



UNITED STATES  
DEPARTMENT OF VETERANS AFFAIRS



Ludeman Family Center for  
Women's Health Research  
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

# Subclinical Autonomic Neuropathy in Type 2 Diabetes

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## BACKGROUND

- Diabetes (DM) confers an excess risk of cardiovascular disease (CVD) and decreased cardiorespiratory fitness (CRF), a predictor of premature mortality<sup>1</sup>.
- T2D includes impaired insulin sensitivity, vasodilation, and mitochondrial function<sup>2,3</sup>. These cardiac and systemic abnormalities may contribute to impaired CRF.
- Cardiac autonomic neuropathy is a common complication of T2D that is often not detected until late in disease progression<sup>4</sup>.
- As Autonomic nervous system (ANS) fibers innervate the heart and vasculature, dysfunction impairs control of both heart rate and vascular dynamics<sup>4</sup>. This can lead to decreased heart rate variability (HRV), prolonged QT, impaired exercise tolerance, and impaired blood pressure regulation which can result in arrhythmia, myocardial ischemia, and sudden death<sup>5</sup>.

## HYPOTHESIS:

**ANS function is decreased in participants with uncomplicated T2D and correlates with cardiac measures**

## METHODS

**Participants:** Data from participants of 3 studies age 22-70, with and without uncomplicated diabetes, were included.

**RR interval with cycled breathing (HR Variation with Respiration):** Laying supine, patient breathes 5 times per minute while running continuous ECG. HR variability is calculated. Values <10 beats per minute (BPM) indicate autonomic insufficiency.

**RR variations with Valsalva (Valsalva Ratio):** RR variation calculated by dividing average tachycardic beats by average bradycardic beats. Values <1.10 indicate autonomic insufficiency.

**Postural Blood Pressure (BP)/Heart Rate (HR):** Blood pressure and pulse measured after 5 minutes resting supine and two minutes standing. A drop in systolic BP >20 mmHg or an increase in HR >20 bpm indicates autonomic insufficiency.

## REFERENCES

- Abushamat, L, et al. *J Endocr Soc.* 2020.
- Regensteiner, J and Reusch, J. *Med Sci Sports Exerc.* 2009.
- Wahl, M et al. *Front Endocrinol (Lausanne).* 2018.
- Vinik, A, et al. *Diabetes Care.* 2003.
- Verotti, A, et al. *Front Endocrinol (Lausanne).* 2014.

## RESULTS

Table 1. Baseline Characteristics

	T2D (N=53)	OWC (N=56)	p-value
Age (years)	54.2±11.84	47.7±11.4	<b>0.004</b>
Sex (% female)	36%	52%	
American Indian/Alaska Native (%)	0%	4%	
Asian (%)	6%	2%	
Black/African American (%)	19%	9%	
White (%)	70%	82%	
Hispanic (%)	13%	13%	
BMI (kg/m <sup>2</sup> )	32.4±4.6	31.2±5.2	0.21
Body Fat (%)	36.3±7.8	37.4±7.6	0.47
Systolic Blood Pressure (mmHg)	124.7±9.2	118±9.7	<b>0.0004</b>
Diastolic Blood Pressure (mmHg)	83.6±7.5	82.8±7.3	0.59
Duration of DM (years)	6.7±5.9	0±0	
Hemoglobin A1c (%)	6.8±0.8	5.3±0.3	<b>&lt;0.0001</b>
Total Cholesterol (mg/dL)	164.1±34.1	179.5±37	<b>0.03</b>
Triglycerides (mg/dL)	162.8±127.3	119±67.2	<b>0.03</b>
HDL (mg/dL)	43.8±9.8	48.3±9.7	<b>0.02</b>
LDL (mg/dL)	97.9±28.9	115.2±32.9	<b>0.005</b>
Glucose Infusion Rate (mg/kg/min) <sup>+</sup>	4.4±2.1	6.4±2.4	<b>&lt;0.001</b>

<sup>+</sup>N=41 in T2D group.

## ANS Function by Diabetes Status

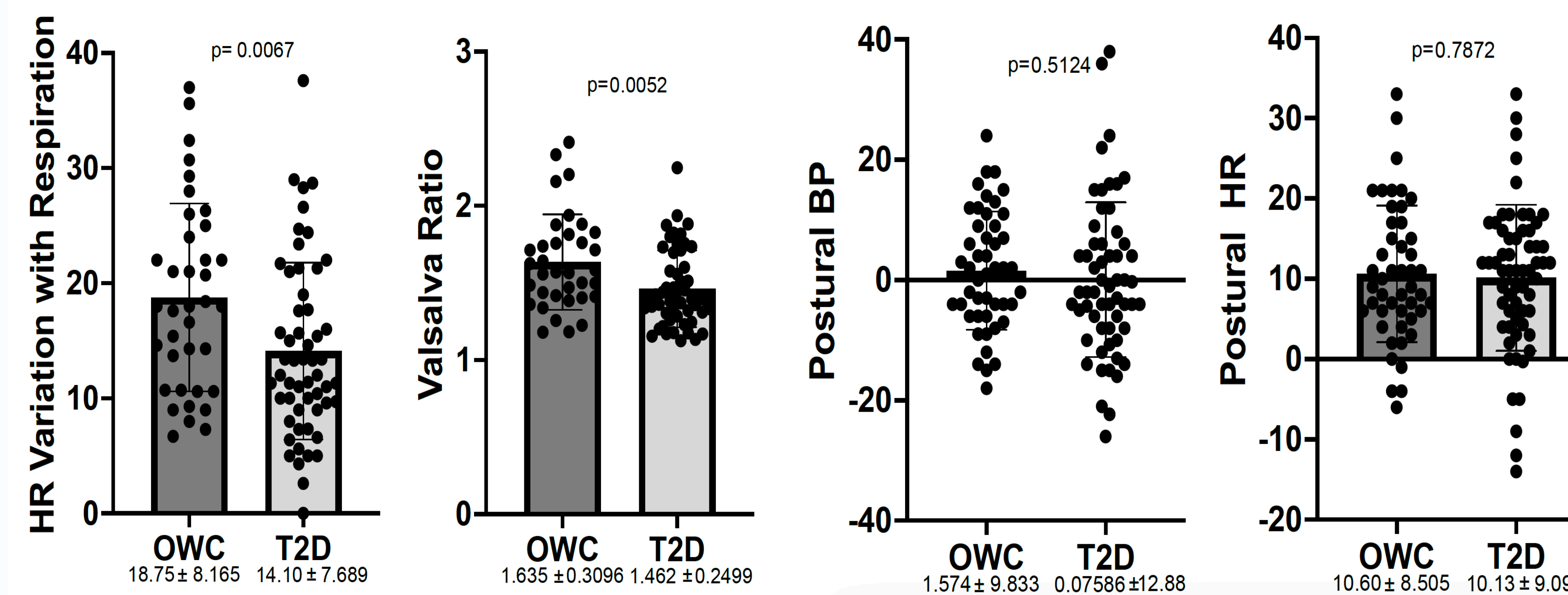


Figure 1. Data collected from participants of 3 studies combined to compare baseline ANS function measures in participants with T2D and overweight controls (OWC). Compared using a simple T-test. Mean and standard deviations listed below categories.

## ANS Function by Diabetes Status and Age

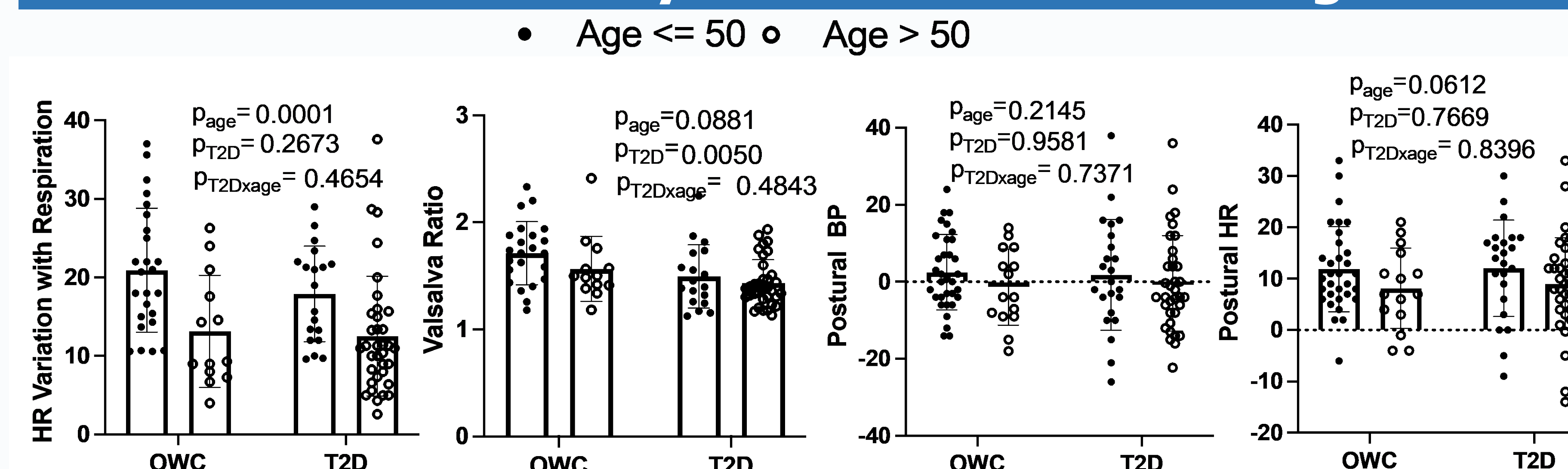


Figure 2. Data collected from participants of 3 studies combined to compare baseline ANS function measures in participants with T2D and overweight controls (OWC). Compared by age and diabetes status using 2-way ANOVA.

## ANS Function Correlation with Age

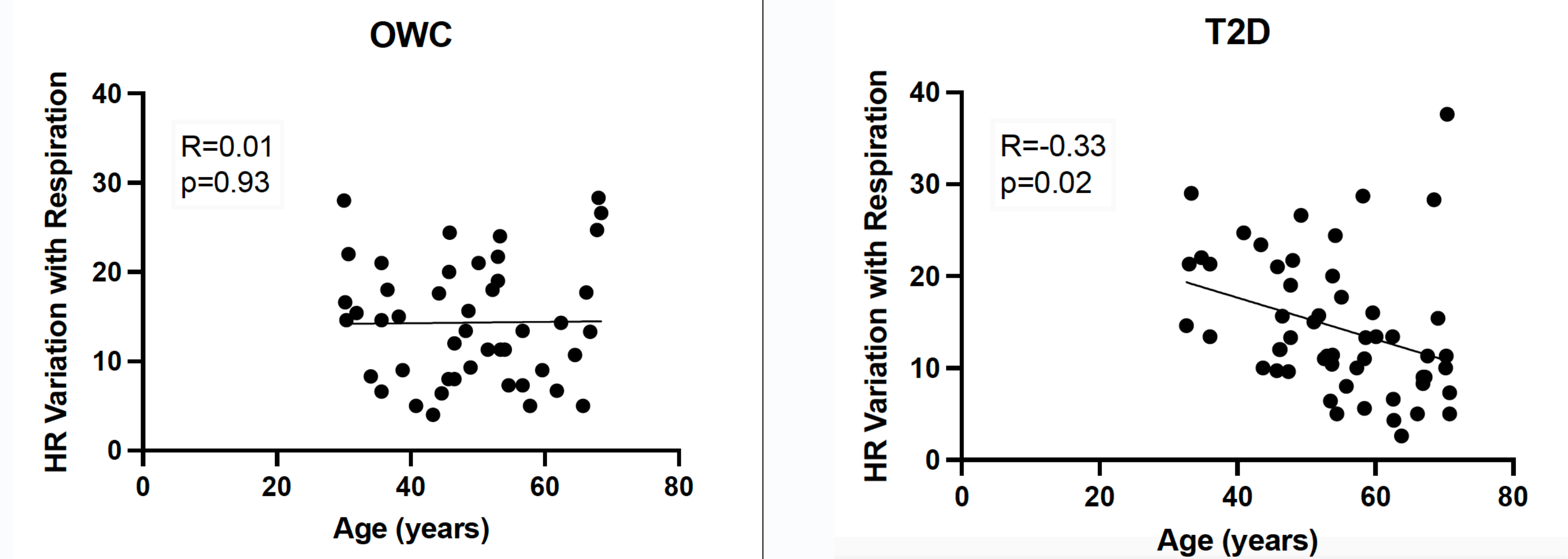


Figure 3. HR variation with respiration correlated with age using Pearson correlation coefficient.

## ANS Function Correlated with Cardiac Endpoints

	OWC				T2D			
	Valsalva Ratio	HR Variability with Respiration	Postural BP	Postural HR	Valsalva Ratio	HR Variability with Respiration	Postural BP	Postural HR
EDV (mL)	-0.29 (0.24)	-0.07 (0.77)	0.15 (0.43)	-0.14 (0.44)	<b>0.58 (0.02)</b>	0.14 (0.61)	-0.10 (0.68)	-0.03 (0.91)
Stroke Volume (mL)	-0.30 (0.22)	-0.23 (0.31)	-0.06 (0.73)	-0.005 (0.98)	<b>0.55 (0.03)</b>	0.18 (0.49)	-0.05 (0.83)	-0.29 (0.19)
Free Wall Thickness (mm)	0.1 (0.69)	-0.32 (0.16)	-0.07 (0.69)	0.01 (0.95)	<b>0.65 (0.008)</b>	0.005(0.99)	0.38 (0.09)	0.04 (0.88)
Rad. Peak strain (%)	-0.41 (0.09)	-0.10 (0.68)	-0.05 (0.80)	0.14 (0.48)	0.07 (0.81)	0.15 (0.59)	<b>-0.49 (0.03)</b>	-0.18 (0.43)
Circ. Peak Strain (%)	-0.46 (0.05)	-0.36 (0.12)	-0.02 (0.91)	0.24 (0.20)	-0.12 (0.68)	0.04 (0.88)	<b>-0.48 (0.03)</b>	-0.17 (0.45)
Longitudinal, diastolic peak SR	-0.08 (0.76)	-0.26 (0.26)	-0.20 (0.30)	-0.06 (0.76)	-0.07 (0.82)	<b>0.68 (0.007)</b>	-0.02 (0.93)	-0.21 (0.38)

Figure 4. Data collected from participants of 3 studies combined to compare baseline ANS function measures in participants with T2D and overweight controls (OWC), correlated with cardiac endpoints

## SUMMARY

- There are signals for autonomic dysfunction in people with otherwise uncomplicated diabetes
- Changes in heart rate variability are exacerbated by age in people with diabetes
- Subclinical cardiac functional changes correlate with changes in autonomic function only in people with diabetes

## CONCLUSION

**Early detection of autonomic neuropathy in the clinic may highlight the people at risk for progression of cardiac dysfunction**