Title

Normobaric hypoxic conditioning to maximise weight-loss and ameliorate cardio-metabolic health in obese populations: A **systematic** review

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Running head

Therapeutic use of hypoxia in obese individuals.

Key words

Obesity, hypoxia, altitude training, weight loss, cardio-metabolic health**.**

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Abstract

Background: Normobaric hypoxic conditioning (HC) is defined as exposure to systemic and/or local hypoxia at rest (passive) or combined with exercise training (active). HC has been previously used by healthy and athletic populations to enhance their physical capacity, and improve performance in the lead up to competition. Recently, HC has also been applied acutely (single exposure) and chronically (repeated exposure over several weeks) to overweight and obese populations with the intention of managing and potentially increasing cardio-metabolic health and weight loss. At present, it is unclear what the cardio-metabolic health and weight loss responses of obese populations are in response to passive and active HC. **Exploration of potential benefits of exposure to both passive and active HC may provide pivotal findings for improving health and well being in these individuals.**

Methodology: A systematic literature search for articles published between 2000 and 2017 was carried out. Studies investigating the effects of normobaric HC as a novel therapeutic approach to elicit improvements in the cardio-metabolic health and weight loss of obese populations were included.

Results: Studies investigated passive (n = 7; 5 animal, 2 human), active (n = 4; all human) and a combination of passive and active (n = 4; 3 animal, 1 human) HC to an inspired oxygen fraction (FiO_2) between 4.8–15.0%, ranging between a single session and daily sessions per week, lasting from 5 days up to 8 months. **Passive HC led to reduced insulin concentrations (-37 – +22%) in obese animals and increased energy expenditure (+12 – +16%) in obese humans, while active HC lead to reductions in body weight (-4 – -2%) in obese animals and humans, and blood pressure (-8 – -3%) in obese humans, compared to a matched workload in normoxic conditions.** Inconclusive findings, however, exist in determining the impact of acute and chronic HC on markers such as triglycerides, cholesterol levels and fitness capacity. Importantly, most of the studies that included animal models involved exposure to severe levels of hypoxia ($FiO_2 = 5.0\%$; simulated altitude >10,000 m) that are not suitable for human populations.

Conclusions: Overall, normobaric HC demonstrated **observable** positive findings in relation to insulin and energy expenditure (passive), and body weight and blood pressure (active), which may improve the cardio-metabolic health and body weight management of obese populations. However, further evidence on responses of **circulating** biomarkers to both passive and active HC in humans is warranted.

Word count: 391

71   **1. Introduction**

72   Obesity has been labeled as the global epidemic of the 21st century (78). In the United

73   Kingdom alone, 58% of women and 65% of men are considered to be overweight or obese,

74   i.e., defined as having a **body mass index (BMI) of 25–29.9 or ≥30 kg.m^2**, respectively (49).

75   Compared to the early 1990s, whereby obesity prevalence was estimated to be ~15%, those

76   living in today's society have a 1 in 4 chance of becoming obese (49). Further, co-morbidities

77   such as cardiovascular disease, type II diabetes and cancer are at greater risk of development

78   in obese popuations resulting in the possibility of higher mortality rates (21).

79   Obesity is typically caused by a consistently positive energy balance, i.e., greater

80   calories consumed *versus* those expended, which eventually leads to excess fat accumulation

81   (28) – the negative impact of which is profound in terms of health consequences. Carrying

82   additional weight can result in elevated blood pressure (7), metabolic deficiencies (28) and

83   mechanical complications (11) amongst other factors – all of which create an increased

84   functional demand on the body of obese individuals. Further, the increased mechanical

85   demand during weight-bearing activities of obese populations may be deleterious on lower

86   limb joints (i.e., knee and ankle) and limit the functional capabilities compared to healthy and

87   normal weight populations (70). **Aside from bariatric surgery, that is primarily available**

88   **for the most severe cases (BMI ≥40 kg.m^2 [3]), various interventions including diet**

89   **manipulation, caloric restriction, and increased physical activity and exercise (12), are**

90   **proposed to counteract these problems.**

91   For weight loss to be considered clinically significant, a change of ≥3% in body

92   weight is required (12) – and then ≤3% change to be deemed as weight maintenance over the

93   duration of several months (65). Typically, weight loss **is achieved in the first six months of**

94   commencing a new diet and/or exercise programme, but a plateau is then reached and often

95   the weight lost is subsequently regained (66). Given the inadequacy of current weight

96   management strategies, innovative approaches are warranted for clinically-relevant weight

97   loss treatment and significant improvements in the health and general well-being of those

98   who are overweight and obese beyond what is achieved to date.

99   Hypoxia is defined as a reduced (or insufficient) oxygen (O_2) supply to tissues caused

100   by decreases in O_2 saturation of arterial blood (24). Hypoxic conditioning (HC) relates to

101   passive (i.e., during rest) or active (i.e., during exercise) exposure to systemic (whole body)

102   and/or local (tissue) hypoxia, resulting in a decrease in arterial O_2 availability (38). HC can

103   be implemented acutely (single exposure) or chronically (multiple exposures over prolonged

104   periods of time). Permanent residence in a hypobaric hypoxic (terrestrial altitude due to

105   lower-than-sea level barometric pressure) environment has shown to reduce the likleyhood of

106   becoming obese (68). Several studies have reported weight loss (1, 58, 81), reduced blood

107   pressure (35, 61) and improved metabolic function (35, 61, 64, 72, 73) after a 1–3 week

108   residential stay (e.g. hotel and food provided, light entertainment acitivites throughout the

109   day, no structured exercise program) at terrestrial altitude (**1500–8800 m**). However,

110   permanent living or travelling regularly to terrestrial altitude may not be feasible to all (i.e.,

111   re-location, elevated cost, lack of time). In obese populations, this practice could also lead to

112   side effects such as physiological and metabolic deficiencies (44), including obstructive sleep

113   apnea (**30**) or the development of acute mountain sickness (81).

114   Alternatively, exposure to normobaric hypoxia (or simulated altitude via a reduced

115   inspired O_2 fraction [FiO_2]), is increasingly popular as the number of commercially-available

116   devices permitting simulated hypoxic exposure is growing. Primarily, this intervention allows

117   living at or near sea level and then exposing, periodically, individuals to hypoxic conditions

118   at rest or whilst exercising. **This is typically accomplished by breathing through a mask**

119   **or staying in an environmentally controlled chamber/room/tent whereby the FiO_2 is**

120   **typically reduced to 15–12% (equivalent to simulated altitudes of ~2600–4300 m)**. In

121   sedentary overweight males, for instance, passive acute (single 3-hour exposure session)

122   normobaric HC increased energy expenditure and altered fuel utilisation (reduced glucose

123   and increased lipid oxydation), while further passive HC (multiple 3-h exposure sessions on 7

124   consecutive days) magnified these metabolic adjustments (77). For a range of exercise

125   intensities (55–65% of maximal O_2 uptake [$VO2_{max}$] / 60–70% of maximum heart rate

126   [HR_{max}]) and similar levels of simulated altitude (~2600 m), other studies (18, 32, 46, 51, 76)

127   have suggested that active HC induces specific molecular adaptations that do not occur when

128   training in a normoxic environment (66). These positive adaptations, in particular, include

129   increased basal noradrenaline levels (**4**), arteriole diameter and peripheral vasodilation (**45**),

130   mitochondria number (**66**), glycolytic enzyme activity (16), insulin sensitivity (40), as well as

131   reduced diastolic blood pressure (63) and leptin levels (29). Such physiological adaptations

132   would in turn improve the metabolic phenotype of obese individuals.

133   Recent reviews have investigated the impact of O_2 availability as a therapeutic

134   intervention for body weight management (56), intermittent hypoxia for fat loss and

135   enhancement of cardiovascular health (66), the role of hypoxia in energy balance (28),

136   hypoxic conditioning for several pathological diseases (67) and the effectiveness of hypoxic

137   training on cardio-metabolic risk factors (71). **Overall, these reviews tend to agree that**

138   **both hypoxia and hyperoxia (i.e., environmental conditions posing a challenge to O_2**

139   **homeostasis) may play a significant role in the processes associated with obesity and**

140   **weight loss paradigm.** However, the aforementioned reviews are limited in terms of

141   systematically examining the potential impact of passive and active HC on markers of cardio-

142   metabolic health and well-being (71), while some focus solely on human research with no

143   consideration of findings from animal models (66, 71). Further, combining the literature on

144   HC of populations with a multitude of diseases (e.g., cardiovascular and pulmonary) does not

145   provide conclusive evidence in relation to the specific treatment of obese populations (67).

146 Due to the mechanical restrictions and weight loading implications on lower limbs (i.e., on

147 the knee and ankle joints) when completing exercise in at-risk (obese, overweight and

148 sedentary) populations (70), the exploration of potential benefits of exposure to both passive

149 and active HC may provide **pivotal** findings for weight loss and maintenance strategies.

150 Therefore, the aim of this **systematic** review is to a) summarise the current literature

151 surrounding passive and active normobaric HC as a therapeutic method for improving cardio-

152 metabolic health and managing weight-loss in obese animals and humans, and b) offer

153 perspectives for future research within this area of literature.

154

155 **2. Materials and methods**

156 *2.1. Literature search*

157 A literature search was carried out in the Pubmed, ScienceDirect, Scopus, Web of

158 Science and SportsDiscus databases. **The terms (intermittent hypoxia OR passive hypoxic**

159 **exposure OR hypoxic training OR altitude training OR live-low train-high) AND**

160 **(obesity OR overweight OR weight loss OR physiological response OR metabolic**

161 **response OR cardiovascular response) were combined to search the full text of**

162 **experimental articles published after 2000 and before January 2017**. Each title, abstract

163 and full text were assessed for relevance to the topic and selected if they met the inclusion

164 criteria as follows: an original research article; randomised and controlled design; human or

165 animal experimentation; overweight (BMI: 25–30 $kg.m^2$), obese (BMI: 30–38 $kg.m^2$) and/or

166 sedentary participants; normobaric hypoxic intervention; assessment of at least one of the

167 following parameters: blood pressure, glucose concentrations, insulin levels or cholesterol;

168 English language; and published in a peer-reviewed journal. **Exlcusion criteria were:**

169 **athletic/sport population/performance focus; involved obstructive sleep apnoea; clinical**

170 **studies; implemented hypobaric/no hypoxia; or included a physically active or**

171 **adolescent population.** Only full text articles were reviewed. In addition to the literature

172 search, references were scanned for further relevant articles and were included if they met the

173 inclusion criteria.

174

175 *2.2. Assessment of Methodological Quality*

176 A modified scale to assess the methodological quality of the studies retrieved in this

177 review was carried out following selection of full text articles. The modified version was

178 applied due to the greater representation for experiments employing a training intervention,

179 compared to the Delphi, PEDro and Cochrane scales (53). A 10 item quality rating guide

180 included the criteria listed below and guided the assessment scoring of each study as follows:

181 0 = clearly no; 1 = maybe; 2 = clearly yes; range = 0 (poor)–20 (excellent).

182 1. Inclusion criteria were clearly stated;

183 2. Subjects were randomly allocated to groups;

184 3. Intervention was clearly defined;

185 4. Groups were tested for similarity at baseline;

186 5. A control group was used;

187 6. Outcome variables were clearly defined;

188 7. Assessments were practically useful;

189 8. Duration of intervention was practically useful;

190 9. Between-group statistical analysis was appropriate;

191 10. Point measures of variability;

192

193 **3. Results**

194 *3.1. Search results*

195   Fig. 1 illustrates a flow chart of the search results. The search yielded a total of 212

196   publications. After removal of irrelevant titles, 23 items remained in relation to the focus of

197   the review, reduced to eight following abstract assessment, and subsequently four full texts

198   that met the inclusion criteria. Additionally, a further eleven full text items were added via

199   reference list searching.

200   *Fig. 1 near here*

201

202   *3.2. Methodological quality assessment*

203   The average quality of the 15 studies included in this review was 16/20 according to

204   Paul et al. (53). One study scored 20/20, and the lowest score was 12/20.

205

206   *3.3. Study characteristics*

207   **Table 1 illustrates the details of the studies included in this review. Eight studies**

208   **used animal models (2, 6, 34, 37, 52, 55, 59, 79). Five of these implemented a protocol of**

209   **passive HC only (2, 34, 52, 55, 59), two active normoxic periods followed by passive HC**

210   **(6, 79), and one used passive and active HC combined (37). All animal studies included**

211   **obese rodents (mice or rats) aged between 3 and 24 weeks, seven used male (2, 6, 37, 52,**

212   **55, 59, 79) and one involved female (34) models. Five of the animal model groups were**

213   **genetically obese (2, 6, 55, 59, 79), while three were fed a high-fat diet (34, 37, 52). Other**

214   **than one study stating leptin deficiency in their animal models (34), no other difference**

215   **in the health of animals across studies was mentioned.**

216   **Seven of the eligible studies investigated human participants (18, 32, 46, 51, 69,**

217   **76, 77). Two of these employed passive HC only (69, 77), four active HC only (32, 46, 51,**

218   **76), and one investigated both passive and active HC (18). Four of the human**

219   **investigations were composed of both males and females (18, 32, 51, 76), with the**

remaining three including males only (46, 69, 77). Further, four studies used obese (BMI = 30–37.1 kg.m2 [18, 32, 51, 76]), one overweight (BMI = 27 kg.m2 [77]) and one sedentary (normal weight with a BMI = 22.2 kg.m2 [69]) participants. The body composition of one participant cohort was not reported (46). Participants were aged between 21–51 years. Where mentioned, participants were free from hypertension (18, 77), diabetes (76), stroke (18), acute and chronic cardio-vascular, pulmonary and respiratory diseases/infections (18, 69, 76, 77), barriers to physical activity (32), altitude/hypoxic exposure (32, 76), medication to control weight or metabolism (32, 69, 77), alcohol/drug abuse and smoking (33, 69, 76, 77), and exercise (32, 46, 69, 77) within ≥3 months of enrolling.

Table 1 near here

3.4. *Animal studies*

3.4.1. *Passive hypoxic exposure*

The five investigations reviewed implemented two modes of passive HC, namely intermittent and sustained hypoxia. Intermittent protocols adopted a pattern of 30 s of exposure to hypoxia followed by 30 s of exposure to normoxia, lasting for 8 h (2) and 12–16 h per day (55). There were modifications to this approach in two of the investigations as follows: 40 and 80 s of exposure to hypoxia and normoxia, respectively (52), and 2 x 15-min periods of exposure to hypoxia interspersed with 5 and 10 min of exposure to normoxia (34). Only Rodriguez et al. (59) implemented a sustained exposure period of 24 h per day. The hypoxic level ranged between $FiO_2 = 4.8\%$ (2, 52, 55, 59) and 14.3% (34), while most studies used a FiO_2 of ~5.0% (2, 52, 55, 59) All interventions involved daily exposure. Most studies examined responses over a prolonged period of time (2–6 weeks [2, 34, 52, 59]), with only

Polotsky et al. (55) investigating both short-term (5 days) and long-term (12 weeks) responses.

3.4.2. Combined passive and active hypoxic exposure

Chen et al. (6) and Wu et al. (79) implemented a live high-train low (LHTL) intervention, with 90-min exercise sessions (moderate-intensity swimming) carried out in normoxia, followed by sustained passive HC periods (8 h per day, $FiO_2 = 14.0\%$). Lu et al. (37) employed a live high-train high (LHTH) intervention, with implementation of 60-min active HC (moderate-intensity running), and the remaining hours of the day living in the same hypoxic environment ($FiO_2 = 13.6\%$). These interventions ranged between 4–6 weeks.

3.5. Human studies

3.5.1. Passive hypoxic exposure

Wang et al. (69) and Workman & Basset (77) both implemented sustained passive HC periods corresponding to a period of 60 min and 3 h, respectively. The hypoxic level during these sessions was controlled via two methods: FiO_2 clamped at 12–15% (69), and manipulation of FiO_2 to clamp the arterial O_2 saturation (SpO_2) at ~80% (77).

Whereas Wang et al. (69) implemented a 4-week intervention (5 days of exposure per week, 60-min sessions), Workman & Basset (77) investigated responses to both a single 3-h session as well as the same period of exposure and hypoxic level on an additional 6 consecutive days.

3.5.2. Active hypoxic exposure

Active investigations have used a live low-train high (LLTH) approach and implemented exercise of a moderate intensity (55–65% $VO2_{max}$ / 60–70% HR_{max}). Exercise

269 programmes were typically cardiovascular-based (running, cycling, stepping [32, 46, 51,

270 76]), with one study adding strength training (40–50% of 1 repetition maximum, 3 sets of 15

271 repetitions, interspersed with 2–3-min rest periods [32]).

272 The FiO_2 in all studies was 15.0%. Typical exercise prescription included sessions of

273 60–90 min in duration, performed three times per week, over a 4-week period (32, 46, 76),

274 with one study implementing a longer training period of eight weeks (51). Kong et al. (32)

275 took their participants to a sea-level residential camp for 4 weeks, which permitted a greater

276 amount of time for exercise per week (22 h) and dietary control. Although, the hypoxic group

277 spent only 6 h in hypoxia per week (exercise modality unknown) with the remainder of the

278 sessions (16 h) carried out in normoxic conditions.

279

280 *3.5.3.   Combined passive and active exposure*

281 Gatterer et al. (18) utilised a combination of passive and active HC via a LLTH

282 approach over a period of 8 months. Participants completed 90-min moderate intensity (65–

283 70% of HR_{max}) exercise sessions on an exercise ergometer of their choice (cycle, treadmill,

284 cross-trainer), immediately followed by 90 mins rest, all in hypoxic ($FiO_2 = 12–14\%$)

285 conditions, twice weekly.

286

287 **4.   Discussion**

288 *4.1. Animal studies*

289 *4.1.1.   Passive hypoxic exposure*

290 **Table 2 presents the overall findings of the animal studies included in this**

291 **review.** Glucose concentrations are commonly measured in obese animals following passive

292 HC as an indirect marker of insulin sensitivity, however, the findings of this measure are

293 inconsistent. Polotsky et al. (55) and Ling et al. (34) both found reductions in fasting glucose

concentrations following intermittent HC, despite exposure time/cycle (30 s :30 s *versus* 15 min :5–10 min, respectively) and severity of hypoxic exposure (FiO_2 = ~5.0% *versus* 14.3%, respectively) being largely different between protocols. In contrast, Briancon-Marjollet et al. (2) reported significant glucose concentration increases in obese rats after 8 h of intermittent (30 s :30 s) HC to an extreme hypoxic level (FiO_2 = 5.0%) per day over 2 weeks. Other investigations have shown unchanged values when animals were exposed intermittently to similar hypoxic levels using protocols of 40 s :80 s for 8 h (52) and 30 s :30 s for 12 h (55) per day. It seems that the common response of glucose concentrations in obese animals, passively exposed to varying levels of hypoxia, is yet to be verified. **This variation in the present findings may be partly explained through the differences in pre-analytical conditions of sampled tissue, which was subsequently utilised for glucose concentration assessment (84).**

Insulin is receiving a great deal of attention due to its dominance in Type II Diabetes control and development (26). In obese rats, insulin concentrations were unchanged following intermittent HC for 8 h per day (40 s :80 s [52]; and 30 s :30 s [2]). This is perhaps due to the severity of the hypoxic stimulus (FiO_2 = ~5.0%) blunting improvements in this health marker (50). Only one study has reported significant increases in insulin levels, which occurred following both a 5 day (+356%) and 12 week (+185%) hypoxic intervention in obese mice (55). The highly significant increase in insulin concentrations shown here may not actually be of benefit. Perhaps, exacerbation of insulin resistance occurred, leading to hyperinsulinemia (79). It is interesting to note that the hypoxic level employed in these studies was similar (FiO_2 = ~5.0%), and animals were intermittently exposed to hypoxia over 1 :1 (30 s :30 s) and 1 :2 (40 s :80 s) sequences. Reducing the severity of hypoxia during exposure periods may prevent dramatic increases, as reported here by Polotsky et al. (55),

318   and protect against subsequent exacerbation and development of hyperinsulinemia. This

319   assumption, however, needs to be verified in an obese human population.

320   Varying findings of cholesterol following HC have been reported. Reductions in total

321   cholesterol were found following hypoxic exposure (15 min :5–10 min, 8 times per day for

322   40 days, $FiO_2 = 14.3\%$) in both lean and obese mice (34). Contrastingly, an increase in total

323   cholesterol values occured following HC (40 s :80 s for 8 h per day over 14 days, $FiO_2 =$

324   5.0%) in obese rats, and in control (no hypoxic exposure) lean and obese rats (52). In another

325   study, no difference was reported in both lean and obese animals exposed to hypoxia (30 s

326   :30 s for 8 h per day over 14 days, $FiO_2 = 5.0\%$) or those who received no hypoxic exposure

327   (2). Although the variance is apparent, it is difficult to interpret findings due to there being a

328   lack of individual evaluation of levels of high-density (HDL) and low-density (LPL)

329   lipoprotein. Increases in total cholesterol in response to HC may in fact be a result of an

330   increase in the HDL/LDL ratio, which would actually be beneficial but is not yet clear in the

331   current literature.

332   Leptin, a satiety hormone, is suggested to be associated with weight loss due to its

333   action on hypothalamic metabolism and appetite suppression, potentiating a reduced energy

334   intake (47). It is also considered a growing marker of weight loss during and following HC

335   (50). Studies have reported increases in leptin in both hypoxic and normoxic groups (2, 52),

336   but there was no assessment of body weight changes. Increases in serum leptin have been

337   found following intermittent, moderate hypoxic and normoxic exposure of 15 min :5–10 min,

338   respectively, compared to those who received no exposure to hypoxia (34), which was also

339   aligned with slower rates of weight gain (+79% *versus* +100%, respectively). Notably, the

340   animal models were fed a high-fat diet during the course of the intervention, which therefore

341   may explain the reports of weight gain in this study. It could be that the weight gain was a

342   result of increases in muscle mass of the animal models, but this measure was not assessed.

In summary, a small amount of evidence suggests that leptin may be a marker associated with weight loss, due to the findings of slower weight gain following passive HC.

Triglycerides, an important part of fat storage (13), have been found to increase following intermittent (40 s :80 s) HC for 8 h per day over 2 weeks in obese rats (+30% [52]). Notwithstanding, equal changes occurred in the control group (+30%), whom didn't received any hypoxic treatment. In addition to this, mean arterial blood pressure increased similarly in both groups. This may have been a result of the investigators feeding animals a high-fat diet alongside the hypoxic intervention, and subsequently blunting the potentially beneficial effects. These findings further highlight the co-morbidity relationship between obesity and hypertension whilst consuming a high-fat diet, which will not be reduced with severe hypoxic levels as shown in other studies (2, 52).

Finally, only three studies have measured body weight before and after a chronic passive hypoxic intervention in obese animals. Ling et al. (34) found weight to increase equally in the hypoxic group (+79%) and the control group (+78%). Rodriguez et al. (59) reported weight to increase in the hypoxia group (+9%) but with slightly greater increases in the control group (+13%). **Previously, weight loss has generally been observed in the first days of exposure (41, 42). However, this has not been the case in the present review.** Finally, Polotsky et al. (55) reported no change in any group. The discrepancy in findings of body weight following passive HC presented here may be due to a lack of dietary control. From an experimental perspective, controlling caloric intake may be difficult in animal models and subsequently leads to disparate changes in weight (i.e., weight gain). Only Polotsky et al. (55) stated what the animal models were fed throughout the intervention and reported no change in body weight. **The majority of available studies presented here**

actually report weight gain after repeated passive HC over 4–12 weeks. To summarise, passive HC in obese animals, fed a high-fat diet, does not lead to conclusive weight loss.

Table 2 near here

4.1.2. *Combined passive and active hypoxic exposure*

Unlike passive HC alone, reductions in fasting glucose and insulin responses have typically been found following a combination of passive HC and normoxic active periods (6, 79). Interestingly, the hypoxic level (FiO_2 = ~14.0%) as well as the duration and mode of exercise employed (1.5 h of swimming) was similar across studies. Notably, Wu et al. (79) also found reductions in fasting glucose concentrations within the group whom carried out normoxic exercise without passive HC. This raises questions as to whether exercise alone is more effective than a combination of exposure modes. **Passive HC and normoxic active periods, when combined, could potentially improve metabolic and hormonal responses of obese animals.** Pending confirmatory research, this could at least in part be ascribed to improved insulin sensitivity and cellular glucose uptake.

The primary question regarding the use of passive and active HC is whether it leads to more benefical health outcomes than a similar workload completed in normoxic conditions. Lu et al. (37) concluded that, compared to a control group, who received no exposure to hypoxia or exercise completion, obese rats lost significant amounts of weight, fat mass, LDL and total cholesterol after a combination of 60-min running sessions in hypoxic conditions (FiO_2 = 13.6%) and permenant residence in the same hypoxic environment, conducted over 4 weeks. Therefore, perhaps the increased physical workload, regardless of the conditions the animal models were in, led to improvements in cardio-metabolic health and reductions in weight. Notably, HDL cholesterol was reduced in the hypoxic group (37), presenting a negative effect of active hypoxic exposure, as HDL cholesterol is deemed as 'good'

392 cholesterol (17). The change in HDL levels may be a reflection in the overall reduction in

393 total cholesterol. Therefore, this may have led to a reduction in HDL and LDL, but with the

394 maintenance of relative concentrations and HDL:LDL ratio.

395   The remaining two combined normoxic active periods and passive HC studies

396 included in this review, which measured weight pre- and post-intervention, reported similar

397 findings. Both Chen et al. (6) and Wu et al. (79) implemented identical protocols consisting

398 of daily 90-min swimming sessions in normoxic conditions followed by passive HC (FiO_2 =

399 14.0%, sustained for 8-h per day). Both studies found greater body weight attenuation of the

400 obese animal models, in comparison to the increase in the control group (no passive and

401 active exposure). Further, weight did not change in the group who completed exercise in

402 normoxic conditions without passive HC (6, 79). These findings suggest that a combination

403 of passive and active HC is possibly more beneficial for weight control than a matched

404 workload in normoxia. To date, however, the mechanisms that induce this response remain

405 unclear (28). Possible increases in daily metabolic rate of only those in the hypoxic groups,

406 causing a negative energy balance, may have occurred. Or perhaps appetite was surpressed

407 through increased leptin concentrations, resulting in a reduced calorie intake. However,

408 neither of these reponses were assessed in these investigations.

409

410   *4.2.* Human studies

411   *4.2.1. Passive hypoxic exposure*

412   **Table 3 presents the overall findings of the human studies included in this**

413 **review.** Only two studies included in this review have implemented passive HC in humans.

414 Blood pressure remained unchanged following acute (single 3-h session) and short-term (3-h

415 session per day for 7 days) exposure to a SpO_2 of ~80% (77). Additionally, unchanged body

416 weights occurred following daily HC (1 h) for 4 weeks to severe (FiO_2 = 12.0%) and

16

417   moderate (FiO_2 = 15.0%) hypoxia (69). However, the participants included in these studies

418   had a healthy BMI (22–27 $kg.m^2$), yet deemed as sedentary, which may explain the

419   ineffective treatment on blood pressure and body weight. Moreover, it could be suggested

420   that the participant cohort in these studies (69, 77) required a more severe level of hypoxia to

421   elicit positive responses. In support of this, recent reviews (50, 67) have indicated a linear

422   continuum between no additive effect and a deleterious effect with HC that is dependent on

423   the severity of the hypoxic stimulus. Therefore, previously employed passive HC protocols in

424   humans may not be beneficial to improve cardio-metabolic health (reduce blood pressure) or

425   lose weight.

426   In their study, Workman & Basset (77) assessed metabolic responses, via a 30-min

427   metabolic rate determination test pre- and post-intervention. They found increases in energy

428   expenditure following acute (+16%) and short-term (+12%) HC, as did lipid metabolism

429   (+44% and +29%, respectively); whereas, glycogen metabolism decreased (-31% and -49%,

430   respectively). Collectively, these findings suggest that passive HC may be an effective

431   modality to induce a shift in fuel utilisation and expend a greater quantity of lipid-based

432   energy stores. Over a longer duration, this may lead to a substantially consistent negative

433   energy balance which may promote measurable weight loss. To date, such a protocol has not

434   been employed in an obese human population.

435   *Table 3 near here*

436

437   *4.2.2. Active hypoxic exposure*

438   Metabolic responses have been assessed following active HC (60–90-min moderate-

439   intensity cardiovascular activity, 3 sessions per week, 4–6 weeks, FiO_2 = 15.0%) in obese

440   humans. Netzer et al. (51) reported greater enhancements in triglycerides, total cholesterol

441   and HDL in those whom completed 8 weeks training for 90-min at 60% of HR_{max} in hypoxic

442 *versus* normoxic conditions. In other studies, no change has been found in both the hypoxic

443 and normoxic groups for triglycerides, total cholesterol and HDL following a similar exercise

444 intensity range and duration over 4 weeks (46, 76). Morishima et al. (46) also reported that

445 glucose concentrations decreased in both the hypoxic (-8%) and normoxic (-7%) group over

446 the course of the intervention. These findings are interesting as all intervention groups

447 exercised under the same hypoxic level and completed the same type of exercise at an

448 'absolute' intensity, i.e. an intensity regardless of the environmental condition. Consequently,

449 differences in findings may have been related primarily to the total duration of the studies (8

450 [51] *versus* 4 weeks [46, 76]). Therefore, it appears that further improvements in metabolic

451 markers such as triglycerides, total cholesterol and HDL with HC would require an

452 intervention of more than 4 weeks in duration for positive effects.

453 In two studies, fasting insulin reductions have been found in both hypoxic (FiO_2 =

454 15.0%) and normoxic exercise (60 mins, moderate intensity, 3 times per week, for 4 weeks)

455 groups over the course of an intervention (hypoxia: -37%, normoxia: -33% [76]; hypoxia: -

456 22%, normoxia: -36% [46]). Although not significant, baseline assessment in both studies of

457 insulin concentrations were ~2 arbitary units larger in the hypoxic compared to normoxic

458 group. Therefore, this may explain the insignificant effect of the hypoxic stimulus as those in

459 the control group started the intervention at a lower concentration. Additional consideration

460 of other hormonal markers, such as growth horomone and insulin-like growth factor, that

461 may further lead to enhancements of potential weight loss through promotion of mechanistic

462 responses (60) warrant further investigation.

463 Hypertension is extremely prevelant in obese populations, causing an increased strain

464 on an already laboured cardiovascular system (33). Kong et al. (32) implemented

465 cardiovascular- and strength-based exercise in an obese population and found significant

466 improvements of systolic (-8%) and diastolic (-7%) blood pressure after 4 weeks of 22 h of

467 exercise per week in the hypoxic group. Notably, their hypoxic group participants completed

468 6 h of the weekly training schedule (type of exercise session unknown) in a hypoxic

469 environment, with the remainder carried out in normoxic conditions. Whereas, those who

470 carried out all of the 22 h training load in normoxic conditions had less improvement in

471 systolic (-3%) and diastolic (-1%) blood pressures. Compared to the normoxic group,

472 Wiesner et al. (76) also reported a similar reduction in systolic (-2% *versus* -2%) but greater

473 reduction in diastolic (-4% *versus* -1%) blood pressures in the hypoxic group over a similar

474 duration of 4 weeks, yet with a reduced volume of exercise (180 min per week). All in all,

475 active HC demonstrates more supportive evidence for improved blood pressure responses

476 compared to active normoxic periods. That said, a previous review (62) concluded significant

477 benefits to blood pressure values following active HC compared to normoxic conditions in

478 those with various cardiovascular diseases, including normalisation and 3 month maintenance

479 of stage 1 hypertensive patients (39). It could also be suggested that multiple combinations of

480 exercise (cardiovascular and strength) carried out in hypoxic conditions are more beneficial

481 than cardiovascular exercise alone to reduce blood pressure in obese populations. This is

482 supported by the findings of Kong et al. (32), perhaps through enhanced vascular endothelial

483 growth factor transcription leading to improved human vasculature control and capillary

484 action (82).

485   Reductions in heart rate, for a given exercise workload, have been observed for both

486 hypoxic (-18%) and normoxic (-20%) groups post-intervention (32), yet only statistically

487 significant in the normoxic group. In other studies, no change in heart rate during an exercise

488 test before and after the intervention period was found in the hypoxic or normoxic group (46,

489 76) – although lactate accumulation was reduced in both intervention groups (hypoxic: -11%,

490 normoxic: -13% [76]). It could be suggested that due to obese humans having a lower

491 baseline fitness level compared to athletic and healthy populations, it is likely that any form

492 of training will lead to an improved recovery response, via assessment of heart rate.

493 Arguably, adding in an additional stimulus such as hypoxia likely reduces the potential of an

494 increased recovery, and therefore, be less beneficial than the same workload in normoxic

495 conditions.

496 Kong et al. (32) showed non-significant reductions in BMI (-6%) and weight (-7%) of

497 the hypoxic group, however, obese humans in the normoxic group also showed non-

498 significant weight loss post-intervention (-4%). Netzer et al. (51) reported non-significant

499 reductions in weight and BMI in the hypoxic group, however, this did not occur in the

500 normoxic group. In another study, no change was found in BMI and fat mass following both

501 the hypoxic ($FiO_2 = 15.0\%$) and normoxic intervention (moderate-intensity cycling, 3 times

502 per week, 4 weeks), but the normoxic group did lose slightly more weight after the

503 intervention compared to those in the hypoxic group (-1% *versus* -0.5%, respectively [46]).

504 Overall, reductions in weight, BMI and individual tissue mass are found following active HC

505 (moderate-intensity cardio-based exercise, 3 sessions per week, 4–8 week duration). This also

506 occurs without hypoxia but to a lesser extent. Non-significant improvements in these studies

507 may be strengthed if the small participant cohorts (~10 individuals per group) were increased

508 to permit a greater effect size. Alternatively, it could be considered that participants became

509 acclimatised to the hypoxic level ($FiO_2 = 15.0\%$), which was consistently maintained

510 throughout the whole intervention period (4–8 weeks). This could have lead to a rapid plateau

511 of adaptations in body composition as the absence of periodisation may not perpetuate

512 beneficial gains.

513

514   *4.2.3. Combined passive and active hypoxic exposure*

515 Gatterer et al. (18) employed a 90-min moderate intensity (65–70% HR_{max})

516 cardiovascular-based active HC ($FiO_2 = 14.0\%$) and a 90-min period of passive HC ($FiO_2 =$

517 12.0%) twice per week, for 8 months in obese males and females. After 5 weeks, similar

518 changes in both hypoxic and normoxic groups were reported for body weight (-2% and -1%)

519 and fat mass (+1% and -1%). After 3 months, these responses were futher improved in

520 comparison to the baseline assessment in the hypoxic (body weight: -4%, fat mass: -1%) as

521 well as normoxic (body weight: -3%, fat mass: -2%) group. Additionally, similar reductions

522 were found in both hypoxic and normoxic groups for values of systolic (-3% and -2%) and

523 diastolic blood pressure (-3% and -3%). Following completion of the 8 month intervention

524 period, those in the hypoxic group displayed reductions in fat mass (-1%) and blood pressure

525 (systolic: -4%, diastolic: -2%). However, similar responses were found in the normoxic group

526 (fat mass: -2%; systolic blood pressure: -6%; diastolic blood pressure: -5%). Interestingly,

527 body weight was equally reduced in both groups (-3%) post-intervention. In the only

528 available study, it seems that a combination of both passive and active HC has no added

529 benefit compared to a matched workload in normoxic conditions on weight loss and cardio-

530 metabolic responses assessed here. The main explantion would be that unaltered stimuli (i.e.,

531 hypoxic level, exercise intensity/duration) throughout the intervention lead to a near plateau

532 in most measures assessed over this 8 month period.

533

534 **5. Additional considerations**

535 At present, it is difficult to affirm that overall fitness is improved following active HC

536 *versus* similar exercise training in normoxia of obese populations. Exercise performance in an

537 obese population, assessed via total running distance over the course of a 4-week

538 intervention, showed a tendency of being higher in the hypoxic compared to the normoxic

539 group (+18% [32]). In contrast, workload during hypoxic in reference to normoxic sessions in

540 other studies was typically lower (-17.5% [76], -20% [46]). When exercising in hypoxia,

541 exercise may be perceived as 'harder' (majored internal load as evidenced by higher heart

rate, rating of perceived exertion or blood lactate values) *versus* a matched workload in normoxia, leading to a reduced total workload. Therefore, it may be that obese humans require multiple exercise modalities to continue exercising at a clamped intensity and complete a greater total workload.

Cardiorespiratory fitness (VO_{2max}) is a key determinant of morbidity and mortality (74). Following active HC (60-mins cardiovascular-based exercise, 55–65% VO_{2max}, 3 times per week, for 4 weeks) non-significant increases in this determinant have been reported (46, 76). However, these enhancements were visible in both the hypoxic and normoxic exercise groups (+5.6% *versus* +3.1% [76], +12.6% *versus* +8.7% [46]; hypoxia *versus* normoxia, respectively). Taken as a whole, this could indicate that the mode of exercise is primarily responsible for gains (i.e., not the addition of the hypoxic stimulus). Undoubtedly, detection of adaptations to the intervention is paramount to select training intensity, modality and duration for successful interventions in obese populations. One may argue that the studies included in the present review have primarily implemented exercise performance tests that are overly challenging for obese populations, due to the requirement of exercising to volitional exhaustion (46, 76). Other sea-level training studies of obese populations have incorporated a 10-m walk test (23), a 6-minute step test (5) and a 6-minute walk test (27) to assess post-intervention changes in aerobic exercise performance. To date, the inclusion of such performance tests is lacking in the field of HC.

Other than one study which utilised a fixed SpO_2 (77), all studies presented in this review have implemented a fixed FiO_2 during exposure to hypoxia. One potential issue, however, is that the variance in individual response to a given simulated altitude is significant. In support of this, Hamlin et al. (22) concluded that for exposure to the same hypoxic level ($FiO_2 = 10.0\%$), there is a greater inter-individual variability in the extent of arterial desaturation compared to a clamped SpO_2 of 75%. Additionally, obese humans are

567 considered as having a higher 'resistance to hypoxia' in comparison to healthy humans, and

568 thereby a delayed/minimal desaturation (or SpO_2 decrease) when exposed to low hypoxic

569 doses ($FiO_2 \leq 12.0\%$ [54]). To negate this, implementing fixed SpO_2 values may minimise the

570 number of 'non-responding' participants to a given hypoxic stimulus. Costalat et al. (8)

571 recently investigated individualised intermittent passive exposure to hypoxia (SpO_2 ~80%),

572 including normoxia phases (re-oxygenation to ~95%), in overweight and obese individuals.

573 However, this investigation was not included in this review due to a lack of a

574 control/normoxic condition.

575

576 **6. Perspectives and significance**

577 **Multiple reviews investigating the effects of reduced inspired O_2 levels on those**

578 **whom are obese and/or overweight have been published within the last decade.**

579 **However, our paper is the first to highlight the beneficial effects of passive and active**

580 **HC in both obese animals and humans on a variety of physiological, metabolic,**

581 **hormonal and cardiovascular responses. These novel findings may be pivotal in**

582 **improving the health and well being of these individuals. The rapid development of HC**

583 **devices offers significant potential for real-world application as a therapeutic, cost-**

584 **effective and accessible treatment.**

585

586 **7. Where next?**

587 Due to the consideration of HC as a treatment for obesity being relatively new, there

588 are many avenues for future mechanistic and performance-led research to be conducted to

589 improve cardio-metabolic health and promote weight loss.

590

591 *7.1. Exercise intensity*

23

592   A number of studies in this review mention a reduced workload of participants

593   carrying out moderate-intensity, continuous exercise in hypoxia compared to those in

594   normoxia (46, 76), which has also been proposed elsewhere when clamping the metabolic

595   demand (20). It would be interesting to investigate whether the cardio-metabolic responses of

596   obese populations are significantly different between relative and absolute exercise intensities

597   using direct comparisons (i.e., same participants), which may inform which exercise intensity

598   is more suitable for setting training goals in this population. For example, cycling at 100

599   watts in hypoxic conditions will create a greater physiological strain (increased heart rate,

600   cardiac output) on the human body compared to the same absolute intensity in normoxic

601   conditions; thus inducing a higher internal (physiological) load for a matched external (power

602   output) load. When cycling at a similar relative intensity, the internal load most likely will be

603   reduced during hypoxia to match the external load of exercising in normoxia, as

604   demonstrated by Wiesner et al. (76). Further research of this area is required to validate this

605   claim and differentiate the effect of adding hypoxia in comparison to the effect of exercising

606   at different intensities. **It could be that, clamping the metabolic demand (i.e., working at a**

607   **given relative exercise intensity in hypoxia *versus* normoxia) may be beneficial for obese**

608   **populations. Arguably, the muscoskeletal system load is likely reduced in O_2-deprived**

609   **environments and thereby could prevent further damage to joints, tendons and ligamets**

610   **during locomotor activities (e.g., outdoor or treadmill walking).**

611   In line with current American College of Sports Medicine (12) and UK National

612   Health Service recommendations (49), the reviewed literature here suggests that a moderate-

613   intensity, continuous exercise training programme (60–75% HR_{max} for 60–90-min, 3 times

614   per week) is the recommended method to achieve weight loss. However, a growing body of

615   literature is indicating that implementation of high-intensity intermittent exercise (3–5 sets of

616   high-intensity exercise periods at 75–95% HR_{max} for 2–5 min interspersed with shorter

recovery periods of 2–3 min) in obese populations is beneficial (19, 54, 75). Not only is this form of exercise more time- and metabolically-efficient (36), but also would be more beneficial for weight loss compared to moderate-intensity during normoxia (9, 60, 83). In prescribing such exercise, a careful manipulation of work :rest ratios depending on the aim of the session (aerobically *versus* anaerobically-based responses) is needed.

7.2. *Psychological aspect of weight loss*

A large, and often underestimated, factor in achieving weight loss is related to psychological behaviours. Exercising regularly requires motivation and enjoyment to maintain adherence (31). At present, pleasure-displeasure responses of healthy populations exercising at a high-intensity in normoxic conditions are varied with both positive affects (43) and negative moods (48) reported. To our knowledge, this type of investigation does not exist during and following HC of obese humans. Implementing such affect-perceptual measurements would significantly aid levels of adherence to achieve weight loss through long-term interventions. **Interestingly, Ekkekakis & Linds (14) concluded that enjoyment was reduced when obese populations had an imposed exercise intensity 10% greater than a self-selected speed. It remains to be verified whether implementation of self-selected speeds during shorter work periods in hypoxia would be more applicable in an obese population, as previously reported (14, 25).**

7.3. *Differences within obese populations*

Although this review is focused on the treatment of obese (BMI: 30–38 kg.m^2) populations, some studies have been included with participant groups of overweight and sedentary animals and humans, with a large majority of evidence derived from obese animal findings. Further comparative research is warranted to investigate the responses of different

642 stages of obese populations (e.g., I, II and III [10]), males *versus* females, and young *versus*

643 older populations with or without associated complications (i.e., pre-diabetes).

644

645   **7.4.** *Experimental considerations*

646   Finally, determining the extent of metabolic stress associated with HC for inducing

647 clinically relevant (>3%) weight losses (66) should be a key focus area. Arguably, many

648 confounding variables likely affect determination of the optimal dose-response during HC,

649 such as food consumption, in the lead up to and following the completion of sessions. If these

650 were to be controlled, and short-term (single session) cardio-metabolic responses were to be

651 assessed in obese populations, it will be possible to implement the 'optimal' exposure

652 protocol (i.e., most beneficial dose, duration and intensity) for long-term improvements in

653 cardio-metabolic health and weight loss, as proposed recently by Serebrovskaya et al. (62).

654 Additional consideration of potential drawbacks associated with HC, such as onset of

655 obstructive sleep apnoea and acute mountain sickness, should be made to increase the

656 possibility of developing optimal passive and active HC protocols.

657

658 **8. A summary of passive and active HC protocols**

659   **Table 4 states a summary of passive and active HC protocols in relation to the**

660 **literature presented in this review for improving cardio-metabolic health and**

661 **promoting weight loss in obese humans. HC-induced physiological, metabolic,**

662 **cardiovascular and hormonal responses are undoubtedly highly individual.**

663 **Importantly, all of the animal models and human participant cohorts included here**

664 **were free from associated cardio-metabolic complications. In reality, this may not**

665 **always be the case. Therefore, we recommend full general practitioner clearance to be**

666 **obtained from prior to undertaking any HC, similar to the process of beginning any**

physical activity programme/dietary intervention. Positive outcomes would also likely depend on the level of hypoxia employed and careful manipulation of key variables structuring the HC routine (e.g., number of cycles, duration, intensity, mode of exercise and/or periodisation). Importantly, this summary should be interpreted with caution and seenas a starting point only, as it is based upon the findings of a small amount of evidence (passive: 7 studies; active: 8 studies). We therefore encourage clinicians and researchers to refine them to reach a consensus.

Table 4 near here

9. Conclusions

The findings of this review in obese populations suggest that a) passive HC could lead to reduced insulin concentrations (-37 – -22%) in animals and increased energy expenditure (+12 – +16%) in humans, while active HC may reduce body weight (-4 – -2%) in both animals and humans as well as blood pressure (-8 – -3%) in humans; b) inconsistent findings and limited understanding still exist for determining the impact of acute and chronic HC on markers such as triglycerides, cholesterol levels and fitness capacity; and c) a large majority of studies include animal models exposed to severe levels of hypoxia (FiO_2 = ~5.0%) that are not suitable for obese humans. Also, published findings, at present, do not clearly show changes in responses of heart rate, fat and muscle mass following HC being significantly larger than a matched exposure and/or exercise period in normoxic conditions. Nevertheless, the promising findings need larger cohorts, more mechanistic measures and real-world applications of findings to improve the potential clinical impact of this novel intervention. Finally, the industrial and technological advancement, including miniaturised equipment for home use and accessibility to environmental chambers, will certainly contribute to the expansion in the use of these methods.

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954

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958

959 **Figure caption**

960 Fig. 1: Flow chart of literature search results; OSA = obstructive sleep apnoea.

961 **Table 1:** Experimental details of studies included in this review that have investigated passive and active hypoxic conditioning.

Study	Participants				Groups	Exposure type	Approach	Intervention			
	Type	Age	Gender	BMI (kg.m²)				Protocol	Mode	Duration	Level of hypoxia (FiO₂ %)
Briancon-Marjollet et al. (2016)	Zucker rats	9 w	48 M	NM	Obese hypoxia (n = 12)	Passive	N/a	Intermittent (30 s :30 s) 8 h.d	N/a	2 w	5.0
					Lean hypoxia (n = 12)						
					Obese control (n = 12)			N/a			N/a
					Lean control (n = 12)						
Chen et al. (2011)	Zucker rats	14 w	56 M	NM	Obese exercise (n = 7)	Active		90 mins daily exercise	Swimming		N/a
					Lean exercise (n = 7)						
					Obese hypoxia (n = 7)	Passive		Sustained 8 h.d	N/a		14
					Lean hypoxia (n = 7)						
					Obese exercise and hypoxia (n = 7)	Active	LHTL	90 mins daily exercise sustained 8 h.d	Swimming	6 w	20.9, 14.0
					Lean exercise and hypoxia (n = 7)						
					Obese controls (n = 7)	N/a		N/a	N/a		N/a
					Lean controls (n = 7)						
Gatterer et al. (2015)	Humans	51.4 y	22 F, 10 M	37.1	Hypoxia (n = 16)	Combined	LLTH	90 mins moderate (65-70% HR$_{max}$) intensity exercise, 90 mins **rest**	Cycling, running, cross trainer	2x w, 8 m	14.0, 12.0
					Control (n = 16)						N/a
Kong et al. (2013)	Humans	21.1 y	8 F, 10 M	34.3	Hypoxia (n = 10)	Active	LLTH	Moderate (60-70% HR$_{max}$) intensity exercise, strength (40-50% 1 rep max, 3 sets of 15 reps, 2 – 3 min rest periods) training	Running, stepping, cycling, strength exercising	22 h w, 4 w	15.0
					Control (n = 8)						N/a
Ling et al. (2008)	Kunming mice	NM	80 F	NM	Hypoxia-normal diet (n = 20)	Passive	N/a	Intermittent (15 min :5 – 10 min)	N/a	8x d, 40 d	14.3
					Hypoxia-fatty diet (n = 20)						
					Control-normal diet (n = 20)			N/a			N/a

Study	Species	Age	Number	BMI	Group (n)	Exercise	Hypoxia	Description	Mode	Duration	%
					Control-fatty diet (n = 20)						
Lu et al. (2014)	Sprague Dawley rats	3 w	20 M	NM	Hypoxia (n = 10)	Combined	LHTH	1 h exercise 6 d.w, lived in hypoxia	Running	4 w	13.6
					Control (n = 10)	N/a		N/a	N/a		N/a
Morishima et al. (2014)	Humans	31y	20M	NM	Hypoxia (n = 9)	Active	LLTH	60 mins moderate (55 % VO_{2max}) intensity cycling	Cycling	3x w, 4 w	15.0
					Control (n = 11)						N/a
Netzer et al. (2008)	Humans	47.8 y	10 F, 22 M	33.1	Hypoxia (n = 10)	Active	LLTH	90 mins moderate (60% HR_{max}) exercise	Stepping, running, cycling	3x w, 8 w	15.0
					Control (n = 10)						N/a
Olea et al. (2014)	Wister rats	24 w	160 M	NM	Hypoxia obese (n = 40) Hypoxia control (n = 40)	Passive	N/a	Intermittent (40s :80 s) 8 h.d	N/a	2 w	5.0
					Obese (n = 40) Control (n = 40)	N/a		N/a			N/a
Polotsky et al. (2003)	Mice	NM	74 M	NM	Obese short-term hypoxia (n = 15) Lean short-term hypoxia (n = 16)	Passive		Intermittent (30 s :30 s) 16 h.d		5 d	4.8-5.0
					Obese long-term hypoxia (n = 7)		N/a	Intermittent (30 s:30 s) 12 h.d	N/a	12 w	
					Lean short-term controls (n = 15) Obese short-term controls (n = 14) Controls (n = 7)	N/a		N/a		5 d	N/a
Rodriguez et al. (2014)	Mice	10 w	82 M	NM	Obese hypoxia (n = 10) Lean hypoxia (n = 11)	Passive		Intermittent (30 s:30 s) 12 h.d			5.0
					Obese controls (n = 10) Lean controls (n = 11)	N/a	N/a	N/a	N/a	4 w	N/a
					Obese hypoxia (n = 9) Lean hypoxia (n = 10)	Passive		Sustained 24 h.d			10

Study	Species	Age	Sex	BMI	Group		Passive/Active	Protocol	Training	Exercise mode	Frequency/Duration	FiO2
					Obese controls (n = 10)		N/a		N/a			N/a
					Lean controls (n = 11)							
Wang et al. (2007)	Humans	24 y	30 M	22.2	Severe hypoxia (n = 10)		Passive	N/a	Sustained 1 h.d	N/a	4 w	12.0
					Moderate hypoxia (n = 10)							15.0
					Control (n = 10)		N/a		N/a			N/a
Wiesner et al. (2009)	Humans	42.2 y	27 F, 18 M	30	Hypoxia (n = 24)		Active	LLTH	60 mins moderate (65% VO$_{2max}$) intensity running	Running	3x w, 4 w	15.0
					Control (n = 21)							N/a
Workman & Basset (2012)	Humans	28 y	15 M	27	Acute hypoxia (n = 11)		Passive	N/a	Sustained 3 h	N/a	1d	Target SpO2: 80%
					Short-term hypoxia (n = 6)						1x d, 1 w	
					Control (n = 4)		N/a		N/a		N/a	N/a
Wu et al. (2013)	Zucker rats	14 w	56 M	NM	Obese exercise (n = 7)		Active	LHTL	90 mins daily swimming	Swimming		N/a
					Lean exercise (n = 7)							
					Obese hypoxia (n = 7)		Passive		Sustained 8 h.d	N/a		14
					Lean hypoxia (n = 7)							
					Obese exercise and hypoxia (n = 7)		Active		90 mins daily swimming, sustained 8 h.d	Swimming	6 w	20.9, 14.0
					Lean exercise and hypoxia (n = 7)							
					Obese controls (n = 7)		N/a		N/a	N/a		N/a
					Lean controls (n = 7)							

BMI = body mass index; d = day(s); F = female(s); FiO$_2$ = fraction of inspired oxygen; h = hour(s); HR$_{max}$ = heart rate maximum; LHTH = live-high train-high; LHTL = live-high train-low; LLTH = live-low train-high; M = male(s); mins = minutes; m = months; n = number; N/a = not applicable; NM = not measured; rep max = repetition maximum; s = seconds; VO$_{2max}$ = maximal oxygen uptake; w = week(s); y = years.

Table 2: A summary of the findings for animal studies included in this review.

Study	Condition	Glucose	Insulin	Cholesterol	HDL	LDL	Triglycerides	Leptin	BP	Body weight
Briancon-Marjollet et al. (2016)	Obese hypoxia	↑	→	→				↑		
	Lean hypoxia			→				↑		
	Obese control			→				↑		
	Lean control			→				↑		
Chen et al. (2011)	Obese exercise									→
	Obese exercise and hypoxia	↓	↓							→
	Obese controls									↑
Ling et al. (2008)	Hypoxia-normal diet	↓		↓						
	Hypoxia-fatty diet							↑		↑
	Control-normal diet			↓						
	Control-fatty diet									↑
Lu et al. (2014)	Hypoxia			↓		↓	↓			↓
	Control				↓					
Olea et al. (2014)	Hypoxia obese	→	→	↑			↑	↑	↑	
	Hypoxia control			↑				↑		
	Obese						↑	↑	↑	
	Control							↑		
Polotsky et al. (2003)	Obese short-term hypoxia	↓	↑							→
	Lean short-term hypoxia									→
	Obese long-term hypoxia	→	↑							→
	Lean short-term control									→
	Obese short-term control									→
	Control									→
Rodriguez et al. (2014)	Obese hypoxia									↑
	Lean hypoxia									↑
Wu et al. (2013)	Obese exercise	↓								→
	Obese exercise and hypoxia	↓	↓							→
	Obese control									↑

BP = blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; ↑ = increase; ↓ = decrease; → = maintenance.

Table 3: A summary of the findings for human studies included in this review.

Study	Condition	Glucose	Insulin	Cholesterol	HDL	Triglycerides	EE	Lipid metabolism	Glycogen metabolism	HR	BP	La⁺	BMI	Body weight
Gatterer et al. (2015)	Hypoxia					↓					↓			↓
	Control					↓					↓			↓
Kong et al. (2013)	Hypoxia									↓	↓		↓	↓
	Control									↓	↓		↓	↓
Morishima et al. (2014)	Hypoxia	↓	↓	→	→	→				→			→	
	Control	↓	↓	→	→	→				→			→	↓
Netzer et al. (2008)	Hypoxia			↑	↑	↑							↓	↓
Wang et al. (2007)	Severe hypoxa										→			
Wiesner et al. (2009)	Hypoxia		↓	→	→	→				→	↓	↓		→
	Control		↓	→	→	→				→	↓	↓		
Workman & Basset (2012)	Acute hypoxia						↑	↑	↓		→			→
	Short-term hypoxia						↑	↑	↓					

BMI = body mass index; BP = blood pressure; EE = energy expenditure; HDL = high-density lipoprotein cholesterol; HR = heart rate; La⁺ = lactate accumulation; ↑ = increase; ↓ = decrease; → = maintenance.

Table 4: A summary of the passive and active hypoxic conditioning protocols for improving cardio-metabolic health and promoting weight loss of overweight or obese humans, based on the evidence presented in this review.

Variable	Type of exposure	
	Passive	**Active**
Level of hypoxia (FiO$_2$%)	10.0–12.0	13.0–14.0
Number of cycles	5–15	N/a
Intensity	N/a	55–65% VO2$_{max}$ / 60–70% HR$_{max}$
Duration (hours)	1–1.5	1–1.5
Frequency	Daily	2–3 times per week
Periodisation (weeks)	2–4	4–6

FiO$_2$ = fraction of inspired oxygen; HR = heart rate; N/a = not applicable; VO$_{2max}$ = maximal oxygen uptake.