymetrix GeneChip	64 (29–93)	26 (14–54)	56	Radiographic	Radiographic
Rotterdam	868/1464	Illumina HapMap550v3	67 (55–94)	26 (16–56)	59	Radiographic	Radiographic
TwinsUK	51/289	Infinium HapMap 300	54 (37–76)	25 (15–51)	100	Radiographic	Radiographic
Replication cohorts: stage 1							
arcOGEN	1643/4894	Illumina 610 Quad	NA	NA	71	Radiographic/clinical	General population
Chingford*	64/236	NP	63 (54–77)	26 (17–43)	100	Radiographic	Radiographic
Finnish	112/210	NP	67 (51–74)	29 (20–42)	75	TKR	Population-based
Greek	368/606	NP	61 (20–90)	26 (17–34)	72	Clinical	Clinical
GARP	161/758	NP	60 (30–79)	27 (19–47)	63	Radiographic/clinical	Radiographic/clinical
Spanish	262/294	NP	66 (32–94)	31 (18–53)		TKR/clinical	Clinical
Nottingham*	647/237	NP	66 (40–97)	27 (15–51)	53	TKR	Radiographic and clinical
Estonian	69/456	NP	47 (32–60)	28 (15–47)	69	Radiographic	Radiographic
Replication cohorts: stage 2							
deCODE	622/32482†	Illumina and Centaurus (Nanogen)	77 (40–99)	29 (19–49)	63	TKR	Population-based
Swedish	390/839	NP	62 (46–73)	29 (18–51)	63	TKR + concomitant clinical and radiographic diagnosis of OA	General population without TKR

*Numbers excluding the samples already included in the arcOGEN study.
†Same controls as for discovery cohort.
BMI, body mass index; GWA, genome-wide association; NP, not pertinent; OA, osteoarthritis; TKR, total knee replacement.

Table 2 Summary OR and 95% CI of SNPs in the analysis including all European descent data

SNP rs number	Minor (risk) allele	Chromosome	Position	Gene	MAF	OR (95% CI) fixed effects	p Value	I^2 (95% CI)	Cochran Q
rs4730250	G	7	106994931	*DUS4L*	0.17	1.17 (1.11 to 1.24)	9.17×10^{-9}	15 (0 to 49)	0.26
rs10953541	T	7	107031781	*BCAP29*	0.24	1.17 (1.10 to 1.23)	3.90×10^{-8}	19 (0 to 54)	0.23
rs3749132	A	2	68907001	*ARHGAP25*	0.07	1.17 (1.05 to 1.30)	4.08×10^{-3}	47 (0 to 74)	0.04
rs886827	C	7	42285581	*GLI3*	0.27	1.07 (0.99 to 1.16)	0.089	65 (43 to 80)	0.001
rs1886695	G	20	33643949	*CPNE1*	0.16	0.89 (0.84 to 0.95)	1.76×10^{-4}	42 (2 to 66)	0.02
rs10071956	T	5	173093290	Intergenic	0.38	1.12 (1.06 to 1.19)	5.05×10^{-5}	15 (0 to 53)	0.29
rs6816070	G	4	16089455	*LDB2*	0.42	0.91 (0.86 to 0.95)	1.34×10^{-4}	0 (0 to 54)	0.46
rs661924	T	10	21353562	*NEBL*	0.39	1.11 (1.05 to 1.17)	1.82×10^{-4}	30 (0 to 67)	0.18
rs436354	G	5	783271	*ZDHC11*	0.17	1.19 (1.01 to 1.30)	1.79×10^{-2}	41 (2 to 63)	0.06
rs1994104	T	12	83040643	Intergenic	0.13	0.88 (0.80 to 0.96)	3.13×10^{-3}	46 (2 to 70)	0.02
rs9857056	G	3	181698548	Intergenic	0.12	1.11 (1.02 to 1.20)	1.65×10^{-2}	72 (43 to 87)	0.001

Minor allele is the OR allele.
MAF, minor allele frequency; SNP, single nucleotide polymorphism.

and the results from the random effects analysis for the top hits are shown in table S3 in the online supplement.

The two significant SNPs at 7q22, rs4730250 and rs10953541, are highly correlated (D′=1, r^2=0.63 in HapMap-CEU) and are likely to represent the same underlying association signal as shown by conditional association analysis (see table S4 in online supplement). Age and body mass index are considered to be significant risk factors for the development of knee OA.[19–25] We performed an analysis where the top hit was adjusted for these risk factors in deCODE samples and the Rotterdam study. The association of the top hit remained largely unchanged in analyses adjusted for body mass index and age.

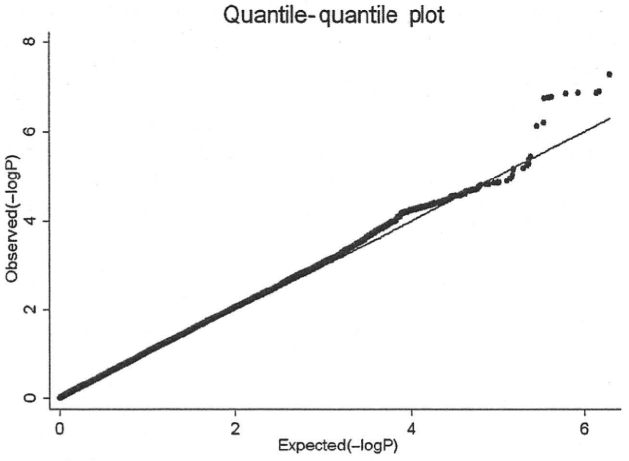

Figure 1 Quantile–quantile plot of the expected versus observed distribution of p values.

In order to assess the credibility of the associations of the two SNPs, we calculated the Bayes factor[18] under a spike and smear prior using an average genetic effect corresponding to an OR of 1.2 and a conservative agnostic prior (assuming no prior knowledge of the association) of 0.0001%. The posterior credibility of these associations was 98% and remained similarly high even with a small alternative effect size of 1.1.

We also tested if the observed signal at the 7q22 region was replicated in East Asian samples (Japanese and Chinese cohorts). The total numbers of cases of knee OA and controls assessed were 1183 and 1245, respectively. rs12535761 was used as a proxy for rs4730250. The two SNPs are in strong LD (r^2=1, D′=1 in HapMap Asian samples). The finding was not replicated in the Asian samples with a summary effect size of 1.03 (95% CI 0.85 to 1.25). A meta-analysis including both European and Asian samples with 7892 cases and 45 684 controls yielded a global summary effect of 1.15 (95% CI 1.10 to 1.22) with a p value of 5.7×10^{-8} for rs4730250 with low heterogeneity (I^2=19%).

Expression patterns of genes in 7q22 cluster

The associated signal at 7q22 is located within a large (500 kb) LD block which contains six genes: *PRKAR2B* (protein kinase, cAMP-dependent, regulatory, type II, β), *HPB1* (HMG-box transcription factor 1), *COG5* (component of oligomeric golgi complex 5), *GPR22* (G protein-coupled receptor 22), *DUS4L* (dihydrouridine synthase 4-like) and *BCAP29* (B cell receptor-associated protein 29).

We performed additional experiments to get more information about the genes in the cluster and their potential role in joint biology and pathology. Analysis of mRNA expression data in a chondrocyte pellet indicates that *BCAP29*, *COG5*, *DUS4L* and *HBP1* expression levels were higher than in monolayer cultures, suggesting that they are expressed in an environment that

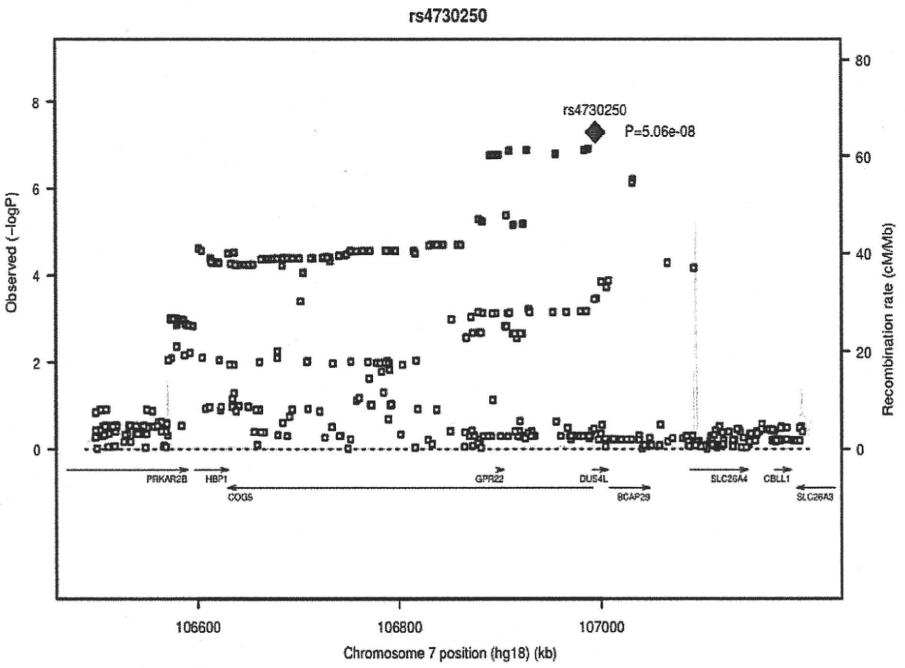

Figure 2 Regional association plot of rs4730250. Statistical significance of the associated SNPs are illustrated on $-\log_{10}$ scale. The p value of the rs4730250 and the other 10 selected SNPs are based on the meta-analysis of all datasets (both genome-wide association (GWA) studies and replication studies); p values for the other SNPs are based on the meta-analysis of the GWA studies. The sentinel single nucleotide polymorphism (SNP) is shown in blue. The correlation of the sentinel SNP is shown on a scale from minimal (gray) to maximal (red). SNPs in red have $r^2\geq0.8$ with the sentinel SNP and SNPs in orange have $r^2\geq0.5$. Chromosome positions are based on HapMap release 22 build 36.

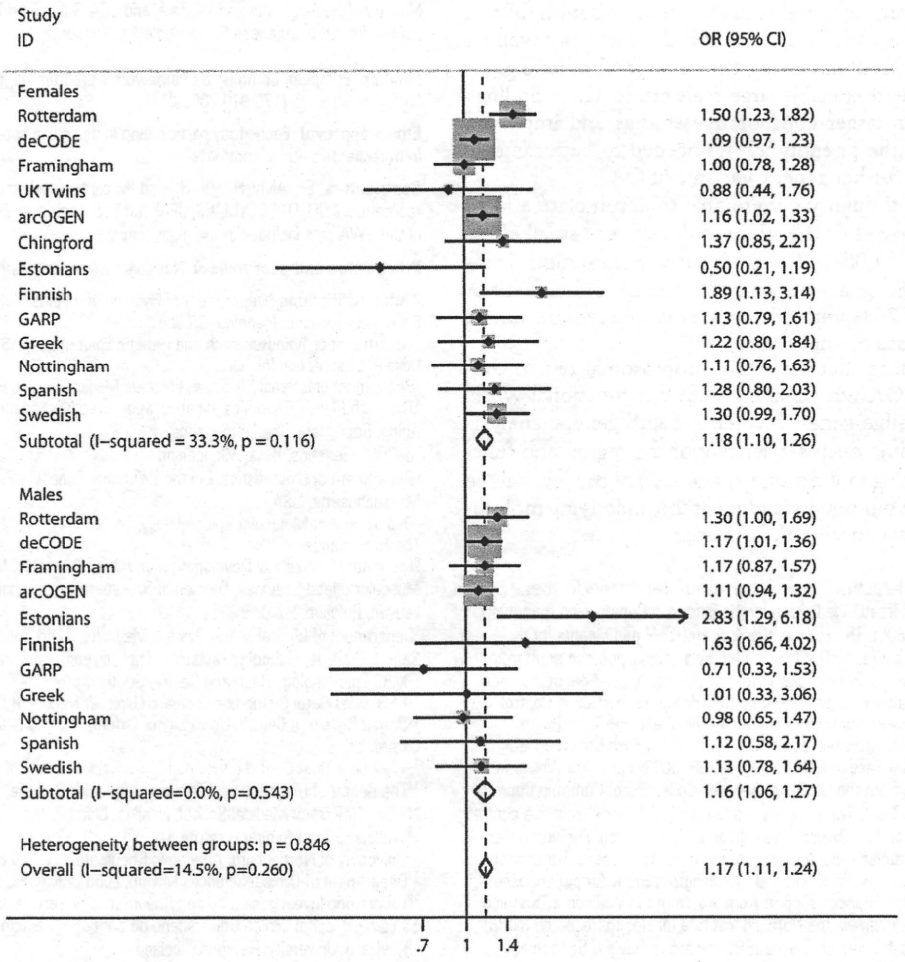

Figure 3 Forest plot of study-specific estimates (black boxes) and summary OR estimates and 95% CIs (diamonds) for the association between the rs4730250 single nucleotide polymorphism and osteoarthritis of the knee.

more accurately recapitulates articular cartilage (see figure S1 in online supplement). In contrast, no difference was seen for GPR22 and PRKAR2B mRNA expression. In a zebrafish model, the expression of all genes was detectable from the shield stage onwards (see detailed results and figures S2 and S3 in the online supplement).

DISCUSSION

This study provides further evidence for a knee OA signal localising to the 7q22 cluster region and associated with knee OA. The statistical credibility and confidence of this evidence is very high, based on the calculations of the Bayes factor. The same locus has been identified and proposed as an OA susceptibility locus from the Rotterdam study for the prevalence and progression of OA.[9] Our study and the earlier Rotterdam study do include overlapping populations. However, our study was specifically targeting the knee OA phenotype. An additional three European cohorts and two Asian populations were used for further replication. Our study uses the largest sample size in the genetics of knee OA research to date with almost 8000 cases of knee OA analysed.

The most significant hits identified by our study are located within a large (500 kb) LD block that contains six genes: *PRKAR2B*, *HPB1*, *COG5*, *GPR22*, *DUS4L* and *BCAP29*. The top hit rs4730250 is annotated in intron 3 of the *DUS4L* gene. Any of the genes at the 7q22 region may confer risk for knee OA as the LD pattern across the region is high.

The gene expression data support the epidemiological findings but do not exclude any of the six candidate genes. Specifically, the zebrafish experiments show that both *COG5* and *DUS4L* are expressed in developing cartilage, supporting the notion that either of these genes could have a biological function during chondrogenesis. The studies in the dedifferentiation model of human chondrocytes (3D vs 2D culture) show that *BCAP29*, *COG5*, *DUS4L* and *HBP1* all have different expression patterns in 3D culture (chondro-like cells) from 2D culture (dedifferentiated cells), suggesting that these four genes may play a role in cartilage metabolism.

A major issue in the field of OA is the definition of the disease phenotypes.[4 26] Different criteria may introduce bias and dilute the effect. The cases in our study were defined either clinically by the presence of a knee replacement or radiographically using the K/L system. The K/L system is, however, far from perfect and can be affected by differences in the position of the knee in which the x-rays were obtained, observer biases, interpretation of grading criteria and random error.[27 28] Similarly, there are no standard criteria for replacing knee joints. This may introduce heterogeneity and move the observed effects towards the unity and so underestimate the true strength of an association. In our study we synthesised data with a standardised definition of the

phenotype; however, small individual locus effects with ORs in the range of 1.1–1.2 as for other chronic diseases may well be plausible for knee OA, explaining the paucity of other significant hits despite the reasonable large-scale effort. These findings highlight that even larger collaborative studies and improved standardisation of the phenotypes are needed to better understand and identify further genetic variants of OA.

Moreover, even though we were able to accumulate a large sample size, the power of the study to detect very small effect sizes in the range of 1.05–1.15 is inadequate. For example, identification of a GWS signal with an effect size of 1.15 and minor allele frequency of 20% with 80% power would require almost 7000 additional cases of knee OA.

Our results confirm that the 7q22 chromosomal region confers risk for knee OA which, along with our functional work, implicates six possible genes. Further in-depth genetic analysis of the locus including deep sequencing of the region and functional work including in vitro assays and animal models will be required to deepen our understanding of the underlying molecular pathways associated with the disease.

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Ethics approval Each study participating in this meta-analysis has obtained approval from respective ethics committe.

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Prevalence and correlates of regional pain and associated disability in Japanese workers

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ABSTRACT

Objectives To assess the prevalence and correlates of regional pain and associated disability in four groups of Japanese workers.

Methods As part of a large international survey of musculoskeletal symptoms (the CUPID study), nurses, office workers, sales/marketing personnel and transportation operatives in Japan completed a self-administered questionnaire (response rate 83%) covering experience of pain in six anatomical regions, associated disability and sickness absence, and various possible occupational and psychosocial risk factors for these outcomes. Associations with risk factors were assessed by logistic regression.

Results Analysis was based on 2290 subjects. Rates of regional pain were generally less than in the UK, with a particularly low prevalence of wrist/hand pain among office workers (6% in past month). The strongest and most consistent risk factor for regional pain in the past month was tendency to somatise (ORs (95% CIs) for report of ≥2 versus 0 distressing somatic symptoms 3.1 (2.4 to 4.0) for low back pain, 2.8 (2.1 to 3.8) for shoulder pain, and 2.5 (1.6 to 4.1) for wrist/hand pain). Sickness absence for regional pain complaints in the past year was reported by 5% of participants, the major risk factor for this outcome being absence during the same period for other medical reasons (OR 3.7, 95% CI 2.4 to 5.8).

Conclusions Japanese office workers have markedly lower rates of wrist/hand pain than their UK counterparts. In Japan, as in Western Europe, somatising tendency is a major risk factor for regional pain. Sickness absence attributed to regional pain complaints appears to be much less common in Japan than in the UK, and to be driven principally by a general propensity to take sickness absence.

What this paper adds

- Japanese office workers have markedly lower rates of wrist/hand pain than office workers in the UK.
- In Japan, as in Western Europe, somatising tendency is a major risk factor for musculoskeletal complaints.
- Sickness absence attributed to musculoskeletal disorders appears to be much less common in Japan than in the UK.
- Our findings add weight to a growing body of evidence that the prevalence of musculoskeletal symptoms and resultant disability and sickness absence varies markedly between countries.
- Strategies to control work-related musculoskeletal disorders should take into account the factors that underlie these differences, which may include culturally determined health beliefs and expectations.

INTRODUCTION

Musculoskeletal pain, especially in the back, neck and upper limbs, is a common complaint in many developed countries, and an important cause of disability and work incapacity. It is often attributed to strain from forceful or repetitive occupational activities, and epidemiological research has demonstrated fairly consistent associations of low back pain with work involving heavy lifting and/or repeated bending of the trunk,[1] and of painful disorders of the forearm with work that entails repetitive movements of the wrist or hand.[2]

However, regional pain complaints and associated disabilities are not a simple consequence of physical stresses to tissues. There is strong evidence that they are influenced also by psychological factors such as low mood and a general tendency to worry about common somatic symptoms (somatising tendency).[3 4] In addition, culturally determined health beliefs could also have an important role, and may explain large variations in the incidence and prevalence of pain and disability that have been observed between countries,[5 6] and within countries over time.[5] It is important to understand the contribution of these psychosocial influences if preventive measures are to be optimised.

To help advance knowledge in this area, a multicentre international study, CUPID (Cultural and Psychosocial Influences on Disability), has been established. The study, which is being carried out in 19 countries (both developing and developed) from six continents, involves a baseline cross-sectional survey that will allow comparison of rates of regional pain and associated disability in samples of workers who carry out similar physical activities but in widely different cultural environments. This is followed by a longitudinal component, which explores predictors of persistent and newly incident pain.

In this paper, we report findings from the initial cross-sectional survey that was carried out in Japan as part of the CUPID study, and draw comparisons with experience in the UK.

METHOD

The survey focused on four occupational groups—nurses, office workers, sales/marketing personnel and transportation operatives. All participants worked in or near Tokyo. The nurses were employed

at Tokyo University Hospital, the office workers in administrative and clerical jobs at the same hospital and at four pharmaceutical companies and a private trading company, the sales/marketing personnel at six pharmaceutical companies, and the transportation operatives (mainly lorry drivers and loaders) at two companies transporting baggage and mail.

Within each participating organisation, a manager agreed to act as a coordinator for data collection. The coordinator distributed a self-administered questionnaire to all employees in relevant jobs, with a covering letter from the survey team. Completed questionnaires were then returned to the survey team via the coordinator. A total of 3187 questionnaires were distributed to 1074 nurses, 425 office workers, 380 sales/marketing personnel and 1308 transportation operatives. No reminders were sent to non-responders.

The questionnaire was a Japanese translation of the survey instrument that is being used throughout the CUPID study. The accuracy of the translation was checked by independent back-translation to English and comparison with the original. Amendments were then made as necessary. Among other things, the questionnaire asked about demographic characteristics, hours of work and duration of employment in current job, whether the job involved certain specified activities in an average working day, job satisfaction, mental health, indicators of tendency to somatise, experience of pain during the past month and past year at each of six anatomical sites (low back, neck, shoulder, elbow, wrist/hand and knee), disability for specified everyday tasks arising from such pain, and absence from work in the past year because of musculoskeletal pain or for other reasons. Mental health (mood) was assessed from the relevant subscale from the SF-36 questionnaire,[7] and was graded to three levels defined by approximate thirds of the distribution of scores in all subjects combined. Somatising tendency was assessed using a subset of items from the Brief Symptom Inventory,[8] and was graded according to the number of symptoms (out of a total of seven) that were reported as causing at least moderate concern in the past week.

Data from the completed questionnaires were entered onto computer, and after checks for errors, were analysed using SPSS V.15 and STATA V.10 software. Because a major focus of the study was pain and disability during the past year, subjects were excluded from the main analysis if they had worked in their current job for less than a year.

In addition to the compilation of simple descriptive statistics, logistic regression was used to explore associations with regional pain (classified in various ways) and associated disability and sickness absence. Pain at an anatomical site was considered disabling if during the past month it had made at least one of the everyday activities specified in the questionnaire difficult or impossible. These activities were: getting dressed (all sites of pain), doing normal household jobs (all sites of pain), cutting toe nails (low back), combing or brushing hair (shoulder), bathing/showering (shoulder), opening bottles, jars or taps (elbow and wrist/hand), writing (wrist/hand), locking and unlocking doors (wrist/hand), walking up and down stairs (knee) and walking on level ground (knee). When looking at associations with occupational activities, we defined for each site of pain an activity in an average working day that could cause physical stress to local tissues. These activities were: lifting weights of ≥25 kg by hand (low back); work with the hands above shoulder height for ≥1 h in total (neck and shoulders); repeated bending and straightening of the elbow for ≥1 h in total (elbow); use of a keyboard or other repetitive movements of the wrist/fingers for ≥4 h in total (wrist/hand); and kneeling or squatting for ≥1 h in total (knees). Associations in the logistic regression analyses were summarised by ORs with associated 95% CIs.

RESULTS

Questionnaires were returned by 2651 (83%) of the workers to whom they were issued, but 285 were excluded from analysis because the individual had been in his/her current job for less than a year, and a further 76 because of missing information on age (52), sex (1) or both (23). Of the remaining 2290 subjects, 599 were nurses, 316 were office workers, 355 were sales/marketing personnel and 1020 were transportation operatives, representing 56%, 74%, 93% and 78% of those mailed in the respective occupational groups.

Table 1 summarises various characteristics of the participants. Most of the nurses were women, whereas almost all of the sales/marketing personnel and transportation operatives were men. The majority of subjects were employed full-time, including 30% of the sample (mostly sales/marketing personnel and transportation operatives) who indicated that they worked for more than 60 h per week. Reported occupational activities were much as would be expected, with a high frequency of keyboard use by office workers (89%). Transportation operatives and nurses had the highest prevalence of heavy lifting (83% and 66%, respectively) and of repeated bending and straightening of the elbow (78% and 72%). Rates of job satisfaction were relatively low in office workers (28%) and sales/marketing personnel (31%). Poor mental health and tendency to somatise were most common among nurses. In the study sample overall, the somatic symptoms most frequently reported as distressing were nausea or upset stomach (14%), weakness (12%) and faintness or dizziness (8%).

Table 2 shows the prevalence of pain at different anatomical sites in the study sample as a whole. The lower back was the site most commonly affected by pain, with a prevalence of 28% in the past month. Next most common were pain in the neck (21% in the past month) and shoulder (17%). In comparison, pain in the elbow and wrist/hand was much less frequent. The sites most commonly affected by disabling pain in the past month were the lower back (11%) and knee (8%). Only 4% of subjects had been absent from work during the past year because of low back pain, and absence because of pain in the elbow or wrist/hand was extremely rare.

The prevalence of regional pain by occupational group is summarised in table 3 (data for men and women separately are given in online supplementary tables 1 and 2). At almost all anatomical sites, pain in the past month was most common in nurses or transportation operatives, and least frequent in sales/marketing personnel. However, office workers had the highest prevalence of sickness absence in the past year attributed to regional pain (11%). A total of 251 subjects (11%) reported pain in the past month at three or more anatomical sites, 744 (32%) reported disabling pain at one or more sites during the past month, and 125 (5%) indicated that they had taken sickness absence during the past year because of regional pain.

Table 4 gives results from logistic regression analyses exploring risk factors for pain at different anatomical sites. For each site, two outcomes were examined—any pain in the past month and disabling pain in the past month—the comparator in both cases being no pain at the site in the past month. All analyses were adjusted for sex, age, mental health and occupational group. Significant associations with locally stressful physical activities were observed for pain in the low back (lifting ≥25 kg), wrist/hand (use of keyboard or repeated movements of hands/fingers for ≥4 h) and knee (kneeling or squatting for ≥1 h). However,

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Table 1 Characteristics of participants by occupational group

Characteristic	Nurses (n=599)		Office workers (n=316)		Sales/ marketing personnel (n=355)		Transportation operatives (n=1020)		Total (n=2290)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	20	3.3	181	57.3	331	93.2	1016	99.6	1548	67.6
Female	579	96.7	135	42.7	24	6.8	4	0.4	742	32.4
Age (years)										
19–29	253	42	14	4	103	29	214	21	584	26
30–39	193	32	112	35	178	50	415	41	898	39
40–49	81	14	101	32	63	18	278	27	523	23
50–64	72	12	89	28	11	3	113	11	285	12
Hours worked per week										
Up to 20	30	5	35	11	30	8	142	14	237	10
21–40	248	41	114	36	33	9	97	10	492	21
41–60	286	48	148	47	188	53	214	30	836	37
≥61	20	3	15	5	103	29	552	54	690	30
Missing	15	3	4	1	1	0.2	15	1	35	2
Occupational activities in an average working day										
Use of keyboard ≥4 h	142	24	281	89	99	28	25	2	547	24
Other repeated movements of wrist/fingers ≥4 h	144	24	44	14	36	10	336	33	560	24
Repeated bending and straightening of elbow for ≥1 h in total	434	72	74	23	107	30	795	78	1410	62
Work with hands above shoulder height ≥1 h in total	73	12	5	2	15	4	343	34	436	19
Lifting weights of ≥25 kg by hand	398	66	10	3	33	9	849	83	1290	56
Kneeling or squatting ≥1 h in total	289	48	7	2	43	12	534	52	873	38
Satisfied with current job										
Yes	329	55	91	28	108	31	589	58	1117	49
Mental health										
Good	164	27	142	45	119	34	297	29	722	32
Intermediate	190	32	85	27	121	34	331	32	727	32
Poor	234	39	84	27	110	31	371	36	799	35
Somatising tendency (number of symptoms in past week causing at least moderate concern)										
0	170	28	141	45	146	41	516	51	973	42
1	237	40	107	34	121	34	278	28	743	32
≥2	183	31	66	21	86	24	213	21	548	24

the strongest and most consistent associations were with somatising tendency. For disabling pain in the low back, neck and shoulder, the ORs for report of ≥2 versus 0 distressing somatic symptoms were all 4.5 or higher. Associations with poor mental health (not shown) were much weaker than with somatising tendency, and not statistically significant.

Table 5 presents findings from two regression analyses, one for the risk of pain in the past month at three or more anatomical sites, and the other for disabling pain at one or more anatomical sites in the past month. In each case, the comparator was no pain at any site in the past month. Both variables were strongly associated with somatising tendency and showed a clear, progressive increase in risk in relation to the number of stressful physical activities reported. In addition, both were more frequent at older ages. Associations with poor mental health and job dissatisfaction were much weaker.

In contrast, sickness absence because of regional pain in the past year was unrelated to occupational physical activities and showed no clear association with somatising tendency (table 6). It was, however, strongly associated with sickness absence during the past year for other reasons (OR 3.7, 95% CI 2.4 to 5.8), which was reported by 16% of participants.

DISCUSSION

In this cross-sectional survey of Japanese workers, rates of regional pain were generally lower than have been reported in

Table 2 Prevalence of regional pain by anatomical site

Anatomical site	Any pain in past month		Disabling pain in past month*		Any pain in past year		Pain for ≥1 month in past year†		Pain causing absence from work in past year	
	n	%	n	%	n	%	n	%	n	%
Low back	636	28	255	11	1075	47	293	13	101	4
Neck	484	21	91	4	735	32	209	9	40	2
Shoulder	382	17	107	5	549	24	193	8	25	1
Elbow	123	5	39	2	170	7	36	2	7	0.3
Wrist/hand	161	7	72	3	236	10	69	3	9	0.4
Knee	285	12	181	8	429	19	116	5	27	1

*For definition of disabling pain, please see text.
†Pain for at least 1 month in total.

Table 3 Prevalence of regional pain by occupational group

Category of pain	Nurses		Office workers		Sales/marketing personnel		Transportation operatives	
	n	%	n	%	n	%	n	%
Low back pain in past month	182	30	68	22	68	19	318	31
Neck pain in past month	184	31	85	27	63	18	152	15
Shoulder pain in past month	132	22	61	19	47	13	142	14
Elbow pain in past month	16	3	13	4	11	3	83	8
Wrist/hand pain in past month	39	7	19	6	15	4	88	9
Knee pain in past month	74	12	36	11	34	10	141	14
Pain at ≥3 sites in past month	80	13	34	11	16	5	121	12
Disabling pain at any site in past month*	220	37	79	25	65	18	380	37
Pain at any site causing absence from work in past year	15	3	34	11	13	4	63	6

*For definition of disabling pain, please see text.

the UK, with a particularly low frequency of pain in the wrist and hand. The prevalence of sickness absence attributed to regional pain was also substantially lower than in the UK. Pain at most sites was more common in workers who indicated that they were exposed to stressful physical activities in their job, but the strongest and most consistent risk factor for regional pain and associated disability was somatising tendency. In contrast, risk of sickness absence because of regional pain was related not to physical activities or somatising tendency, but to absence from work because of other health problems.

The occupational groups that were studied cannot necessarily be regarded as representative of the general population of working age in Japan. Nevertheless, they encompass a range of occupational tasks, both manual and non-manual, and provide useful insights into patterns of musculoskeletal symptoms and disability in a cultural environment that is notably different from that in, say, Western Europe. Furthermore, the high response rate that was achieved makes it likely that the samples of workers who participated were fairly typical of the occupational groups from which they were drawn.

A concern always in international studies of this type is that the meaning of questions may be distorted in translation between languages. Thus, care was taken to check the accuracy of the Japanese questionnaire by back-translation to English. It remains possible that a term such as "pain" is understood somewhat differently in Japan. However, this should not affect the relative frequency of the symptom at different anatomical sites, and is less likely to have been a problem in relation to more objective outcomes such as sickness absence.

Another possible source of error was incomplete recall of symptoms, particularly if they last occurred many months before the questionnaire was completed. For this reason, we based most of our analysis on pain and disability that was reported in the past month. An exception was sickness absence, for which a longer time period was required to give meaningful numbers of cases. However, we would expect spells of sickness absence to be more memorable than more minor episodes of pain.

The prevalence of pain at most of the anatomical sites considered was somewhat lower than has been recorded in UK workers who were surveyed using similar questions.[6] For example, low back pain in the past month was reported by 28% of the Japanese workers as compared with 28% in a sample of white UK office workers and 37% in a group of white UK manual workers, while the corresponding figures were 21% versus 26% and 23% for neck pain, 17% versus 20% and 24% for shoulder pain, and 5% versus 10% and 9% for elbow pain. More remarkable, however, is the much lower prevalence of wrist/hand pain in Japanese workers (7% vs 30% and 23%). This lower prevalence extended to Japanese office workers (6% with wrist/hand pain), most of whom were regular users of computer keyboards. The difference in the prevalence of wrist/hand pain

Table 4 Risk factors for regional pain in past month

Risk factor	Low back		Neck		Shoulder		Elbow		Wrist/hand		Knee	
	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)
Any pain in past month†												
Physical activity‡	421	1.9 (1.4 to 2.5)	87	1.2 (0.9 to 1.6)	76	1.2 (0.9 to 1.7)	81	1.2 (0.8 to 2.0)	86	1.9 (1.3 to 2.6)	144	2.0 (1.5 to 2.7)
Somatising tendency§												
0	348	1	240	1	98	1	71	1	90	1	160	1
1	113	1.7 (1.3 to 2.3)	106	2.3 (1.8 to 3.1)	77	1.9 (1.4 to 2.6)	16	1.2 (0.7 to 2.1)	29	1.6 (1.0 to 2.5)	52	1.7 (1.2 to 2.4)
≥2	158	3.1 (2.4 to 4.0)	125	3.2 (2.4 to 4.2)	97	2.8 (2.1 to 3.8)	31	2.5 (1.6 to 4.1)	38	2.2 (1.4 to 3.3)	71	2.6 (1.9 to 3.6)
Job dissatisfaction	260	1.3 (1.0 to 1.6)	225	1.1 (0.8 to 1.4)	201	1.1 (0.9 to 1.5)	68	1.1 (0.7 to 1.7)	64	1.5 (1.0 to 2.1)	133	1.1 (0.8 to 1.4)
Disabling pain in past month†												
Physical activity‡	180	2.2 (1.5 to 3.4)	24	1.6 (0.9 to 2.7)	24	1.1 (0.6 to 1.8)	24	0.7 (0.3 to 1.4)	39	1.8 (1.1 to 3.0)	95	2.0 (1.4 to 2.9)
Somatising tendency§												
0	128	1	37	1	39	1	20	1	32	1	90	1
1	38	1.6 (1.0 to 2.4)	17	2.3 (1.2 to 4.2)	19	2.5 (1.4 to 4.5)	4	1.0 (0.3 to 2.9)	18	2.7 (1.4 to 4.9)	38	2.1 (1.4 to 3.2)
≥2	82	4.5 (3.2 to 6.4)	33	5.0 (2.9 to 8.4)	45	7.2 (4.4 to 11.8)	14	3.9 (1.8 to 8.2)	21	3.4 (1.8 to 6.3)	51	3.3 (2.2 to 4.9)
Job dissatisfaction	157	1.5 (1.1 to 2.0)	36	1.1 (0.7 to 1.8)	38	1.2 (0.8 to 2.0)	18	0.7 (0.3 to 1.3)	27	1.5 (0.9 to 2.7)	79	1.1 (0.8 to 1.6)

*For each anatomical site and pain outcome, ORs were derived from a logistic regression model that included all of the risk factors presented together with sex, age (in four strata), mental health (in three strata) and occupational group.
†Risks are relative to no pain at site in past month.
‡Stressful occupational activity in an average working day defined as lifting weights of ≥25 kg by hand (low back), work with the hands above shoulder height for ≥1 h (neck and shoulder), repeated bending and straightening of elbow for ≥1 h (elbow), use of a keyboard or repeated movements of hands/fingers for ≥4 h (wrist/hand), kneeling or squatting for ≥1 h (knee).
§Number of somatic symptoms causing at least moderate concern in past week.

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Table 5 Risk factors for multi-site and disabling pain in the past month

Risk factor	Pain at ≥3 sites		Disabling pain at any site	
	n	OR* (95% CI)	n	OR* (95% CI)
Sex				
Male	144	1	327	1
Female	97	1.8 (0.9 to 3.7)	161	0.8 (0.4 to 1.3)
Age (years)				
19–29	44	1	107	1
30–39	84	1.7 (1.1 to 2.6)	179	1.4 (1.0 to 1.9)
40–49	72	4.4 (2.7 to 7.1)	136	2.7 (1.9 to 3.9)
50–64	41	4.4 (2.5 to 7.8)	66	2.6 (1.7 to 4.0)
Number of stressful occupational physical activities†				
0	11	1	36	1
1	49	2.8 (1.3 to 5.9)	104	1.9 (1.2 to 3.0)
2	46	3.1 (1.5 to 6.6)	97	2.2 (1.3 to 3.5)
3	50	4.3 (2.0 to 9.3)	106	2.8 (1.7 to 4.5)
4	50	6.0 (2.7 to 13.2)	89	3.5 (2.1 to 5.9)
5	35	9.3§ (4.0 to 21.5)	56	5.0¶ (2.8 to 9.0)
Somatising tendency‡				
0	108	1	259	1
1	55	3.4 (2.3 to 5.1)	90	2.2 (1.6 to 3.0)
≥2	78	6.2 (4.1 to 9.3)	139	4.5 (3.3 to 6.2)
Mental health				
Good	57	1	119	1
Intermediate	73	1.3 (0.8 to 1.9)	146	1.2 (0.9 to 1.6)
Poor	111	1.4 (0.9 to 2.1)	223	1.5 (1.1 to 2.1)
Job satisfaction				
Satisfied	148	1	281	1
Dissatisfied	93	1.3 (0.9 to 1.9)	207	1.2 (0.9 to 1.6)
Occupational group				
Nurses	77	1	140	1
Office workers	33	1.1 (0.6 to 2.2)	61	0.8 (0.5 to 1.3)
Sales/marketing personnel	14	0.9 (0.3 to 2.2)	46	0.6 (0.3 to 1.1)
Transportation operatives	117	1.1 (0.5 to 2.5)	241	0.6 (0.3 to 1.1)

*OR relative to no pain at any site. ORs for each pain outcome were derived from a single regression model incorporating all of the variables.
†Occupational activities in an average working day (lifting weights of ≥25 kg by hand, work with the hands above shoulder height for ≥1 h, repeated bending and straightening of the elbow for ≥1 h, use of a keyboard or repeated movements of hands/fingers for ≥4 h, kneeling or squatting for ≥1 h).
‡Number of somatic symptoms causing at least moderate concern in past week.
§p for trend <0.001.
¶p for trend <0.001.

Table 6 Risk factors for sickness absence because of regional pain in past year

Risk factor	n	OR* (95% CI)
Sex		
Male	86	1
Female	26	0.7 (0.4 to 1.5)
Age (years)		
19–29	17	1
30–39	49	1.4 (0.8 to 2.5)
40–49	31	1.3 (0.7 to 2.6)
50–64	15	1.2 (0.5 to 2.5)
Number of stressful occupational physical activities†		
0	13	1
1	42	1.2 (0.6 to 2.5)
2	22	1.0 (0.5 to 2.1)
3	14	0.7 (0.3 to 1.6)
4	13	0.8 (0.3 to 2.0)
5	8	0.9 (0.3 to 2.4)
Somatising tendency‡		
0	71	1
1	16	1.0 (0.5 to 1.8)
≥2	25	1.4 (0.9 to 2.4)
Mental health		
Good	35	1
Intermediate	23	0.7 (0.4 to 1.2)
Poor	54	1.6 (1.0 to 2.7)
Job satisfaction		
Satisfied	52	1
Dissatisfied	60	0.9 (0.6 to 1.5)
Sickness absence in past year for reasons other than regional pain		
No	67	1
Yes	45	3.7 (2.4 to 5.8)
Occupational group		
Nurses	13	1
Office workers	33	2.9 (1.2 to 6.7)
Sales/marketing personnel	13	1.1 (0.4 to 3.3)
Transportation operatives	53	2.5 (1.0 to 6.3)

*OR relative to no sickness absence for regional pain in past year. ORs were derived from a single regression model incorporating all of the variables.
†Occupational activities in an average working day (lifting weights of ≥25 kg by hand, work with the hands above shoulder height for ≥1 h, repeated bending and straightening of the elbow for ≥1 h, use of a keyboard or repeated movements of hands/fingers for ≥4 h, kneeling or squatting for ≥1 h).
‡Number of somatic symptoms causing at least moderate concern in past week.

between Japanese and UK office workers was much larger than that between manual and non-manual workers in the UK, or between white workers in the UK and those of South Asian origin.[6]

Also notable is the low rate of sickness absence that was attributed to regional pain complaints. Overall, only 4% of study participants had been absent from work in the past year because of low back pain, 2% for neck pain, 1% for shoulder pain, 0.3% for elbow pain and 0.4% for wrist/hand pain. In comparison, reported rates in UK workers were more than three times higher.[6] Workers from Japan tend to claim compensation and take time off work for illness attributed to occupation less often than their counterparts in the USA.[9] However, the differences we found are not explained simply by low overall rates of sickness absence in Japan—16% of participants reported absence in the past year because of non-musculoskeletal illness. Rather the proportion of absence attributed to musculoskeletal disorders was much lower than in the UK.

Earlier studies of musculoskeletal symptoms in Japan have focused mainly on low back pain,[10–22] with prevalence rates varying from 13% (in female nursing students [18]) to 83% (in nurses[19]), according to the population studied and case definition. Where assessed, rates of neck pain have been lower than those for low back pain in the same study,[16–19] and the prevalence of pain in the wrist or hand has been even lower.[19 21]

Although there are many published surveys of regional pain in other countries, few studies to date have compared rates of musculoskeletal illness between countries, using standardised methods for data collection. In an analysis of data from surveys of the general adult population in 10 developed and seven developing countries, the age-standardised prevalence of chronic back pain was somewhat higher in developing countries (24.3%) than in developed countries (18.5%).[23] A comparative survey of nursing personnel found a higher 12-month prevalence of back complaints among Greek hospital nurses (75%) than in Dutch nurses and caregivers employed in nursing homes (62%).[24] And in another study, rates of pain among manual workers were substantially lower in Mumbai, India, than in the UK, at each of five anatomical sites (low back, neck, shoulder, elbow and wrist/hand).[6] For office workers, the differences were much smaller.

Within our Japanese sample of workers, analysis of risk factors for regional pain revealed expected associations with stressful physical activities. However, associations with somatising tendency were stronger, especially when pain was disabling.

Given that the data analysed were cross-sectional, it is possible that the observed associations between physical activities and regional pain arose in part because of greater awareness, and therefore more frequent reporting, of such activities among workers who found them painful. It seems less likely, however, that the presence of back, neck or arm pain would cause a person to over-report worry about somatic symptoms such as nausea, weakness, or faintness and dizziness. Furthermore, in other countries, longitudinal studies have found that somatising tendency predicted the future incidence and persistence of musculoskeletal pain,[3 4 25 26] and was associated with subsequent poor outcome in patients presenting to primary care or treated by physiotherapy for musculoskeletal disorders.[27–30] Tendency to somatise has also been associated with other complaints, including irritable bowel syndrome[31] and report of symptoms following exposure to pesticides.[32] In comparison with somatising tendency, low mood was a much weaker risk factor for regional pain in the Japanese workers.

In contrast, neither physical activity nor somatising tendency were clearly related to sickness absence because of regional pain, which was associated much more strongly with absence attributed to non-musculoskeletal disorders. It may be that in Japan, the major determinant of variation in rates of absence ascribed to musculoskeletal symptoms is not differences in the occurrence of such symptoms but differences in workers' general inclination to take sickness absence when they perceive a health problem.

In summary, this study provides further evidence that the prevalence of musculoskeletal symptoms varies importantly between countries, and suggests that, as in the UK, a major risk factor for musculoskeletal complaint in Japan is tendency to somatise.

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ORIGINAL ARTICLE

Efficacy, tolerability, and safety of risedronate in Japanese patients with Paget's disease of bone

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Abstract This study evaluated the clinical efficacy of treatment with oral risedronate (17.5 mg once daily) for 8 weeks in 11 Japanese patients with Paget's disease of bone (PDB). Risedronate suppressed the excessive bone turnover associated with PDB and improved several biochemical markers, including serum alkaline phosphatase (ALP), serum bone-specific ALP (BALP), urinary deoxypyridinoline (DPD), and urinary cross-linked N-telopeptide of type 1 collagen (NTX). These markers began to decrease within about 2 weeks after the initiation of treatment in most patients, and the response persisted for up to 40 weeks after the cessation of treatment. Risedronate reduced pain by week 24 in most patients. According to quantitative bone scintigraphy, the lesion with the highest radioisotope (RI) uptake showed a decrease of uptake from 12.7 ± 6.8 to 6.0 ± 2.3 (mean $\pm$ SD) in week 24, although each lesion of patients with polyostotic disease had a different scintigraphic response. Overall, risedronate at a dose of 17.5 mg once daily was well tolerated by patients with PDB, even though the dosage was seven times higher than that approved for the treatment of osteoporosis in Japan (2.5 mg once daily). In conclusion, treatment with high-dose risedronate for 8 weeks resulted in clinically significant and sustained improvement of biochemical markers of bone turnover for 48 weeks in patients with PDB, and this improvement was associated with a decrease of RI uptake by Paget's bone lesions and with reduced pain.

Keywords Risedronate · Paget's disease of bone · Alkaline phosphatase · Pain relief · Bone scintigraphy

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Introduction

Paget's disease of bone (PDB) is a chronic disorder characterized by focal areas of excessive bone turnover [1–3]. PDB is the second most common metabolic bone disease after osteoporosis in both Europe and North America [1, 2], where it has been estimated to affect approximately 1–5% of individuals aged over 55 years [1–6]. Marked geographic variations in the prevalence of PDB have been reported. This disease has a high prevalence in Western Europe, New Zealand, Australia and the United States, whereas a relatively low prevalence has been reported in Northern Europe, and PDB is extremely rare in Asia and Africa [1–7]. Indeed, the overall prevalence of PDB in Japan was reported to be only 2.8 per million, which means that the total number of patients would range between 200 and 300 [7].

There are essentially no differences of the underlying pathophysiology, clinical signs and symptoms, and diagnostic criteria between PDB in Japan and this disease in the high-prevalence countries [2, 3]. However, management of PDB in Japan differs from that in the high-prevalence