**Supplementary Figure Legends**

**Figure S1: A:** Regimen of immunisation and blood sampling. **B**: Study pipeline and participant information.

**Figure S2: Spermidine treatment did not alter memory B cell numbers, total IgA or total IgG levels at 2 weeks.**

**A:** PBMC baseline mean fluorescence intensity (MFI) of p21in placebo and spermidine (Spd) groups 1 (G1) and 2 (G2). **B:** Senescence marker fold change heatmap between baseline and 2 weeks for p21 in CD4 T cell, CD8 T cell and B cell subsets. **C:** Anti-spike IgG intensity (ELISA) at baseline and 2 weeks post spermidine (Spd) for placebo and spermidine (Spd) groups 1 (G1) and 2 (G2). **D:** Raw FluoroSpot values for anti-spike IgG of PBMC-derived B cells 2 weeks post spermidine or placebo. **E:** Memory B cell (CD19+ CD27+IgDlow) proportion fold change from baseline. **F:** FluoroSpot image example results for B cells in IgA and IgG plates. **G:** Total IgG (FluoroSpot) fold change across groups from baseline. **H:** Total IgA fold change across groups. Annotations: Week 2; spermidine (Spd); group 1 (G1); group 2 (G2). Data are presented as Tukey boxplots with statistical comparisons using the Wilcoxon test.

**Figure S3: Enhanced ACE2 inhibition responses against SARS-CoV-2 variants following spermidine supplementation**

**A-I:** ACE2 inhibition (%) across all groups and timepoints, from neutralisation antibody assay against SARS-CoV-2 variants: **(A)** B.1.617 (India), **(B)** P.2 (Zeta), **(C)** B.1.1.7 (Alpha), **(D)** B.1.351 (Beta), **(E)** B.1.526 (New York), **(F)** B.1.617.2 (Delta), **(G)** B 1.617.1 (Kappa), **(H)** B.1.617.3 (India), **(I)** P.1 (Gamma). Annotations: Week 2 (W2); spermidine (Spd); group 1 (G1); group 2 (G2). Data are presented as violin plots with statistical comparisons using the Wilcoxon test.

**Figure S4:** **Spermidine supplementation had no effect on T cell responses against COVID-19 vaccination.**

**A:** ELISpot image example results for T cell plates stimulated with SARS-CoV-2 peptide pools representing the viral S1, S2, membrane (M) and nucleocapsid (N) regions. CEFT peptide pools and concanavalin A (ConA) were used as positive controls. **B-D:** *Ex vivo* IFN-γ ELISpot response fold change at 2 weeks to (**B**) total spike, **(C)** S1**,** **(D)** S2. Annotations: Week 2 (W2); spermidine (Spd); group 1 (G1); group 2 (G2). Data are presented as Tukey boxplots with statistical comparisons using the Wilcoxon test.

**Figure S5: scRNAseq analysis revealed that spermidine treatment induces significant modifications in B cell pathways.**

**A:** Violin plots showing normalized expression of the top three differentially expressed marker genes per identified cell type. **B-C:** Violin plots representing normalised gene expression for select genes differentially expressed between Placebo, G1 and G2 at baseline in the B memory cluster **(B)** FCER2 **(C)** TNFRSF13B **(D)** SLC18B1. **E-F:** B cell gene expression dot heatmaps at baseline (BL) and 2 weeks across groups for **(E)** TLR and PAMP recognition, and **(F)** viral response genes. **G-I:** TFEB target gene expression (scaled) dot heatmaps and pathways of DEGs **(G)** Naïve B cells **(H)** CD8+ T cells **(I)** CD4+ T cells.

**Figure S6: Spermidine supplementation increased TFEB in CD4 T cells.**

**A:** Schematic representation of the proposed mechanism of action of spermidine supplementation in autophagy activation of immune cells. **B-C:** Fold change in TFEB protein levels 2 weeks post spermidine supplementation or placebo in (**B**) CD4+ T cells, (**C**) CD8+ T cells, and (**D)** B cells as measured by flow cytometry. Annotations: spermidine (Spd); group 1 (G1); group 2 (G2). Data are presented as Tukey boxplots with statistical comparisons using the Wilcoxon test.

**Figure S7: Gating strategies to determine cellular composition of B cells and CD4+ and CD8+ T cells.**

**A:** Gating strategy for CD3+, CD19+, CD4+, CD8+ subsets within live cells. **B:** Representative flow cytometry-based assay for LC3-II from PBMCs treated with or without bafilomycin A1 (BafA1) for 2 h prior to staining. **C:** Representative staining of B cells with anti-TFEB or with secondary antibody alone, analysed by flow cytometry**.**

**Figure S8: Flow Cytometry Analysis of Senescence Markers in Mitomycin C-induced senescence in fibroblasts.**

**A-C:** Human dermal fibroblasts were treated with 100 nM mitomycin C (MMC) for 6 days and allowed to recover for a further 6 days to induce cellular senescence. Cells were then stained with antibodies targeting senescence markers, **(A)** p16**, (B)** p21, and **(C)** γ-H2AX, and measured by flow cytometry. **D:** mTORC1 activity measured by phospho-S6 (p-S6) levels was assessed in human CD4+ T cells activated for 3 days (1 µg/ml anti-CD3/28) in the presence of vehicle or 10 nM rapamycin (mTORC1 inhibitor).