Supplementary Table S1. Descriptive statistics for the three cohorts used in the study.

	TwinsUK WGS	TwinsUK GWAS	EPIC GWAS
Subjects (N)	1,268	1,610	13,749
Age (years), mean (SD)	47.4 (10.8)	47.4 (14.4)	62.3 (9.2)
Age range (years)	18.4-74.6	18.3-79	42-82
Height (cm), mean (SD)	162.6 (5.9)	164.3 (8)	166.8 (9.1)
Weight (kg), mean (SD)	66.1 (12.5)	67.7 (12.9)	74.4 (13.2)
Male (%)	0	15.5	45.3
VOS (m/s), mean (SD)	1656.9 (48.9)	1647.2 (47.3)	1634 (41.2)
BUA (dB/MHz), mean (SD)	75.9 (17.3)	76.8 (18.4)	80.3 (19.1)
Fracture rate (%)	28.1	28.6	14.2
Variants analysed*	9,844,025	10,535,635	11,393,289
Subjects (N)	1,268	1,610	13,749

N, number; SD, standard deviation; kg, kilogram; m/s, metres per second; dB/MHz, decibel per megahertz.

*After genotype imputation and removal of variants with MAF <0.005.

Supplementary Table S2. Variants in the *WNT16* gene region associated with BUA at the genome-wide significance level ($P<5\times10^{-8}$) in the TwinsUK WGS discovery cohort.

Variant	EA	OA	EAF	TwinsUK WGS discovery		TwinsUK/EPIC GWAS replication		Meta-analysis	
				Beta	*P*	Beta	*P*	Beta (SE)	*P*
rs10276111	T	C	0.35	0.23	4.9E-8	0.13	1.8E-27	0.14 (0.01)	4.6E-33
rs10233441	A	T	0.36	0.24	4.6E-9	0.14	7.2E-30	0.15 (0.01)	3.1E-36
rs112901683	AC	A	0.36	0.24	7.2E-9	0.14	6.5E-30	0.15 (0.01)	3.8E-36
rs2952556	A	G	0.37	0.25	3.0E-9	0.14	7.9E-30	0.15 (0.01)	2.7E-36
rs7809135	C	T	0.36	0.24	1.2E-8	0.14	1.7E-29	0.15 (0.01)	1.4E-35
rs114816639	T	C	0.35	0.23	3.4E-8	0.13	7.0E-28	0.14 (0.01)	1.4E-33
rs6961083	G	A	0.36	0.24	5.0E-9	0.14	4.6E-30	0.15 (0.01)	2.1E-36
rs7778200	C	T	0.36	0.24	1.1E-8	0.14	2.2E-29	0.15 (0.01)	1.8E-35
rs10241888	A	G	0.35	0.23	2.6E-8	0.13	6.9E-28	0.14 (0.01)	1.2E-33
rs2707521	T	C	0.37	0.24	4.7E-9	0.14	2.5E-29	0.14 (0.01)	1.2E-35
rs1547960	G	A	0.36	0.24	1.2E-8	0.14	3.8E-30	0.15 (0.01)	2.9E-36
rs1547959	C	T	0.36	0.24	1.3E-8	0.14	7.4E-30	0.15 (0.01)	6.5E-36
rs6980043	T	C	0.36	0.24	1.6E-8	0.14	1.8E-29	0.15 (0.01)	1.8E-35
rs6947246	A	G	0.36	0.24	1.1E-8	0.14	7.1E-30	0.15 (0.01)	5.5E-36
rs6952851	G	A	0.36	0.24	1.4E-8	0.14	4.3E-30	0.15 (0.01)	3.7E-36
rs10231005	A	C	0.36	0.24	1.2E-8	0.14	2.3E-30	0.15 (0.01)	1.6E-36
rs76042375	A	G	0.05	0.55	3.5E-8	0.11	3.0E-5	0.14 (0.03)	4.3E-8
rs2707518	T	G	0.39	0.25	3.9E-9	0.17	1.8E-42	0.17 (0.01)	1.7E-49
rs2908007	G	A	0.40	0.23	3.5E-8	0.17	2.9E-45	0.17 (0.01)	1.2E-51

EA, effect allele; OA, other allele; EAF, effect allele frequency; SE, standard error.

Supplementary Table S3. Genetic loci associated with QUS parameters at the suggestive level ($5\times10^{-8} < P < 5\times10^{-7}$) in the gender-combined meta-analysis.

Trait	Locus	Variant	Closest gene	EA	OA	EAF	TwinsUK WGS		TwinsUK GWAS		EPIC GWAS		Meta-analysis	
							Beta	*P*	Beta	*P*	Beta	*P*	Beta (SE)	*P*
BUA	2q14.2	rs76588671	*LOC101927709*	C	T	0.16	0.11	0.03	0.02	0.76	0.08	3.8E-7	0.08 (0.02)	1.8E-7
	8p23.1	rs4512344	*XKR6/ MTMR9*	A	C	0.49	0.11	0.005	-0.04	0.54	0.05	5.5E-6	0.06 (0.01)	3.9E-7
	10q21.1	rs6480949	*MBL2*	T	C	0.11	0.02	0.77	-0.10	0.06	-0.10	1.9E-7	-0.09 (0.02)	3.6E-7
	15q26.2	rs34408206	*MCTP2*	G	A	0.31	0.09	0.03	0.07	0.08	0.06	3.3E-6	0.06 (0.01)	1.6E-7
	19q13.11	rs1559088	*RHPN2/ GPATCH1*	T	C	0.25	0.09	0.04	0.09	0.07	0.07	1.6E-6	0.07 (0.01)	8.2E-8
VOS	2q14.2	rs537474121	*EN1*	-	GTCGT	0.02	0.29	0.05	0.28	0.05	0.25	5.0E-6	0.25 (0.05)	1.9E-7
	7q21.3	rs4448201	*C7orf76*	G	C	0.33	0.05	0.21	-0.07	0.12	-0.07	1.1E-8	-0.06 (0.01)	2.3E-7
	10q21.1	rs11003050	*MBL2*	A	G	0.11	-0.02	0.71	-0.10	0.08	-0.10	5.0E-7	-0.09 (0.02)	3.8E-7
	19q13.11	rs58636263	*GPATCH1*	-	T	0.34	0.21	2.4E-5	0.06	0.27	0.06	5.1E-5	0.07 (0.01)	3.8E-7

EA, effect allele; OA, other allele; EAF, effect allele frequency; SE, standard error.

Supplementary Table S4. Genetic loci associated with QUS parameters at the suggestive level ($5\times10^{-8} < P < 5\times10^{-7}$) in the gender-stratified meta-analysis.

Trait	Locus	Variant	Closest gene	EA	OA	EAF	TwinsUK WGS		TwinsUK GWAS		EPIC GWAS		Meta-analysis	
							Beta	*P*	Beta	*P*	Beta	*P*	Beta (SE)	*P*
Female-specific														
BUA	6q25.1	rs1038304	*CCDC170*	A	G	0.49	0.13	6.8E-4	0.03	0.44	0.07	2.1E-5	0.07 (0.01)	3.4E-7
	11q14.2	rs533931	*TMEM135*	A	G	0.11	-0.11	0.07	-0.10	0.15	-0.12	2.7E-6	-0.12 (0.02)	2.8E-7
	17q23.2	rs4968539	*BCAS3*	C	T	0.27	0.05	0.24	0.04	0.45	0.11	6.1E-8	0.10 (0.02)	1.6E-7
	22q11.21	rs9606132	*SEPT5*	C	G	0.17	-0.12	0.02	-0.11	0.03	-0.09	2.3E-5	-0.10 (0.02)	2.9E-7
VOS	6q22.33	rs7741021	*RSPO3*	C	A	0.48	0.09	0.02	0.03	0.43	0.08	1.8E-6	0.08 (0.01)	2.4E-7
	8p22-p21.3	rs2659678	*PSD3/ LOC100128993*	T	C	0.47	0.06	0.15	0.08	0.06	0.07	4.2E-6	0.07 (0.01)	4.3E-7
	19q13.11	rs58636263	*GPATCH1*	-	T	0.33	0.21	2.4E-5	0.07	0.28	0.08	1.3E-4	0.09 (0.02)	3.1E-7
Male-specific														
BUA	1q31.3	rs10921528	Intergenic	G	C	0.34	ND	ND	-0.23	0.03	-0.10	4.1E-7	-0.10 (0.02)	1.2E-7
	7q36.1	rs12216545	*GIMAP7*	A	G	0.38	ND	ND	-0.11	0.28	-0.10	1.5E-7	-0.10 (0.02)	1.4E-7
	8p23.1	rs73198271	*CLDN23/ MFHAS1*	T	A	0.26	ND	ND	-0.11	0.33	-0.10	3.9E-7	-0.10 (0.02)	3.8E-7
	8p23.1	rs62494425	*PPP1R3B/ LOC101929128*	G	A	0.47	ND	ND	0.09	0.42	0.09	2.3E-7	0.09 (0.02)	2.5E-7

	Region	SNP	Gene	EA	OA	EAF								
	10q22.3	rs2104157	*ZCCHC24*	A	G	0.28	ND	ND	0.18	0.10	0.10	7.2E-7	0.10 (0.02)	3.5E-7
	22q13.31	rs62225284	*TBC1D22A*	C	T	0.23	ND	ND	-0.12	0.29	0.23	2.2E-7	-0.11 (0.02)	2.0E-7
VOS	6q22.33	rs7741021	*RSPO3*	C	A	0.48	ND	ND	0.12	0.25	0.09	4.1E-7	0.09 (0.02)	3.1E-7
	11q14.2	rs636159	*TMEM135*	T	G	0.32	ND	ND	ND	ND	-0.10	2.8E-7	-0.10 (0.02)	4.2E-7
	12p11.22	rs117611356	*CCDC91*	A	C	0.02	ND	ND	0.21	0.56	0.34	3.5E-7	0.07 (0.07)	4.8E-7
	14q32.2	rs2629514	*VRK1*	G	A	0.05	ND	ND	0.03	0.90	0.21	1.6E-7	0.20 (0.04)	3.2E-7
	18q12.3	rs4084232	*SETBP1*	A	T	0.47	ND	ND	ND	ND	0.09	2.6E-7	0.09 (0.02)	3.9E-7

EA, effect allele; OA, other allele; EAF, effect allele frequency; SE, standard error.

Supplementary Table S5. Bioinformatics analysis of variants in strong LD ($r^2 > 0.8$) with top variant from each novel BUA locus.

Locus	Variant	Relative position*	LD with lead variant (r^2)	GERP score	Promoter histone marks	Enhancer histone marks	DNAse	eQTL results
8p23.1	rs439989	-404	0.81	2.41	-	-	-	25 hits
	rs367543	0	1	2.13	-	1 tissue	-	14 hits
	rs106380	+930	0.97	1.94	-	-	-	17 hits
	rs12547955	+1,681	0.86	-2.35	-	2 tissues	1 tissue	21 hits
11q23.1	rs1945120	-16,118	0.8	2.19	-	-	2 tissues	1 hit
	rs7111561	-9,310	0.8	3	-	-	-	1 hit
	rs6589301	-8,873	0.8	1.5	-	-	-	1 hit
	rs6589302	-8,791	0.8	-3.25	-	-	2 tissues	1 hit
	rs7105119	-6,071	0.8	2.74	-	1 tissue	-	1 hit
	rs7952251	0	1	0.24	-	-	-	2 hits
	rs202046393	+42	0.96	ND	-	-	-	2 hits
	rs7109000	+1,895	0.91	-2.36	2 tissues	13 tissues	19 tissues	1 hit
	rs7121746	+3,569	0.81	2.06	1 tissue	3 tissues	2 tissues	1 hit
22q11.21	rs9606138	-1,555	0.98	-0.69	2 tissues	7 tissues	-	3 hits
	rs202240051	0	1	ND	2 tissues	10 tissues	3 tissues	-
	rs9606139	+1,355	1	1.63	14 tissues	9 tissues	28 tissues	3 hits

GERP, genomic evolutionary rate profiling; eQTL, expression quantitative trait locus; ND, no data.

*Relative to lead variant in locus (hg19).