SUPPLEMENTARY DATA

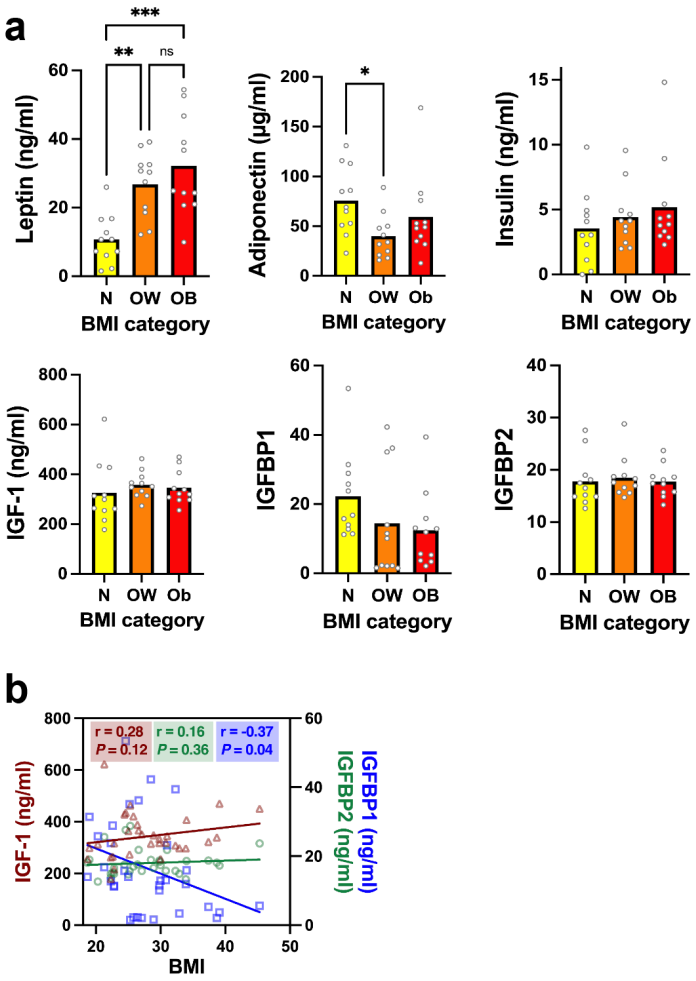

Fig. S1. Serum factor levels from KTB donors with different BMI. a Average levels of leptin, adiponectin, insulin, IGF-1, and IGF binding proteins 1 and -2 in the three BMI categories (N, normal weight; OW, overweight; OB, obese). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. **b** Levels of IGF1, IGFBP1, and IGFBP2 as a function of BMI. Spearman correlation coefficients (r) are indicated with corresponding *P*-values.

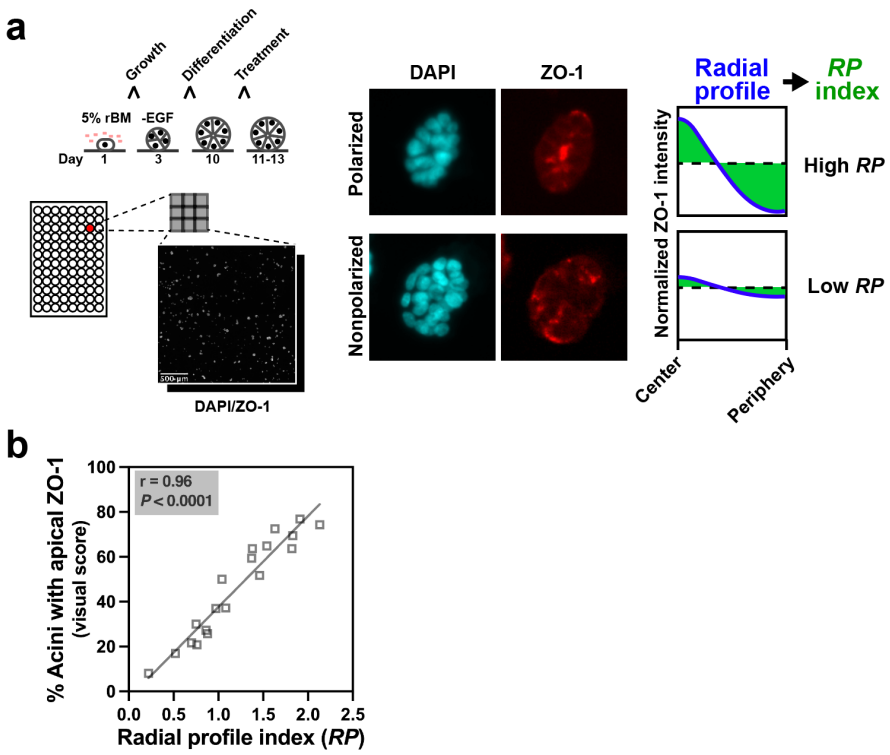

Fig. S2. Automated quantification of epithelial polarity in breast acini. a Breast epithelial cells (HMT-3522 S1) are cultured directly in 3D on glass bottom 96-well plates, without a layer of reconstituted basement membrane (Matrigel). Rather, diluted Matrigel is added to the culture medium on day 1. EGF is removed on day 3 to promote acinar differentiation and avoid cell spreading as monolayers. Acini stained with DAPI (cell nuclei, used for segmentation) and for the TJ marker ZO-1 are imaged with an automated microscope (9 fields per well, 10x magnification). Representative images of non-polarized and polarized acini are shown. The cartoon illustrates radial distributions of ZO-1 staining intensity, from the center to the periphery of the structures. Radial intensity profiles are used to compute *RP* index metrics. **b** Correlation between *RP* values and visual scores of apical ZO-1 distribution. Each symbol represents a treatment condition, with 100 - 380 acini/condition. r, Pearson's coefficient.

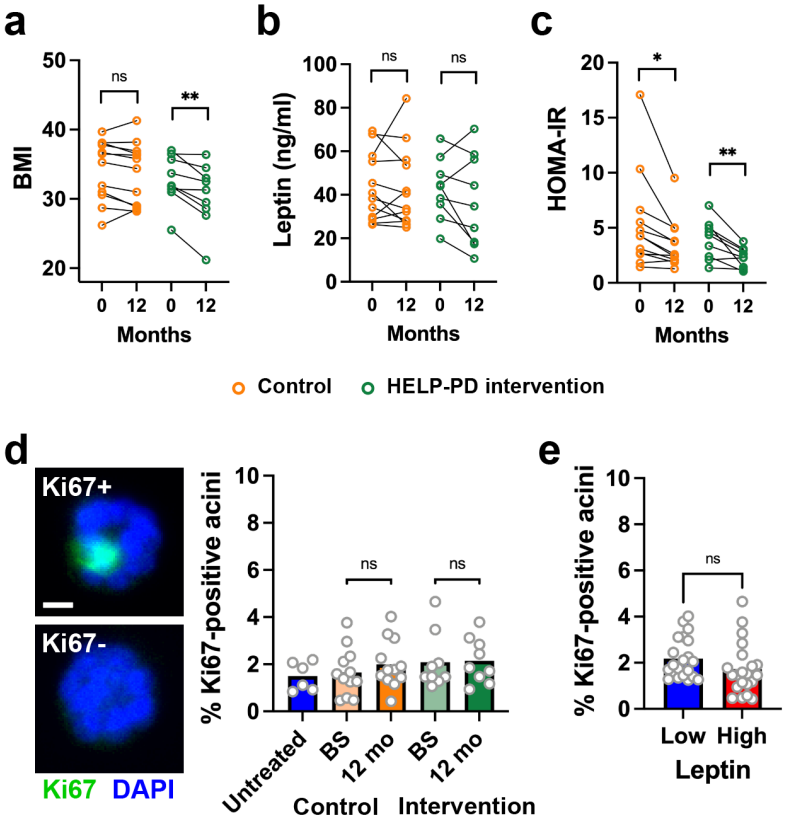

Fig. S3. Outcomes of the HELP-PD study. BMI (**a**), serum leptin (**b**), and homeostatic model assessment of insulin resistance (HOMA-IR; **c**) from female participants to the HELP-PD study, by study arm (control and intervention), at baseline (0 month) and at the 1-year time point. *, $P < 0.05$; **, $P < 0.01$; ns, not significant (paired t-test). **d** Proliferation status of S1 acini treated for 24h with serum from HELP-PD participants. BS, baseline. Representative images of positive and negative acini are shown. Scale bar, 10 µm. **e** Proportion of Ki67-positive acini after classifying HELP-PD participants according to serum leptin levels. ns, not significant.

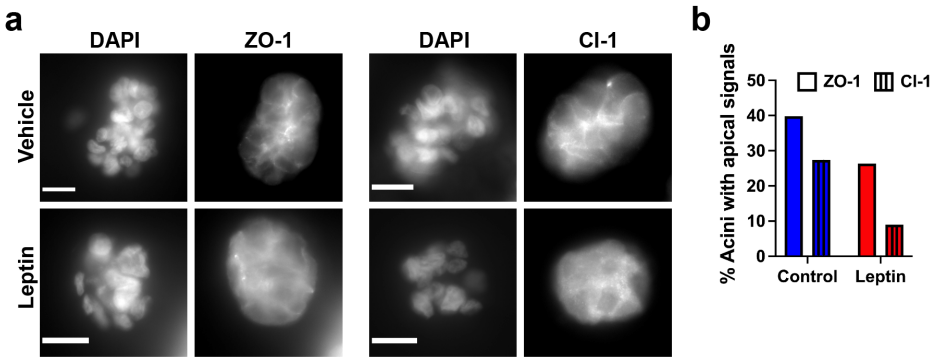

Fig. S4. Loss of epithelial polarity in 184B5 cell acini exposed to leptin. 3D cultures were treated for 24h with vehicle or leptin (100 ng/ml). **a** representative images of cell nuclei (DAPI) and of immunostaining for ZO-1 and claudin-1 (Cl-1). Scale bars, 20 μm. **b** Proportion of S1 acini with apical localization of ZO-1 and Cl-1.

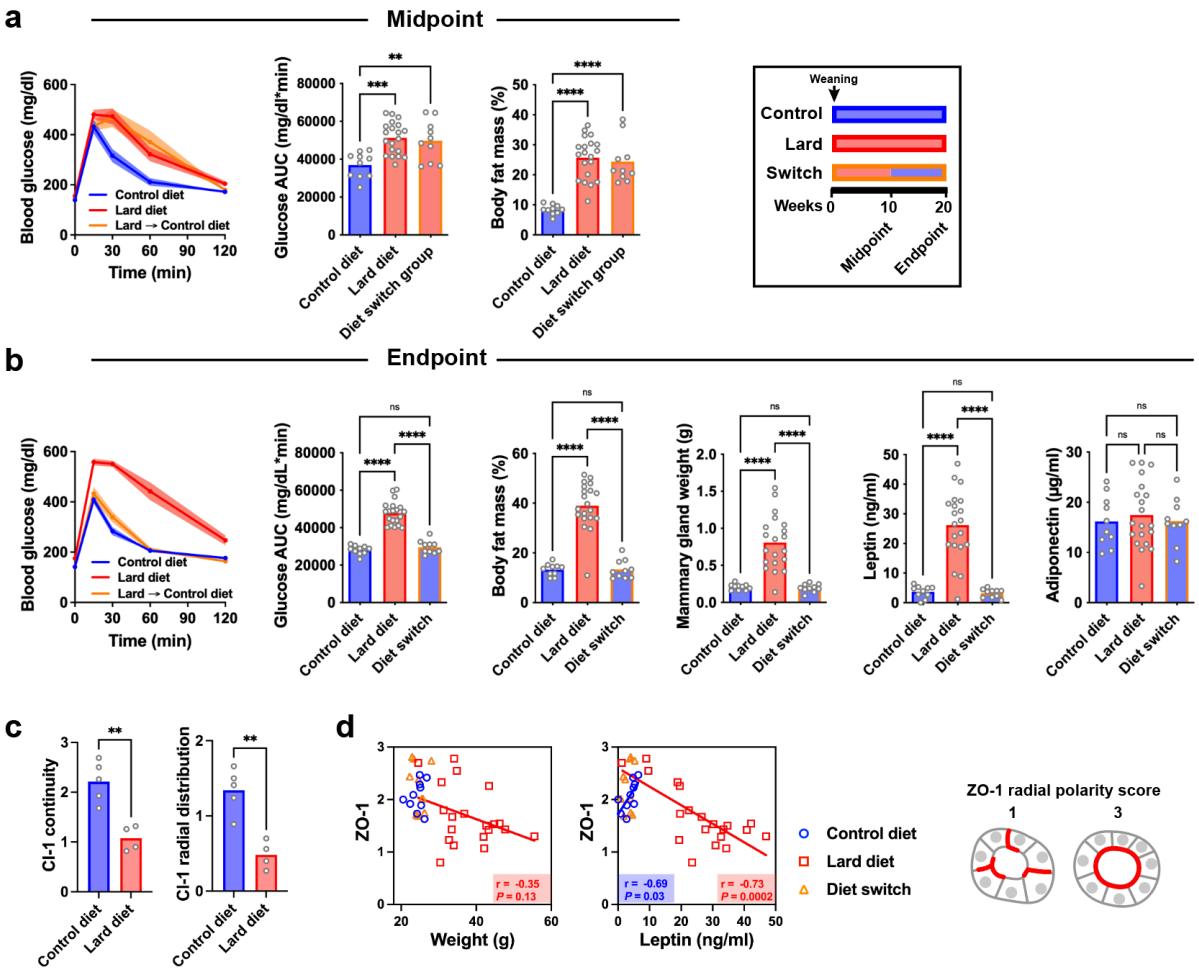

Fig. S5. Body and metabolic characteristics of C57BL/6 mice fed control and lard diets. a Measurements of glucose tolerance and body fat mass at the midpoint, before diet switch in the intervention group. **b** Measurements of glucose tolerance, body fat, mammary gland weights and serum adipokine levels at the endpoint, 10 weeks after switching mice from lard to control diet in the intervention group. AUC, area under curve. **c** Quantification of apical localization of claudin-1 at the study midpoint. **d** Radial distribution of ZO-1 in the mouse mammary glands at the endpoint as a function of animal weight or serum leptin concentration. r, Pearson's correlation coefficient. **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$; ns, not significant.

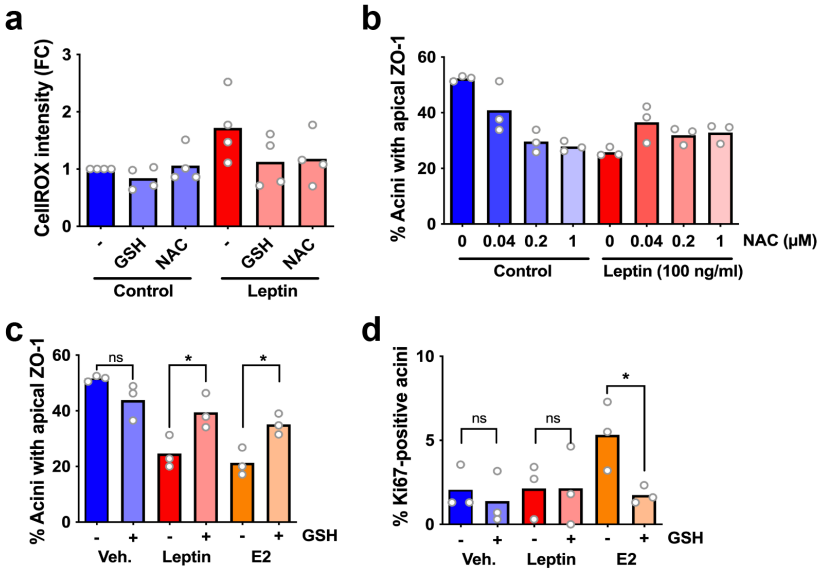

Fig. S6. ROS generation by leptin in breast acini. a ROS levels detected by the general ROS sensor CellROX in S1 cell acini treated for 30 min with leptin (100 ng/ml) or vehicle, in the absence or presence of glutathione (GSH; 0.16 mM) and N-acetylcysteine (NAC; 0.04 μM). **b** Proportion of acini with apical ZO-1 localization after treatment with leptin, in the presence or absence of NAC. **c-d** Apical ZO-1 localization (**c**) and expression of the Ki67 proliferation marker (**d**) in acini treated with vehicle, leptin (100 ng/ml), or β-estradiol (E2; 0.5 ng/ml), in the absence or presence of GSH (0.16 mM). *, $P < 0.05$.