Kunutsor, S. K., Kurl, S., & Laukkanen, J. A. (2017). Association of oxygen uptake at ventilatory threshold with risk of incident hypertension: a long-term prospective cohort study. *Journal of Human Hypertension*. https://doi.org/10.1038/jhh.2017.39

RESEARCH LETTER

Association of oxygen uptake at ventilatory threshold with risk of incident hypertension: A long-term prospective cohort study

Running title: Anaerobic threshold and incident hypertension

Setor K. Kunutsor[1], Sudhir Kurl[2], Jari A. Laukkanen[2,3]

[1]School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, UK; skk31@cantab.net

[2]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

[3]Central Finland Central Hospital, Internal Medicine, Jyväskylä, Finland

Corresponding author: Setor K. Kunutsor, School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, BS10 5NB, UK. Phone: +447539589186; Fax: +441174147924; Email address: skk31@cantab.net

Peak oxygen uptake (peak VO_2) has been suggested as a causal risk factor for future hypertension. Oxygen uptake at ventilatory threshold (VO_2 at VT), is a proxy for peak VO_2, but its relationship with incident hypertension has not been previously investigated. VO_2 at VT was determined at baseline during submaximal exercise testing using respiratory gas analyzers in the Kuopio Ischemic Heart Disease cohort of 1,360 middle-aged men without hypertension, and its relationship with incident hypertension risk was assessed. During a median follow-up of 25.1 years, there were 217 incident cases of new onset hypertension. This study suggested that in middle-aged Caucasian men, VO2 at VT is inversely associated with future risk of hypertension.

Peak oxygen uptake (VO_2), a measure of cardiorespiratory fitness (CRF), is considered the gold standard index of aerobic capacity.[1] Peak VO_2 has been consistently shown to be inversely and independently associated with incident cardiovascular disease (CVD) as well as CVD mortality.[2, 3] Emerging evidence from large-scale epidemiological cohorts also demonstrate peak VO_2 to be consistently associated with future hypertension risk and it has been suggested to be a causal risk factor.[4, 5] Hypertension is an established risk factor for CVD and is included in the standard cardiovascular risk assessment panel.[6] Oxygen uptake at ventilatory threshold (VO_2 at VT), another cardiopulmonary exercise testing (CPX) parameter and often referred to as the anaerobic threshold, is assessed at submaximal levels of CPX.[7] VO_2 at VT is considered as a measure of cardiovascular fitness and a reliable index of aerobic capacity,[1] and has been suggested to be protective of fatal cardiovascular outcomes as well as all-cause mortality.[8] Previous findings have suggested VO_2 at VT to be a suitable proxy for peak VO_2.[8] Though peak VO_2 is a gold standard measure of aerobic capacity, some individuals are unable to achieve this VO_2 level due to exercise-related limitations such as musculoskeletal problems. In such instances, VO_2 at VT, which can be assessed safely at submaximal exercise levels, may be used as a suitable replacement for the assessment of maximal VO_2. To our knowledge, the nature of the relationship between VO_2 at VT and future hypertension risk in general populations has not been previously investigated. We aimed to assess the nature and magnitude of the association between VO_2 at VT and incident hypertension using the

established Kuopio Ischemic Heart Disease (KIHD) population-based cohort comprising healthy middle-aged men from eastern Finland.

Participants in the study were men aged 42-61 years recruited into the Kuopio Ischemic Heart Disease (KIHD) study, a prospective epidemiologic study of the incidence of cardiovascular and other related outcomes among Finnish adults. The institutional review board of the University of Eastern Finland approved the study, and each participant provided written informed consent. Detailed description of blood sample collection, physical measurements, as well as measurements of covariates have been reported previously.[9] VO_2 at VT as well as peak VO_2 were assessed using a respiratory gas exchange analyzer (Medical Graphics, MCG, St. Paul, Minnesota), of which details have been reported in a recent report.[8] Incident hypertension was defined as a physician diagnosis of hypertension, systolic blood pressure (SBP) $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 90 mm Hg, or use of anti-hypertensive medication (beta-blockers, calcium channel blockers, diuretics or angiotensin-converting-enzyme inhibitor/angiotensin receptor antagonists). All physicians or evaluators who assessed follow-up events were blinded to baseline data. All BP measurements including follow-up data were measured under standardized conditions. Baseline BP measurements were assessed after a supine rest of 5-minutes and were measured three times in a supine position, once in standing position, and twice in sitting position with 5-minute intervals, and the arithmetic mean of all available measurements was taken. Incident hypertension was ascertained through record linkage to the National Hospital Discharge Registry and the Social Insurance Institution of Finland register, which contains information on the reimbursement of expenses for antihypertensive medication. There were no losses to follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

The mean age of participants at study entry was 52 [standard deviation (SD), 5] years. The baseline mean (SD) level of VO_2 at VT was 24.57 (6.13) ml/kg/min and the corresponding level as metabolic equivalent was 7.02 (1.75). There were weak to moderate inverse correlations of VO_2 at VT with several

risk markers. Significant positive correlations were observed with peak VO_2 (r = 0.90), high-density lipoprotein cholesterol (HDL-C) (r = 0.26) and physical activity (r = 0.14). Similar correlations were observed for peak VO_2 with several risk markers including HDL-C (r=0.28) and physical activity (r=0.15). During a median follow-up of 25.1 (interquartile range, 19.4-26.9) years, 217 new onset hypertension cases were recorded. The age-adjusted HR (95% CIs) per unit increase in VO_2 at VT for hypertension was 0.95 (0.93-0.97), which remained unchanged on further adjustment for systolic blood pressure, smoking status, history of diabetes mellitus, family history of hypertension, total cholesterol, HDL-C, alcohol consumption, and physical activity 0.95 (0.93-0.98VO_2 at VT was strongly and positively correlated with peak VO_2. Alternatively, comparing the top versus bottom quartile of VO_2 at VT, the corresponding age-, multivariate-, and multivariate plus peak VO_2-adjusted HRs (95% CIs) for hypertension were 0.50 (0.33-0.76), 0.51 (0.33-0.78), and 1.31 (0.66-2.60) respectively (**Table 1**). To put the strength of the association of VO_2 at VT with risk of hypertension into context, direct comparisons were made to the association of peak VO_2 with risk of hypertension. Similarly, peak VO_2 was inversely and independently associated with hypertension risk as shown in **Table 1**. This association remained significant after further adjustment for VO_2 at VT.

Based on this population-based prospective cohort study of apparently healthy middle-aged Finnish men without a history of hypertension at baseline, we have shown an inverse association between VO_2 at VT and future hypertension risk, which was independent of several established risk factors and other potential confounders; however, the association was dependent on peak VO_2. Consistent with previous findings, VO_2 at VT was strongly and positively correlated with peak VO_2 VO_2 at VT was shown to be strongly and positively correlated with peak VO_2. In contrast, an analysis in the same set of participants showed the inverse association between peak VO_2 and hypertension risk to be stronger and was also independent of VO_2 at VT; which suggests that peak VO_2 is a stronger risk indicator for hypertension risk than VO_2 at VT.

To our knowledge, no previous study has evaluated the prospective association VO_2 at VT with risk of hypertension, therefore we are unable to compare the current results with previous work. However, given that VO_2 at VT is strongly correlated with peak VO_2, with both parameters being measures of aerobic capacity;[1, 7, 10] the current results are in line with previous reports that have demonstrated peak VO_2 to be associated with the risk of developing future hypertension.[4, 5]

It has been reported that VO_2 at VT is more strongly correlated with endurance compared with peak VO_2.[11] Though there has been emerging evidence on the potential application of CPX parameters in clinical practice,[7] their use in general population settings have not been well established. VO_2 at VT can be assessed safely at submaximal exercise levels, unlike peak VO_2 which can be difficult to assess sometimes as a maximal exercise level needs to be achieved.[12] Though peak VO_2 remained the best indicator of hypertension risk, our findings do suggest that VO2 at VT could be used as a proxy marker when peak VO_2 cannot be achieved due to other limitations.

Our report is the first prospective evaluation of the association between VO_2 at VT and the risk of future hypertension. Other strengths include the well-established cohort and long-term follow-up. The assessment of VO_2 at VT during exercise test may have potential applications in clinical settings such as the detection of at risk patients. However, our results cannot be generalized to women and other populations. In addition, we could not correct for regression dilution because of absence of repeat measurements of VO_2 at VT, which could have underestimated our associations. Thus, further studies are needed to clarify the role of VO_2 at VT as a risk assessment tool for adverse cardiovascular outcomes such as hypertension.

In conclusion, VO_2 at VT is inversely associated with future risk of hypertension in middle-aged Caucasian men. The prognostic value of VO_2 at VT for future hypertension deserves further study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. *Phys Ther* 2000; **80**(8)**:** 782-807.

2. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M *et al.* Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama* 2009; **301**(19)**:** 2024-35.

3. Laukkanen JA, Makikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. *J Am Coll Cardiol* 2010; **56**(18)**:** 1476-83.

4. Jae SY, Kurl S, Franklin BA, Laukkanen JA. Changes in cardiorespiratory fitness predict incident hypertension: A population-based long-term study. *American journal of human biology : the official journal of the Human Biology Council* 2016.

5. Jae SY, Heffernan KS, Yoon ES, Park SH, Carnethon MR, Fernhall B *et al.* Temporal changes in cardiorespiratory fitness and the incidence of hypertension in initially normotensive subjects. *American journal of human biology : the official journal of the Human Biology Council* 2012; **24**(6)**:** 763-7.

6. Authors/Task Force M, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016; **23**(11)**:** NP1-NP96.

7. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF *et al.* Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; **122**(2)**:** 191-225.

8. Kunutsor SK, Kurl S, Khan H, Zaccardi F, Laukkanen JA. Associations of cardiovascular and all-cause mortality events with oxygen uptake at ventilatory threshold. *Int J Cardiol* 2017.

9. Kunutsor SK, Khan H, Laukkanen JA. gamma-Glutamyltransferase and Risk of Sudden Cardiac Death in Middle-Aged Finnish Men: A New Prospective Cohort Study. *J Am Heart Assoc* 2016; **Feb 8;5(2). pii: e002858. doi: 10.1161/JAHA.115.002858.**(2).

10. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2016; **133**(24)**:** e694-711.

11. Kumagai S, Tanaka K, Matsuura Y, Matsuzaka A, Hirakoba K, Asano K. Relationships of the anaerobic threshold with the 5 km, 10 km, and 10 mile races. *Eur J Appl Physiol Occup Physiol* 1982; **49**(1)**:** 13-23.

12. American College of Sports Medicine (ACSM). ACSM's guidelines for exercise testing and prescription. 9th ed. Philadephia, PA: Lippincott Williams & Wilkins; 2014.

Table 1. Associations of VO_2 at VT and peak VO_2 with incident hypertension

	Events / Participants	Model 1		Model 2		Model 3	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P-value*
VO_2 at VT and incident hypertension							
Per unit (ml/kg/min)	217 / 1,360	0.95 (0.93-0.97)	< 0.001	0.95 (0.93-0.98)	< 0.001	1.02 (0.96-1.07)	0.551
Per 1 MET	217 / 1,360	0.83 (0.77-0.91)	< 0.001	0.84 (0.76-0.92)	0.003	1.06 (0.88 - 1.28)	0.551
Quartile 1 (6.90-20.31)	58 / 340	1 [Reference]		1 [Reference]		1 [Reference]	
Quartile 2 (20.32-24.03)	72 / 340	1.06 (0.75-1.50)	0.748	1.01 (0.71-1.44)	0.943	1.40 (0.94-2.08)	0.101
Quartile 3 (24.04-28.35)	47 / 340	0.66 (0.45-0.97)	0.036	0.72 (0.49-1.08)	0.111	1.24 (0.75-2.07)	0.399
Quartile 4 (28.36-52.21)	40 / 340	0.50 (0.33-0.76)	0.001	0.51 (0.33-0.78)	0.002	1.31 (0.66-2.60)	0.436
P-value for trend			< 0.001		< 0.001		0.538
Peak VO_2 and incident hypertension							
Per unit (ml/kg/min)	217 / 1,360	0.95 (0.93-0.97)	< 0.001	0.95 (0.93-0.97)	< 0.001	0.94 (0.89-0.98)	0.005
Per 1 MET	217 / 1,360	0.82 (0.77-0.88)	< 0.001	0.83 (0.77-0.90)	< 0.001	0.80 (0.68-0.93)	0.005
Quartile 1 (10.25-27.43)	67 / 340	1 [Reference]		1 [Reference]		1 [Reference]	
Quartile 2 (27.44-32.22)	64 / 340	0.83 (0.59-1.17)	0.285	0.81 (0.57-1.16)	0.250	0.84 (0.57-1.24)	0.380
Quartile 3 (32.26-36.94)	51 / 340	0.58 (0.40-0.85)	0.004	0.62 (0.42-0.91)	0.014	0.66 (0.40-1.08)	0.101
Quartile 4 (36.97-65.40)	35 / 340	0.36 (0.24-0.55)	< 0.001	0.38 (0.24-0.59)	< 0.001	0.42 (0.21-0.86)	0.018
P-value for trend			< 0.0001		< 0.0001		0.022

Model 1: Adjusted for age
Model 2: Model 1 plus systolic blood pressure, smoking status, history of diabetes mellitus, family history of hypertension, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and physical activity

Model 3: Model 1 plus peak VO_2 (for VO_2 at VT) or VO_2 at VT (for peak VO_2)

VO_2 at VT, oxygen uptake at ventilatory threshold
1 MET is equivalent to 3.5 ml/kg/min of oxygen uptake at ventilatory threshold