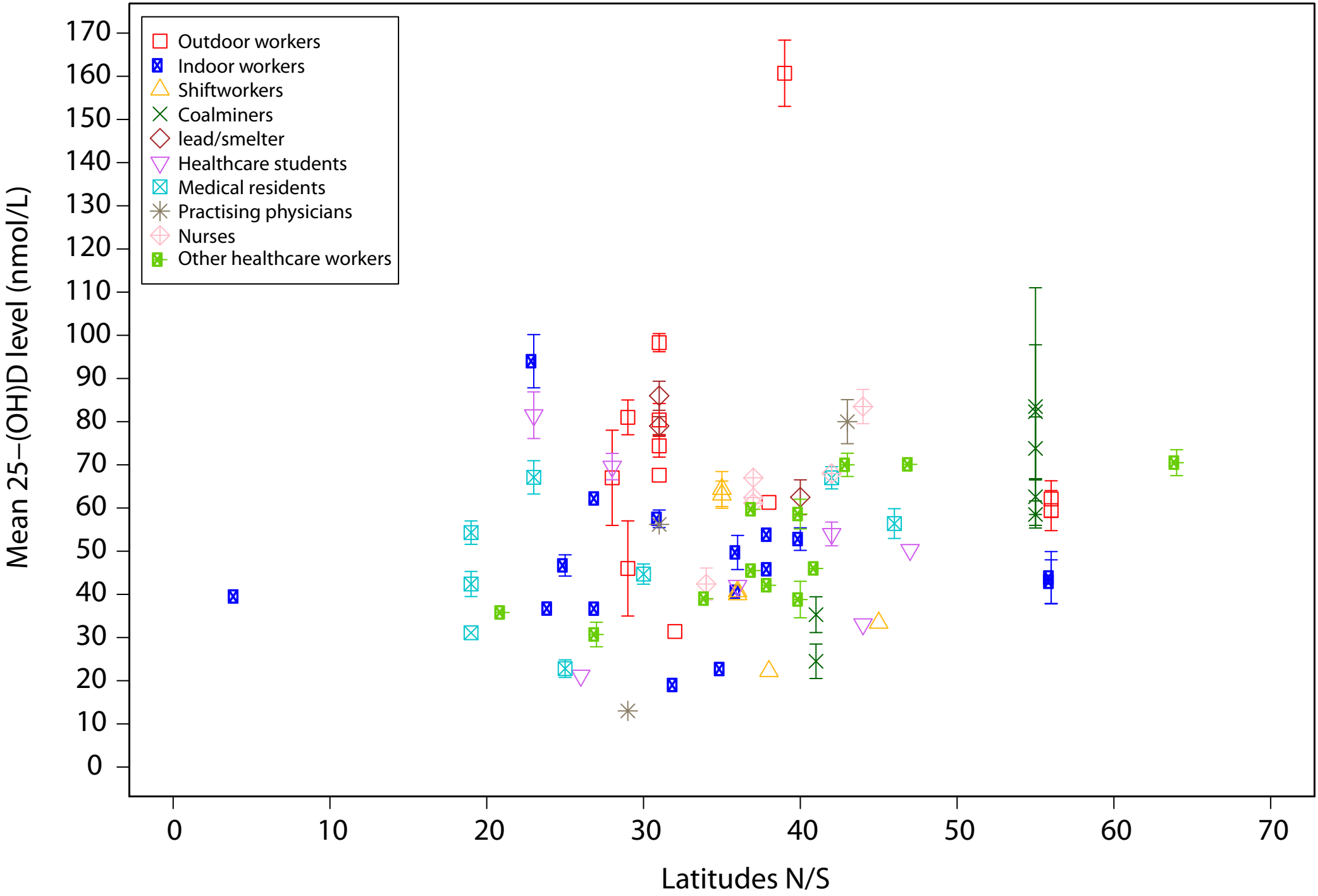Supplementary Fig. 4A