Interleukin-6: diurnal variation and relation to sleep

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Background

The pleiotropic cytokine interleukin-6 (IL-6) has been proposed to participate in the regulation of sleepiness. Early studies reported that IL-6 increases in the blood at night, but estimates of its diurnal phase are conflicting (figure 1).

Aims

We aimed to investigate the effect of time of day on circulating IL-6 using meta-analysis.

Results

Diurnal variation was investigated using 56 datasets with 1100 participants from 43 published reports (figure 2). We confirmed that IL-6 varied across the day, the most conspicuous effect being a trough in the morning (figures 3 and 4). In cross-sectional meta-analyses including 383-1650 participants from 3-7 datasets, we found no link between circulating IL-6 and subjective sleep duration, objective sleep duration, sleep efficiency, nor sleep quality (table 1).

Conclusions

The present observational data are not suggestive of a sleep regulatory role for circulating IL-6.

Table 1. Cross-sectional relationships between sleep measures and circulating IL-6. Results previously published in Hedlund, 2015.

Variable	*k*	*n*	*r*, random effects estimate [95% CI]
PSQI Global Score	7	1650	0.08 [-0.02, 0.16]
Sleep duration, subjective	3	1614	-0.01 [-0.14, 0.12]
Sleep efficiency, polysomnography	5	383	-0.22 [-0.57, 0.08]
Sleep duration, polysomnography	5	986	-0.15 [-0.38, 0.09]

References

Nilsonne G, Lekander M, Åkerstedt T, Axelsson J, Ingre M. Diurnal Variation of Circulating Interleukin-6 in Humans: A Meta-Analysis. *PLOS ONE 2016;11(11):e0165799. doi.org/10.1371/journal.pone.0165799*

Hedlund M. The relationship between IL-6 and sleep – a meta-analysis. Karolinska Institutet; 2015.

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Figure 1

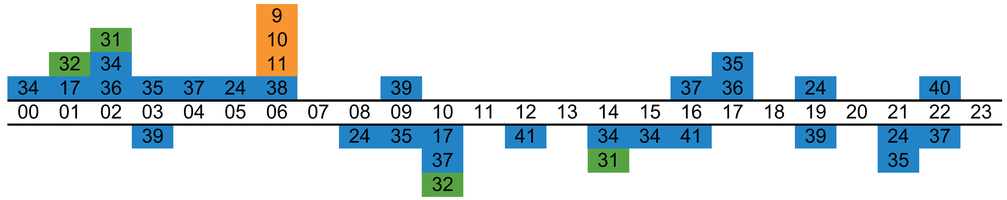

Figure 1: Estimates of phase reported in earlier literature. Every count represents one claim of having located a peak (box above time-line) or a trough (box below time-line) in a dataset. Blue: Studies included in quantitative review. Green: Studies not included in quantitative review. Orange: Earlier meta-analysis. Review papers are not included. Figure is previously published in Nilsonne et al. 2016 and numbers in boxes refer to the reference list in this paper.

Figure 2:Data inclusion. Some of the 43 included studies contained more than one dataset. The final number of datasets was 56. Figure is previously published in Nilsonne et al. 2016.

Figure 2

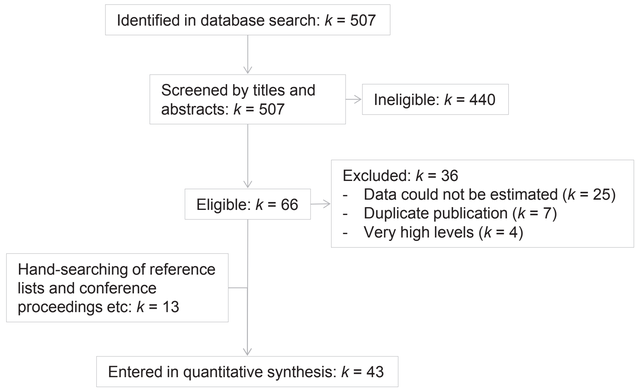

Figure 3

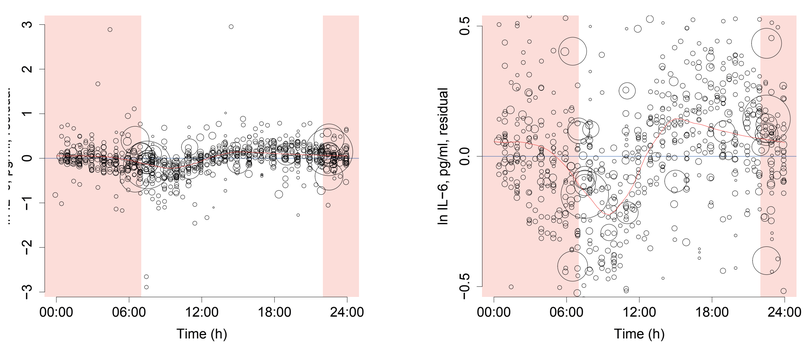

Figure 3: Residuals from null model. Data points sized by regression weight. In the null model, a random intercept for each study and a linear effect of time from catheterization have been included. Therefore, these residuals show the putative diurnal variation to be modeled. To explore this variation, we fitted a weighted LOESS curve (red line). This curve shows a trough in the morning. Note that the shape of the LOESS curve depends on the smoothing parameter. It is therefore possible to generate different LOESS curves from the same data, and not all of them show a peak in the early afternoon. The LOESS curve was fitted on three repeated days of the same data, and the curve for the second day shown, to ensure that the estimates would meet at 00:00 and 24:00. Time from 22:00 to 07:00 is shaded to indicate the night. Left: All data points shown. Rignt: Y axis range restricted to increase resolution. Figure is previously published in Nilsonne et al. 2016.

Figure 4

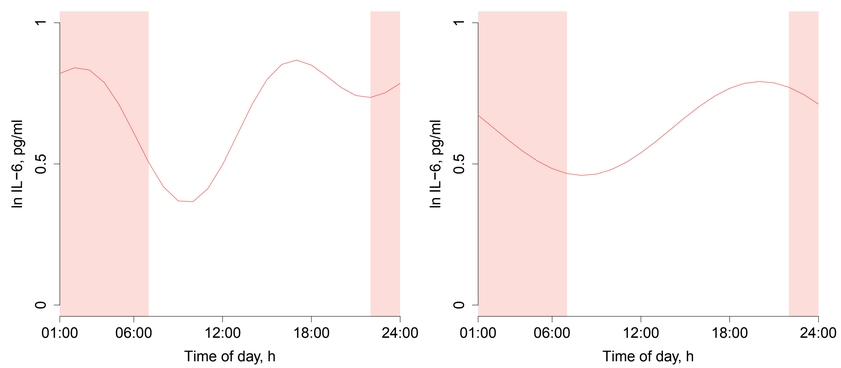

Fig 4. Predicted diurnal time courses from meta-regression models. Left: Best-fitting model including cosinor functions with 24 and 12 h periods. Right: Model including only 24 h period. Time from 22:00 to 07:00 is shaded to indicate the night. Figure is previously published in Nilsonne et al. 2016.