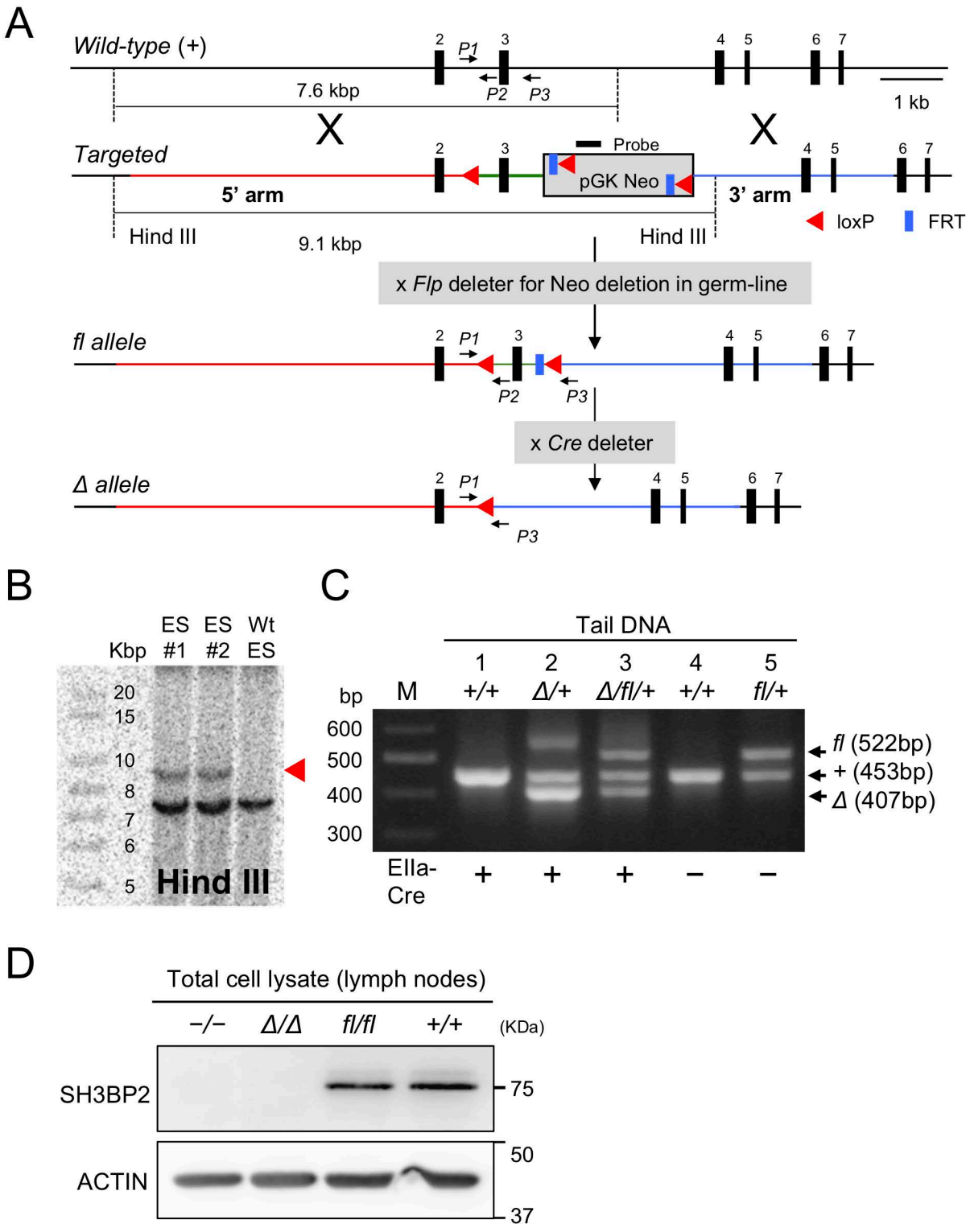
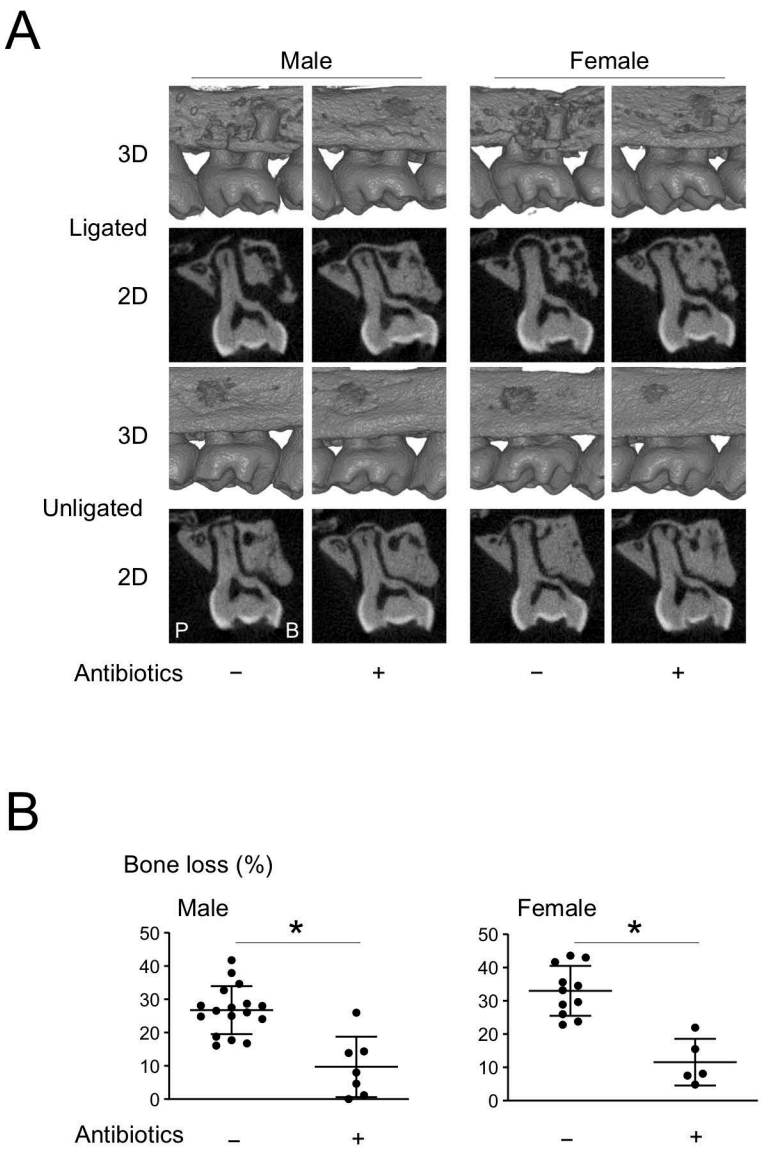
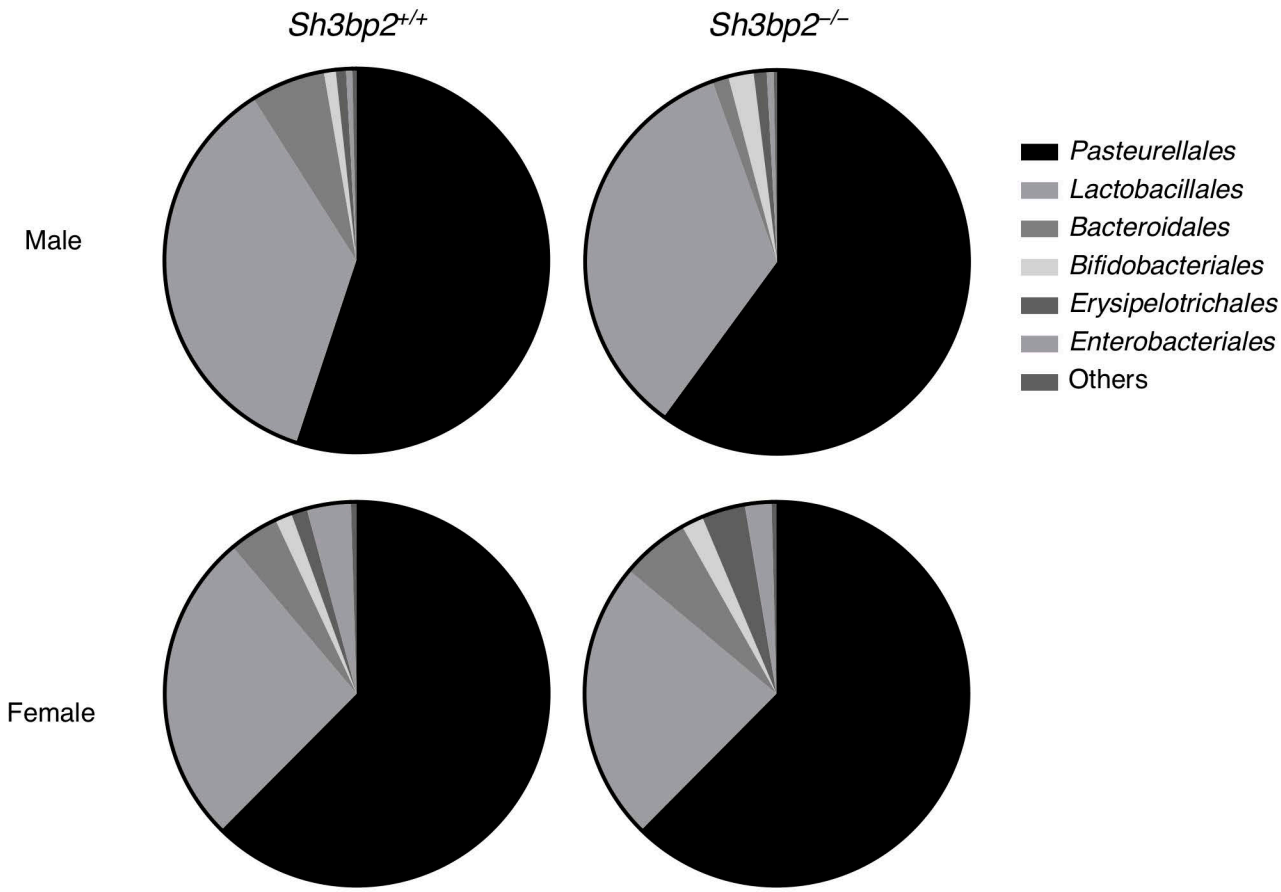


Supplemental Fig. S1: (A) Gene structure of mouse *Sh3bp2* and targeting strategy for *Sh3bp2*-floxed mice. **(B)** Genomic Southern blot analysis for confirmation of single targeted integration. After identification of ES cells (#1&2) that underwent homologous recombination by genomic PCR, genomic DNA from the two ES cell lines were hybridized with a probe against the defensin beta 22 (Defb22) gene added to the Neo selection cassette. Red arrowhead indicates the targeted allele. **(C)** Genomic PCR of tail DNA from *Sh3bp2*$^{fl/+}$ mice crossed with *EIIa-Cre* germ-line deleter mice to confirm *Cre*-induced exon 3 deletion of *Sh3bp2* gene. Primer (P1, P2, P3) locations are indicated in (A). Lane 3 represents a mosaic deletion pattern. **(D)** Western blot analysis with total cell lysate from lymph nodes.



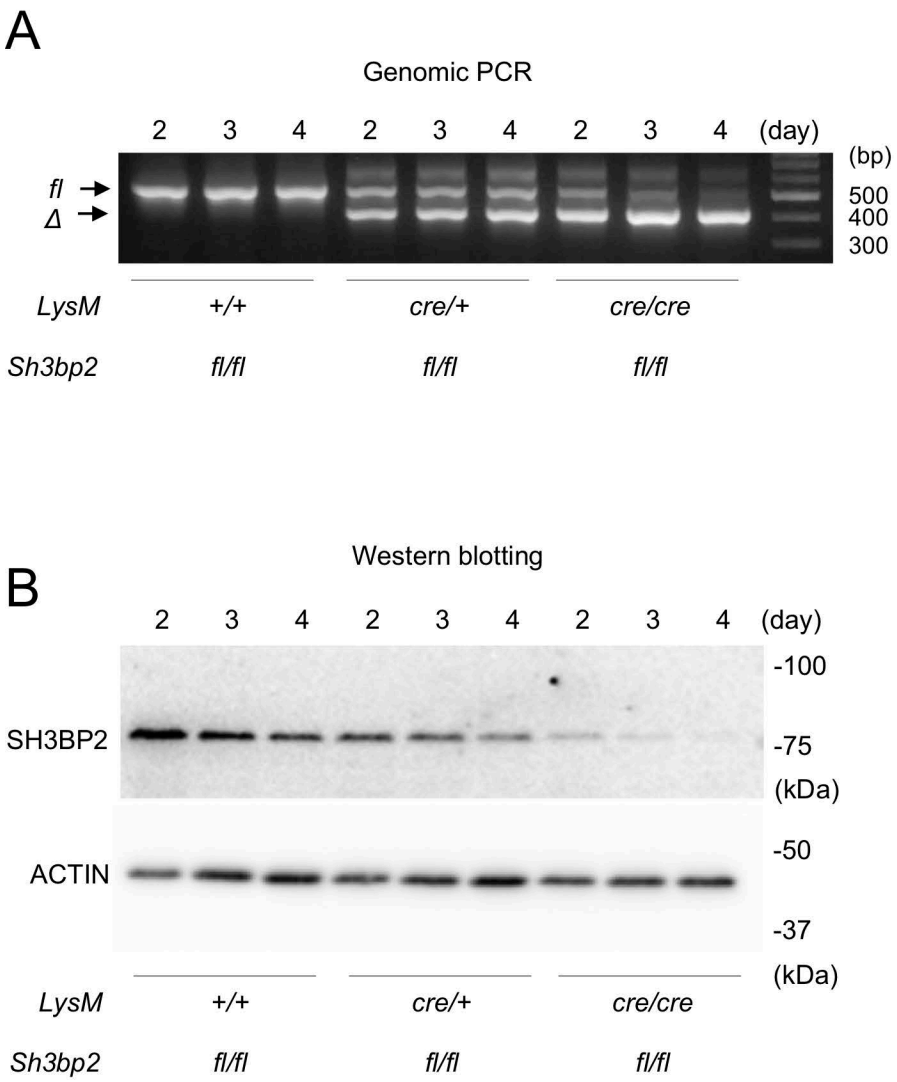
Supplemental Fig. S2: Effect of antibiotic treatment on bone loss in a ligature-induced periodontitis model. Wild-type mice of 10 weeks old were treated with antibiotics in drinking water (ampicillin 1 g/L, vancomycin 0.5 g/L, kanamycin 1 g/L, metronidazole 1 g/L) from 5 days before ligature placement until 5 days after ligature placement (end of the experiment). **(A)** µCT 2D coronal images of the maxilla through the middle of the second molar (bottom) and 3D images surrounding the maxillary second molar (top). P: palatal side. B: buccal side.. **(B)** Bone loss % by µCT analysis. Data are presented as mean ± SD. *$p < 0.05$ with Student's *t*-test.



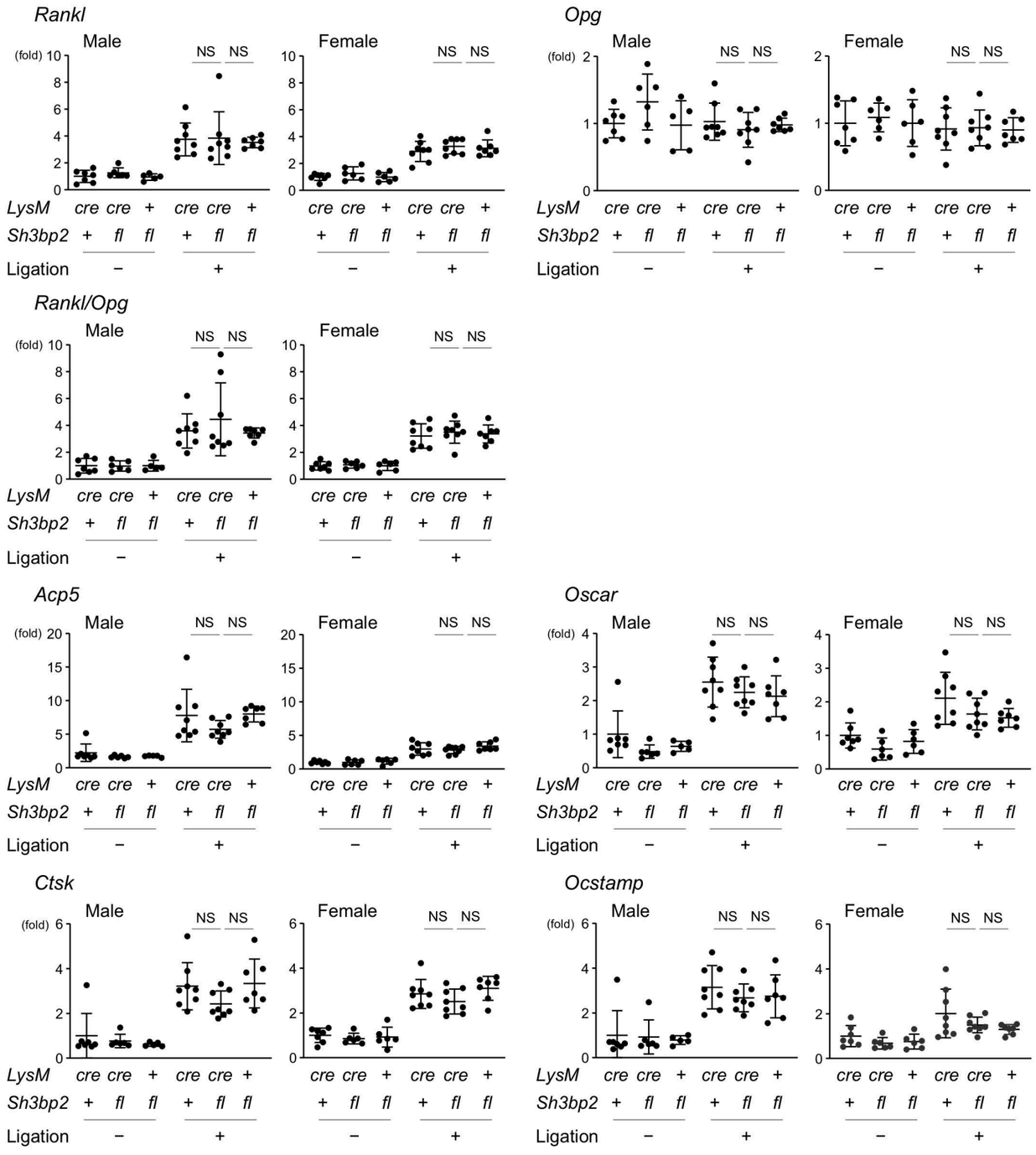
Composition of microbiome in sutures on an order level (%)

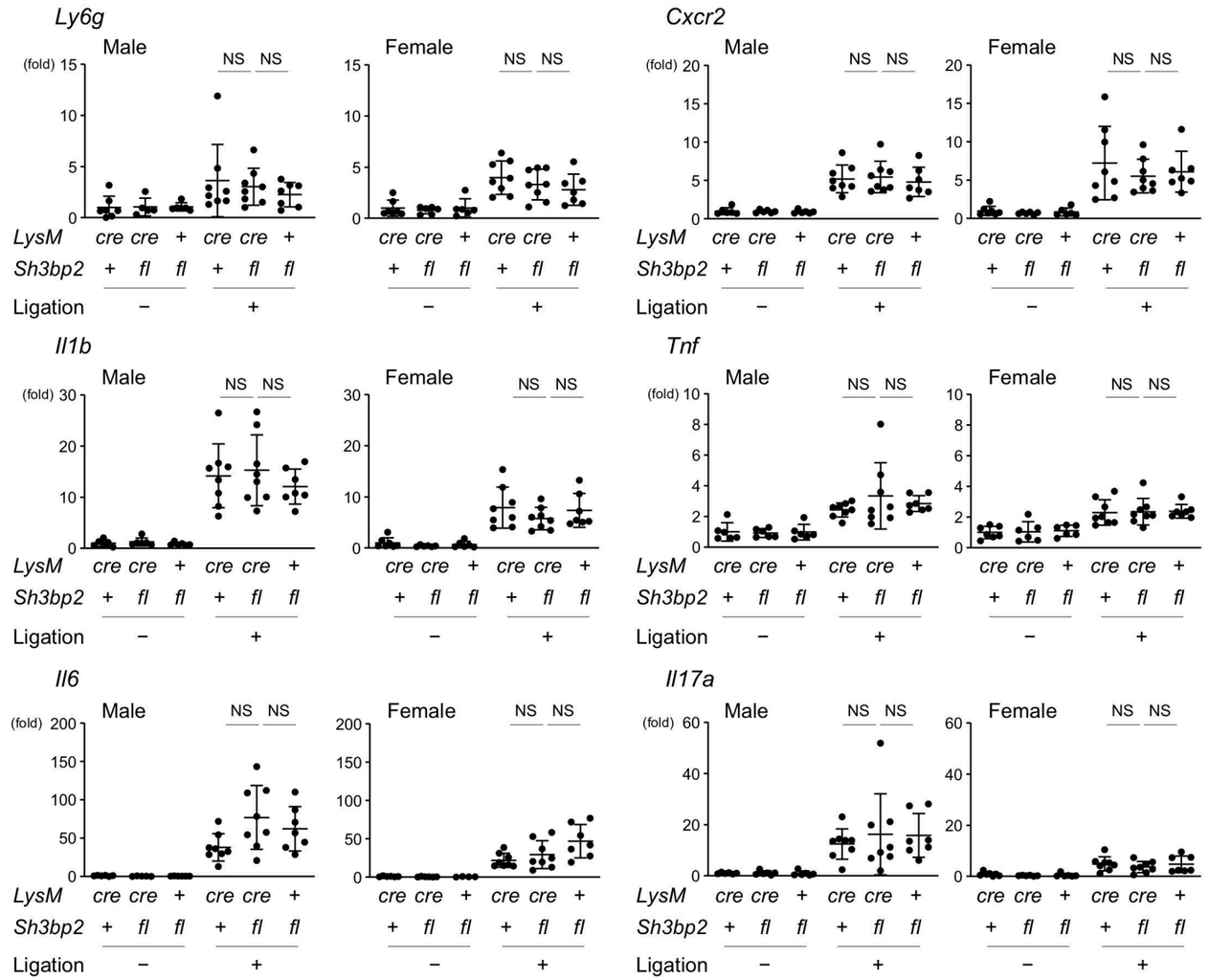
	Male			Female		
Order	*Sh3bp2*$^{+/+}$	*Sh3bp2*$^{-/-}$	*p* value	*Sh3bp2*$^{+/+}$	*Sh3bp2*$^{-/-}$	*p* value
Pasteurellales	55.09 ± 12.04	60.05 ± 4.41	0.56	62.45 ± 2.25	62.44 ± 12.42	1.00
Lactobacillales	35.90 ± 8.62	34.47 ± 4.94	0.82	26.39 ± 2.72	23.65 ± 8.07	1.00
Bacteroidales	6.29 ± 3.66	1.38 ± 0.52	0.14	4.21 ± 2.89	5.75 ± 2.98	0.56
Bifidobacteriales	1.00 ± 1.36	2.13 ± 1.38	0.37	1.40 ± 2.08	1.83 ± 1.83	0.80
Erysipelotrichales	0.86 ± 0.73	1.10 ± 0.78	0.72	1.35 ± 0.77	3.67 ± 4.08	0.70
Enterobacteriales	0.52 ± 0.63	0.59 ± 0.50	0.89	3.71 ± 3.69	2.24 ± 1.84	0.58
others	0.34	0.28		0.49	0.41	

Supplemental Fig. S3: Taxonomic analysis of bacterial composition in ligatures on an order level. Silk sutures placed to induce periodontitis were recovered after 5 days and bacterial DNA was isolated. The V4 region of 16S rDNA was amplified by PCR for library construction and followed by sequencing analysis. Graphs show taxonomic bacterial composition on an order level. Average numbers from 3 independent samples (n = 3) were used for the graphs. *p* values were calculated with Student's *t*-test.

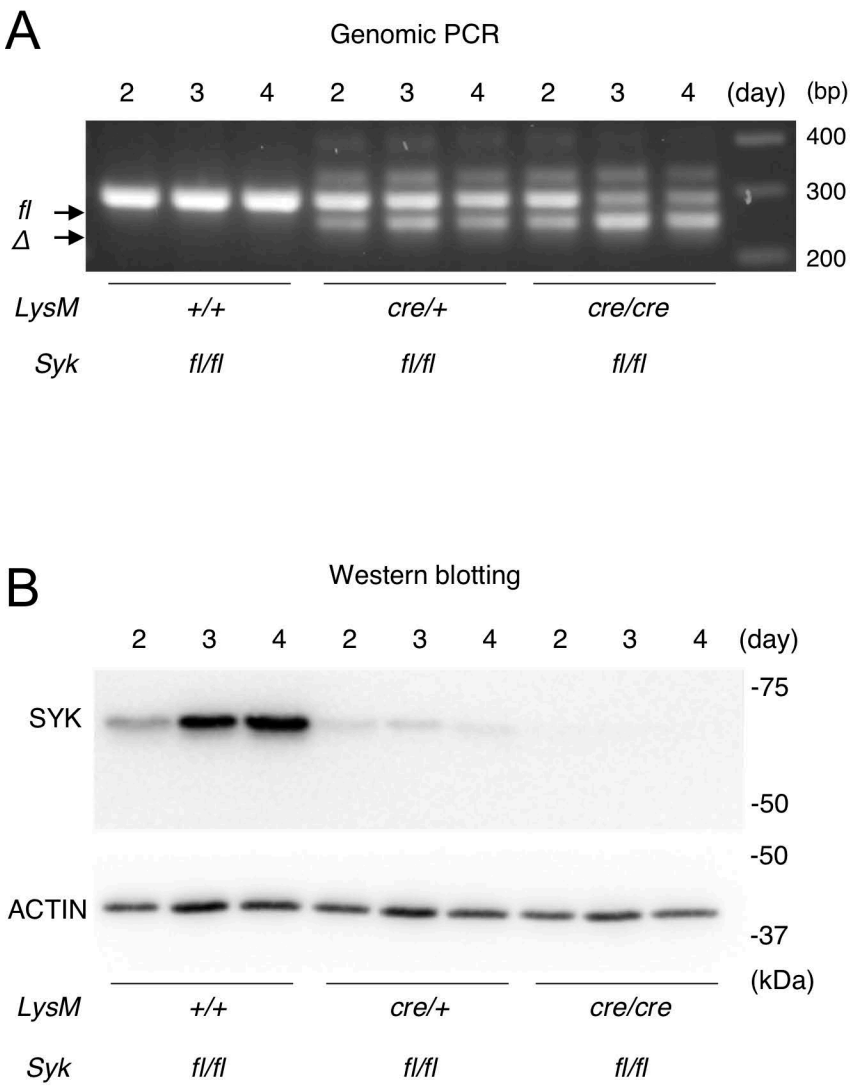


Supplemental Fig. S4: Validation of conditional knockout *of Sh3bp2* with *LysM-Cre* mice. **(A)** Exon 3 deletion of *Sh3bp2 gene* (*Δ*) was confirmed by PCR with genomic DNA from bone marrow-derived M-CSF-dependent macrophages (BMMs). **(B)** Western blotting against SH3BP2 and actin with cell lysates from BMMs.

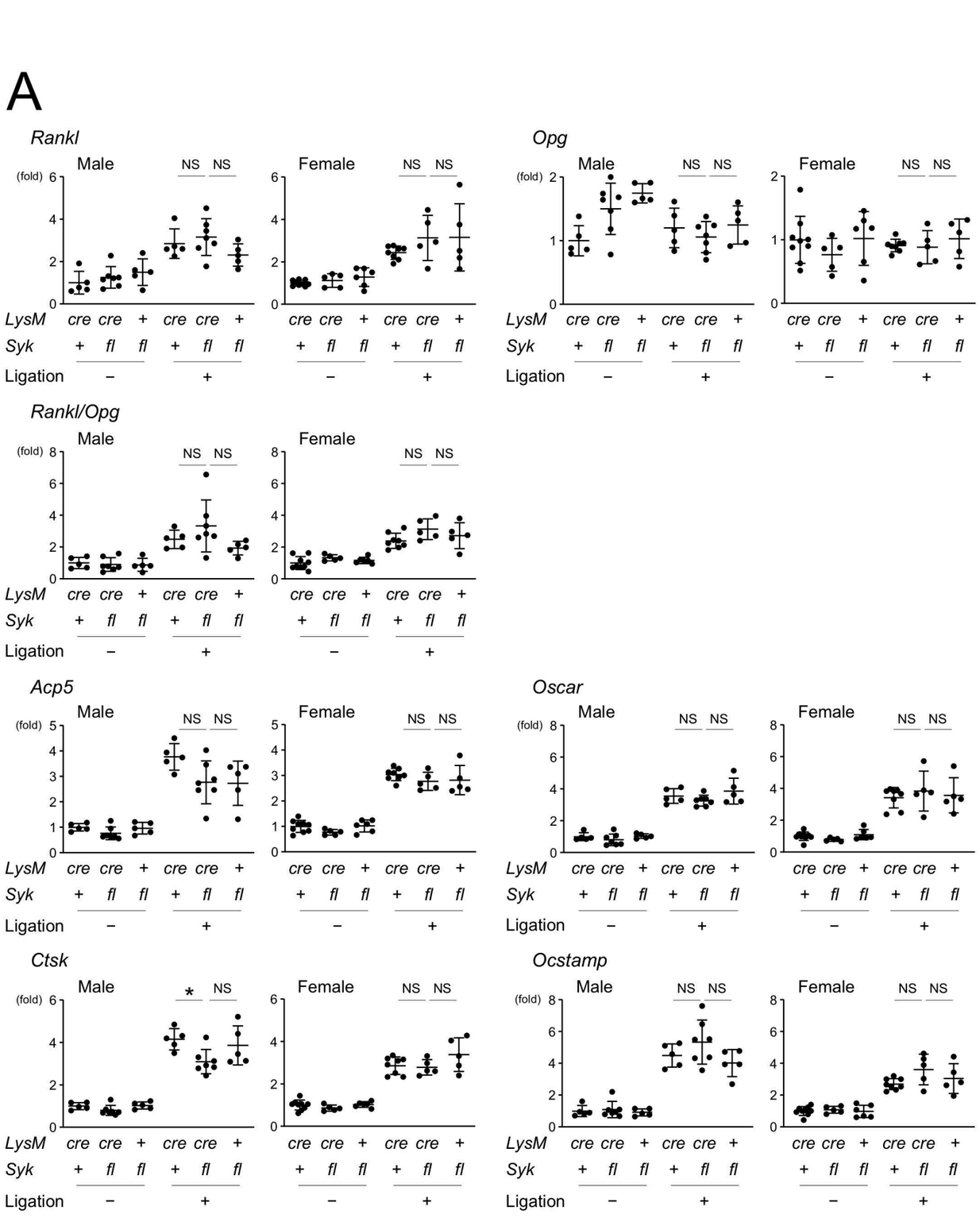


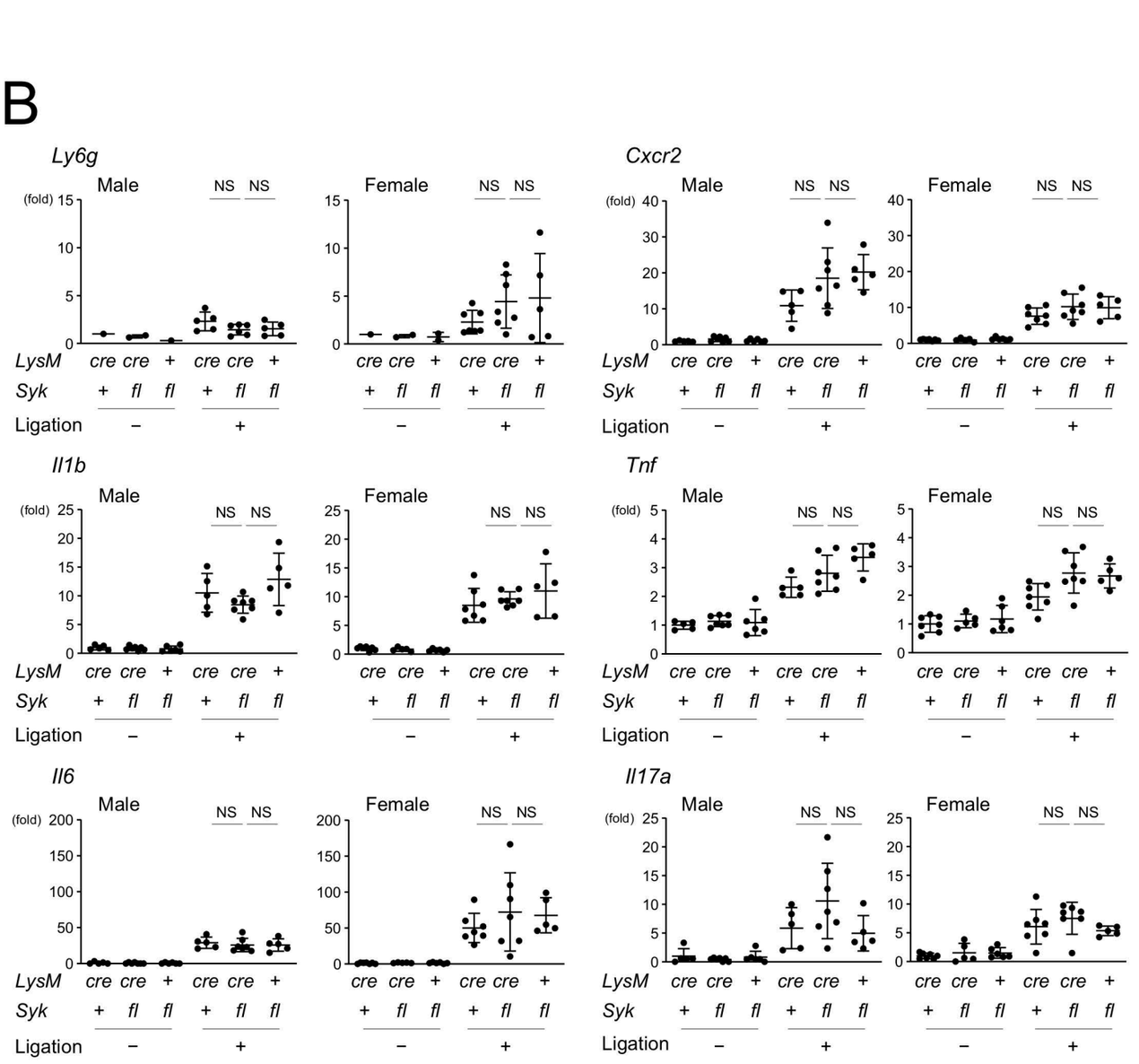


Supplemental Fig. S5: (A) Expression study for osteoclast-regulating and osteoclast marker genes in jawbone by qPCR. Average levels in unligated *LysM*$^{cre/cre}$ *Sh3bp2*$^{+/+}$ mice were set as 1. **(B)** Expression study for neutrophil-associated and inflammatory cytokine genes in gingiva by qPCR. Average levels in unligated *LysM*$^{cre/cre}$ *Sh3bp2*$^{+/+}$ mice were set as 1. Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test. + = +/+, *cre* = *cre/cre*, *fl* = *fl/fl*.

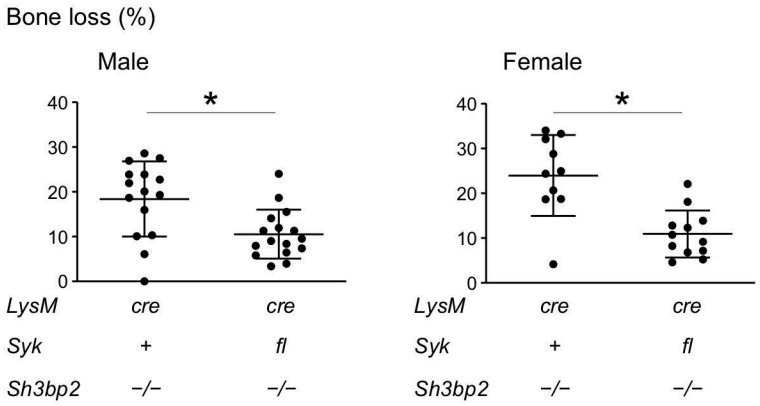


Supplemental Fig. S6: Validation of conditional knockout *of Syk* with *LysM-Cre* mice. **(A)** Exon 1 deletion of *Syk gene* (*Δ*) was confirmed by PCR with genomic DNA from bone marrow-derived M-CSF-dependent macrophages (BMMs). **(B)** Western blotting against SYK and actin with cell lysates from BMMs.

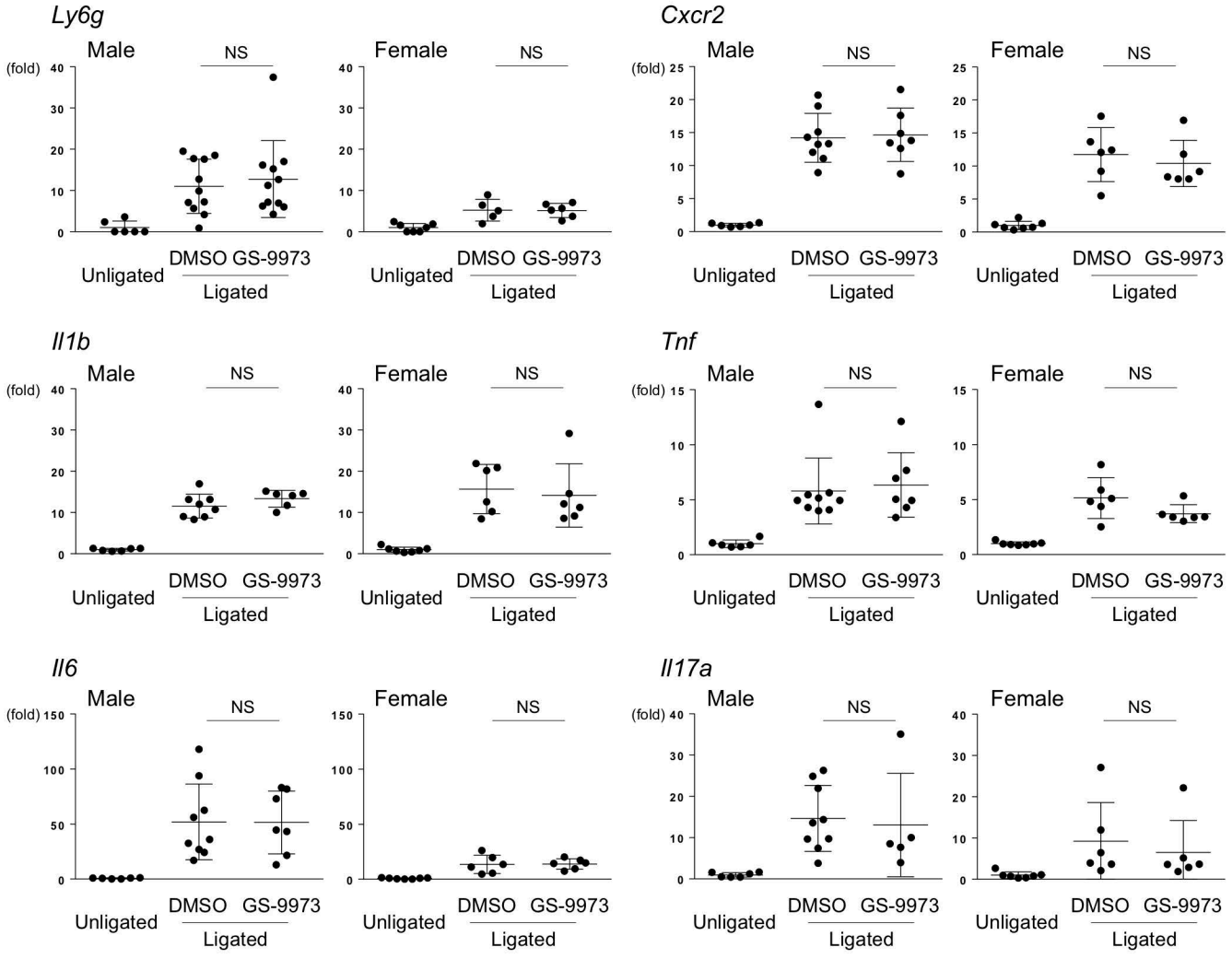




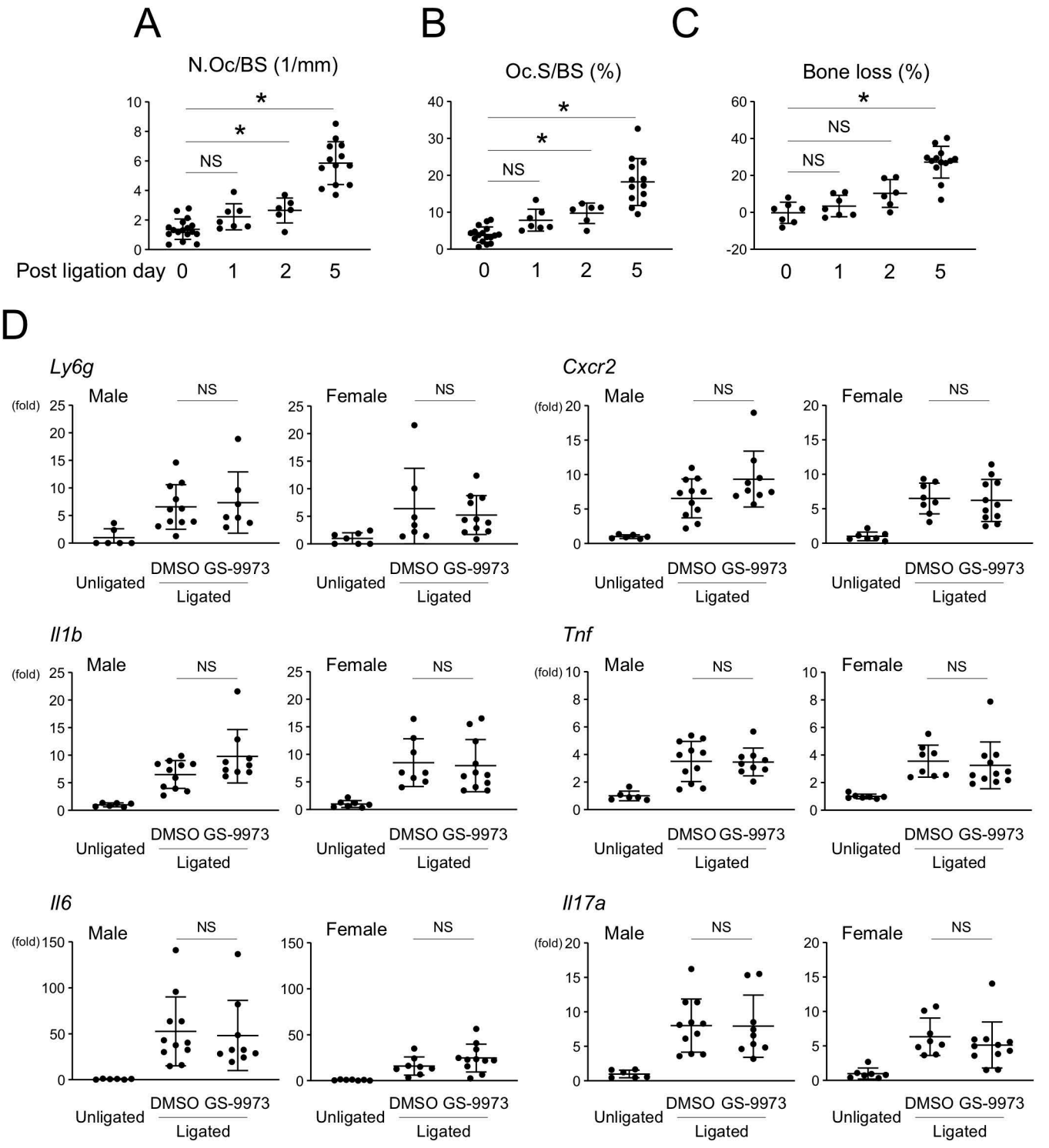
Supplemental Fig. S7: (A) Expression analysis for osteoclast-regulating and osteoclast marker genes in jawbone by qPCR. Average levels in unligated *LysM*$^{cre/cre}$ *Syk*$^{+/+}$ mice were set as 1. **(B)** Expression analysis for neutrophil-associated and inflammatory cytokine genes in gingiva by qPCR. Average levels in unligated *LysM*$^{cre/cre}$ *Syk*$^{+/+}$ mice were set as 1. Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test. + = +/+, *cre* = *cre/cre*, *fl* = *fl/fl*.



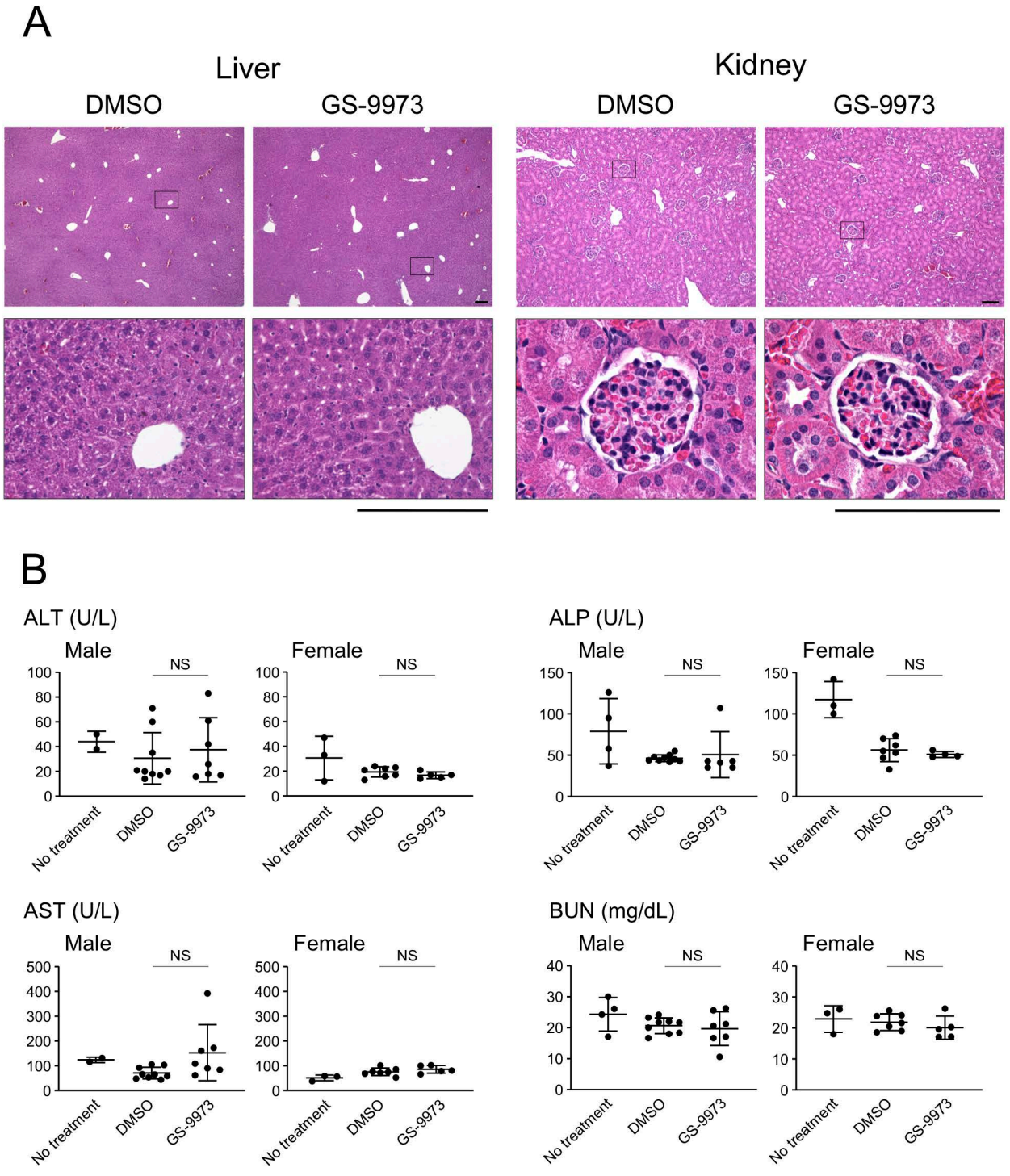
Supplemental Fig. S8: µCT analysis of alveolar bone loss (%) in *LysM*$^{cre/cre}$ *Syk*$^{fl/fl}$ *Sh3bp2*$^{-/-}$ mice with periodontitis. Data are presented as mean ± SD. *$p < 0.05$. NS = not significant. Student's *t*-test. + = +/+, *cre* = *cre/cre*, *fl* = *fl/fl*.



Supplemental Fig. S9: Expression analysis for neutrophil-associated and inflammatory cytokine genes in gingiva from wild-type mice treated with or without GS-9973 from one day before ligature placement. Average levels in unligated wild-type mice were set as 1. Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test.



Supplemental Fig. S10: (A, B) Time course of osteoclast induction after ligature placement. Histomorphometric analysis for TRAP-positive multinucleated cells on alveolar bone surface. Day 0 (12 males, 8 females), Day 1 (4 males, 3 females), Day2 (4 males, 2 females), Day 5 (8 males, 5 females). **(C))** Time course of loss of alveolar bone volume against contralateral unligated side. Day 0 (5 males, 2 females), Day 1 (4 males, 3 females), Day2 (4 males, 2 females), Day 5 (9 males, 6 females). Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test. **(D)** Expression analysis for neutrophil-associated and inflammatory cytokine genes in gingiva from wild-type mice treated with or without GS-9973 from two days after ligature placement. Average levels in unligated wild-type mice were set as 1. Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test.



Supplemental Fig. S11: (A) H&E staining of liver and kidney tissues from 10-week-old wild-type mice injected with GS-9973 daily for 6 times (100 mg/kg, *i.p.*). Bar = 200 μm in the liver and 100 μm in the kidney. **(B)** Serum markers for liver and renal function measured by Element DC Veterinary Chemistry Analyzer (Heska, Loveland CO). Data are presented as mean ± SD. *$p < 0.05$, NS = not significant. ANOVA with Tukey-Kramer post hoc test.