eAppendix 3: Secondary outcomes

Long-term effects

Two studies including 229 participants contributed data on the long-term effects of NHF [28,29]. The follow-up period for these studies ranged from 6 weeks to 12 months.

Secondary outcomes:

Blood oxygen saturation

One study was available for this outcome (total 29 patients) [28]. There was no difference between NHF and control in SpO_2 (MD 0 %, 95% CI 0 to 1). The same study also reported no significant difference in SpO2 at the end of the 6MWT (MD -3 %, 95% CI -9 to 3). The quality of evidence was "very low".

Cardiorespiratory function

There was no available data with regards to heart rate (HR).

Two studies assessed forced expiratory volume in 1second (FEV_1)% (total 196 participants) (24, 25). Nagata et al. showed no significant difference in FEV_1% between groups (MD 0 L/min, 95% -2 to 1) and Storgaard et al. reported a tendency toward improvement in favor of NHF (p=0.056). Detailed data were not available on the original report and we had no answer from the authors in our initiative to get the data. The quality of evidence was "low".

One study assessed forced vital capacity (FVC) (total 29 patients) (24). There was no difference between NHF and control in FVC% (MD 0 %, 95% CI -3 to 3). The quality of evidence was "very low".

Dyspnea (mMRC scale)

Two studies that measured dyspnea used the mMRC dyspnea scale, which is measured from 0 (no dyspnea except with strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing or undressing).

Meta-analysis of two studies showed statistically significant effects of nasal high flow on dyspnea (pooled MD -0.3, 95% CI -0.4 to -0.1; I^2=0%; **eAppendix 5 – Figure S1**). The quality of evidence was "moderate" as shown in the summary of findings for this comparison in **Table 2**.

Nagata et al. also assessed dyspnea during the 6MWT using the BORG scale and shown no significant difference between groups (MD -0.3, 95% CI -1 to 0.4).

Exercise capacity (six-minute walk test)

Meta-analysis of two studies showed no statistically significant effects of nasal high flow on exercise capacity (pooled MD using a random effect model: 18 m, 95% CI -9 to 46; I^2=95%; **Appendix 5 – Figure S2)**. The quality of evidence was "very low" as shown in the summary of findings for this comparison in **Table 2**.

Physical activity

One study was available for this outcome (total 29 participants) [28]. There was no difference between NHF and control in step count/day (MD 233, 95% CI -9 to 475). The quality of evidence was "very low".

Adverse event

Nagata et al. reported 10 events spread over 7 patients in NHF group and 6 events spread over 6 patients in the controlled group. Event directly related to intervention included night sweat (4 patients), nasal discharge (1 patient) and insomnia (1 patient). Among these results, there

were 2 reported severe events (deemed unrelated to the intervention) spread over 2 patients in both groups. On the other hand, Storgaard et al. reported that no adverse or serious adverse event occurred throughout the follow-up period (12 months).

Other outcomes

No data were available for breathing pattern, respiratory mechanics, or comfort.

Subgroup and sensitivity analyses

There were too few studies to perform any of the planned subgroup and sensitivity analyses.

Short-term effects

Three cross-over studies including 98 participants contributed data on the short-term effects of NHF [25-27].

Blood oxygen saturation

Two studies including 78 participants contributed data on blood oxygen saturation [25,26]. Meta-analysis showed no statistically significant effects of NHF on blood oxygen saturation (pooled MD using a random effect model: 0 %, 95% CI 0 to 1; I^2=83%; **Appendix 5 – Figure S3**). The quality of evidence was "very low".

Cardiorespiratory function

Two studies including 78 participants contributed data on HR [25,26]. Meta-analysis showed no statistically significant effects of nasal high flow on heart rate (pooled MD 0 bpm, 95% CI -1 to 0; I^2=49%; **Appendix 5 – Figure S4**). The quality of evidence was "very low".

One study assessed tidal volume (Vt) (30 participants) [25] and reported a significant difference between NHF and control in favor of NHF (MD 0,1 L, 95% CI 0.4 to 1.6). The quality of evidence was “very low”.

Respiratory rate (RR) was assessed in two studies (156 participants) [25,26]. Meta-analysis showed statistically significant effects of nasal high flow on respiratory rate (pooled MD -4 cpm, 95% CI -6 to -2; I^2=0%; **Appendix 5 - Figure S5**). The quality of evidence was “low”.

Overall, minute ventilation (MV) was assessed in one study (total 30 participants) [25] which shown no significant difference between NHF and control in MV (median difference -0 L/min, 95% CI -0.3 to 0.2). The quality of evidence was “very low”.

Respiratory mechanics

There was no available data with regards Pga, Poes and Ptdia.

One study assessed end-expiratory lung impedance [25] and found a significant effect in favor of NHF (mean difference in change from baseline: 61 %, 95% CI 28 to 94). The quality of evidence was “very low”.

Dyspnea

One study was available for this outcome (total 30 participants) [25] and used a visual analogical scale (VAS) which is measured from 0 (no dyspnea) to 10 (maximum dyspnea). There was a difference between NHF and control in dyspnea. COPD patients randomized to the NHF group showed a significant increase in VAS scale (MD 1, 95% CI 0.5 to 1.5). The quality of evidence was “very low”.

Exercise capacity

See *during exercise* section.

Physical activity

No available data.

Comfort

One study was available for this outcome (total 30 participants) [25] and used a visual analogical scale (VAS) which is measured from 0 (no discomfort) to 10 (maximum discomfort. COPD patients randomized to the NHF showed a significant decrease in comfort (MD 1, 95% CI 0.3 to 1.7). The quality of evidence was "very low".

Other outcomes

No data were available for pH, physical activity and adverse event.

Subgroup and sensitivity analyses

There were too few studies to perform any of the planned subgroup and sensitivity analyses.