Υπάρχει αντίστροφη επιδημιολογία στους παχύσαρκους και στους νεφροπαθείς;

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Chairman Working Group on Obesity, diabetes and the high risk patient
European Society Hypertension

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EUROPEAN SOCIETY HYPERTENSION

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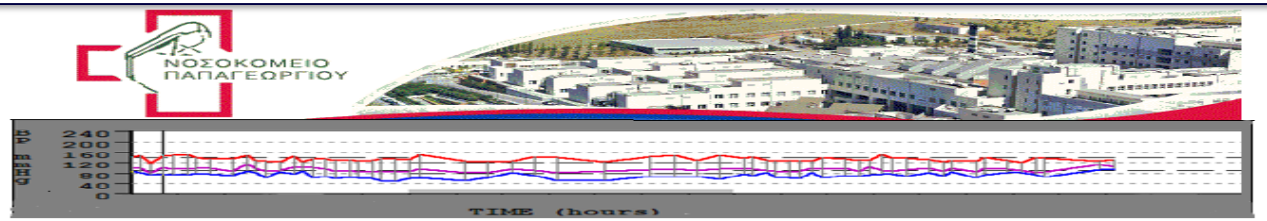

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Obesity in Europe

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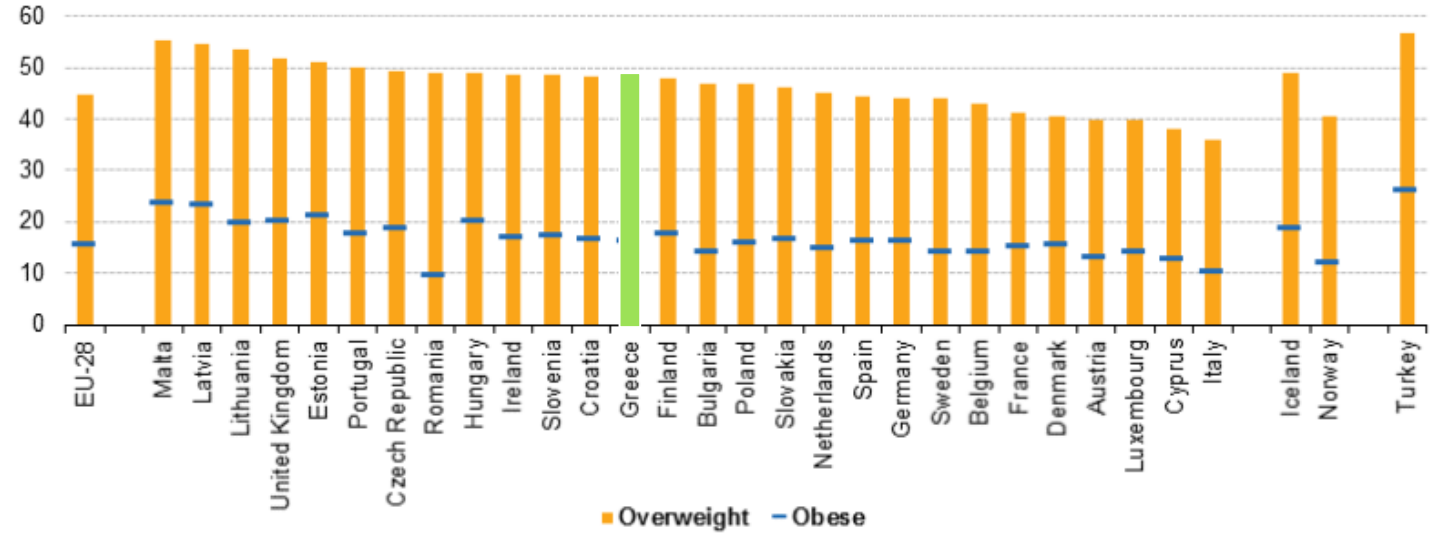


Obesity: definition

- Measurement of the body mass index

BMI= (weight in kg) / (height in meters)^2

kg/m^2

Table 1

Classifications for BMI

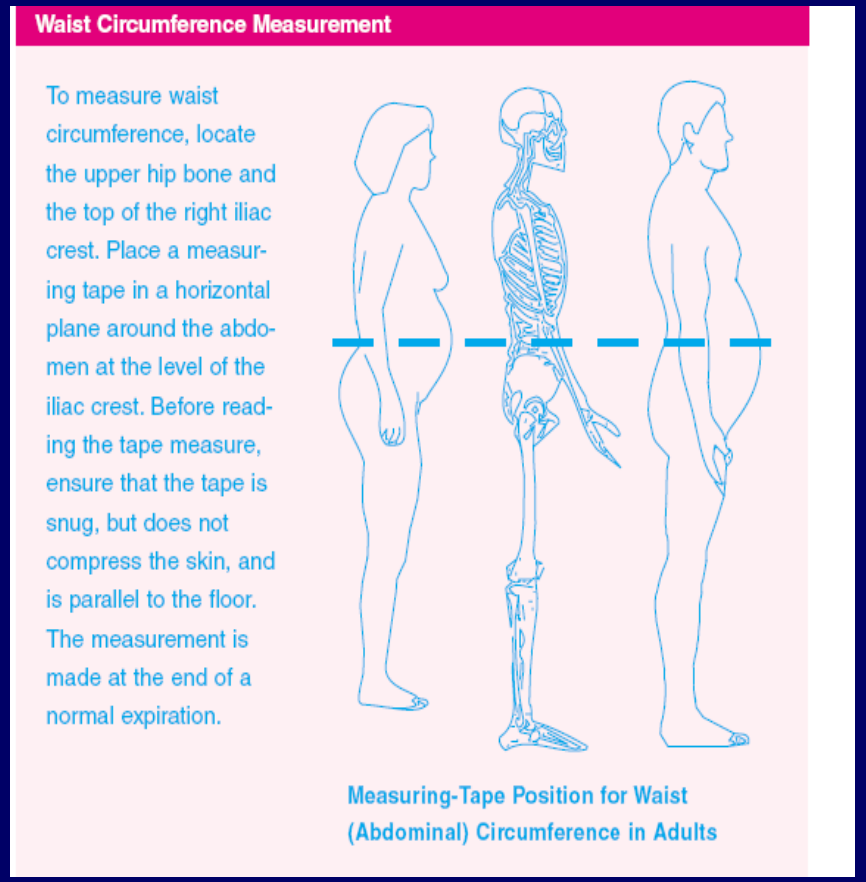
	BMI
Underweight	<18.5 kg/m^2
Normal weight	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity (Class 1)	30–34.9 kg/m^2
Obesity (Class 2)	35–39.9 kg/m^2
Extreme obesity (Class 3)	≥40 kg/m^2

Adapted from the Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults , National institute of health, USA

Measurement of waist circumference

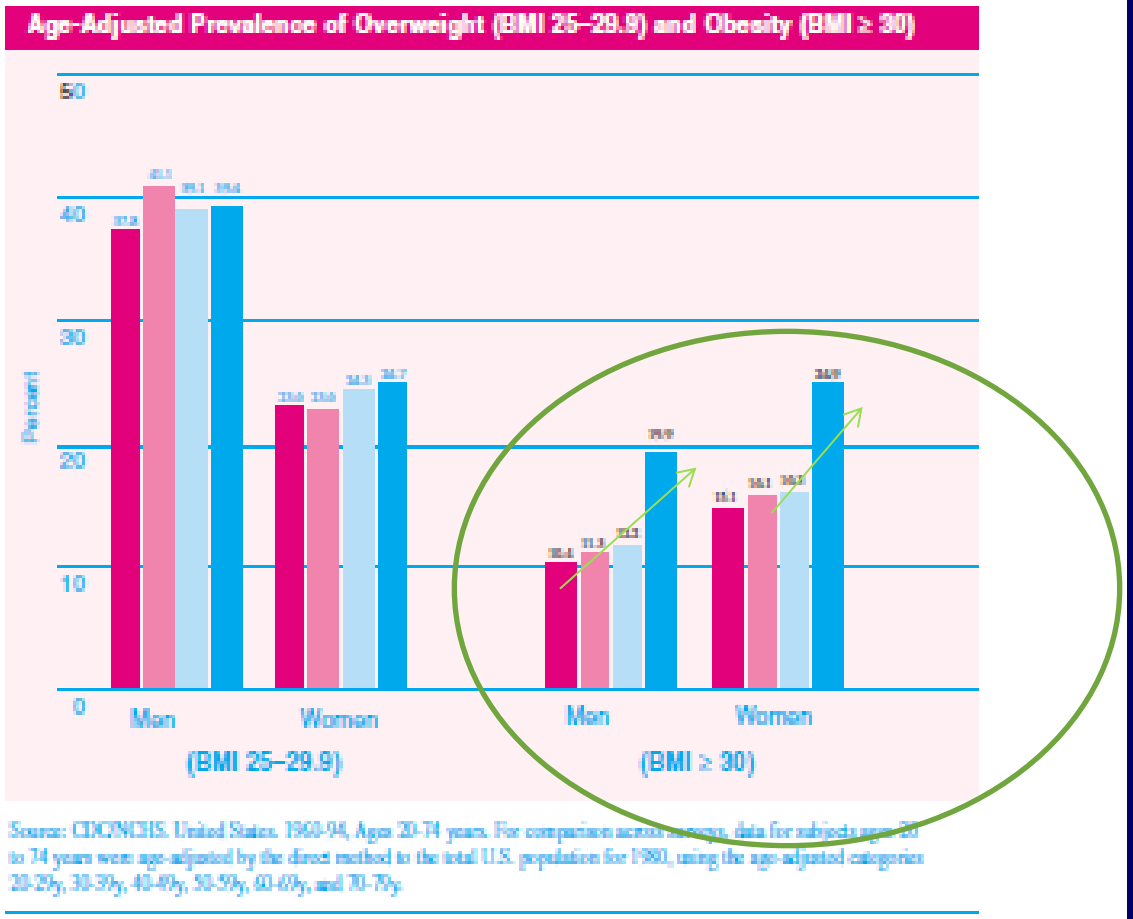
- Measurement of waist circumference is a vailable tool for the assessment of the total cardiovascular risk

- Men with waist circumference >102 cm and women with waist circumference > 88 cm are in increased risk for diabetes, dyslipidemia and hypertension due to the increased abdominal fat



Increased trends for obesity in USA between 1960 -2004

Figure 1

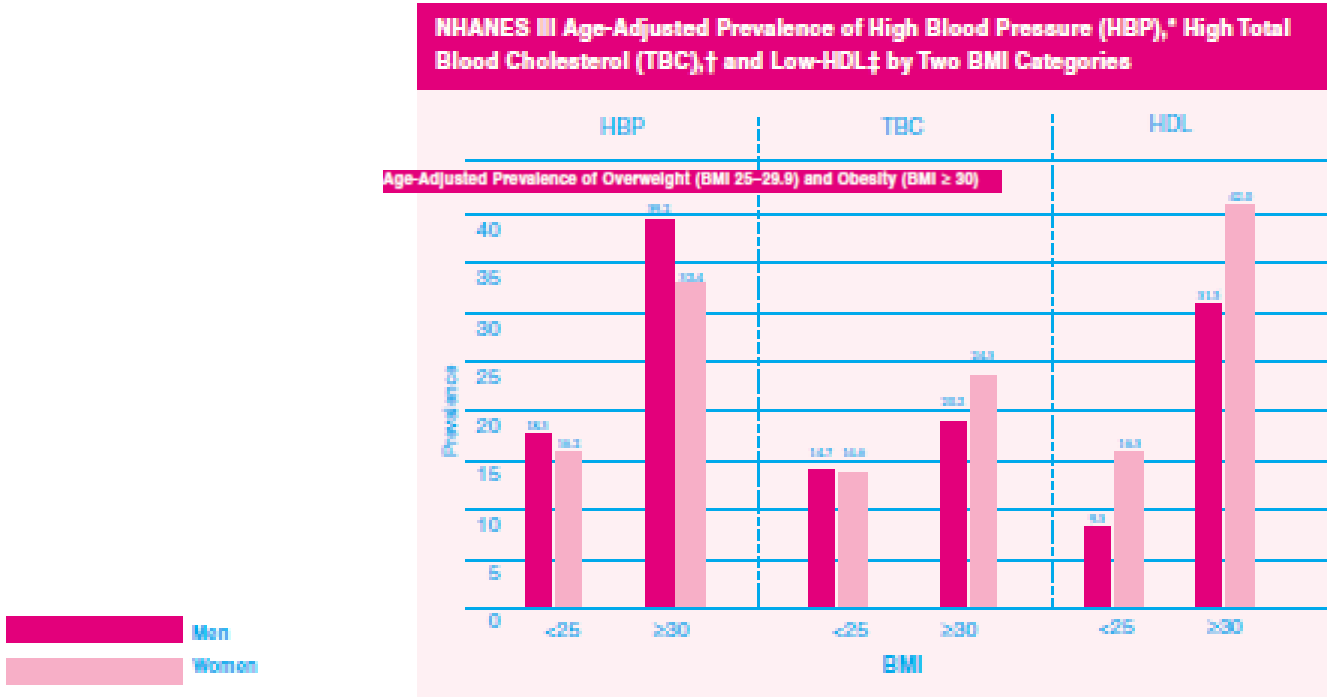


Source: CDC/NCHS, United States, 1960-94, Ages 20-74 years. For comparisons across surveys, data for subjects ages 20 to 74 years were age-adjusted by the direct method to the total U.S. population for 1980, using the age-adjusted categories 20-29y, 30-39y, 40-49y, 50-59y, 60-69y, and 70-79y.

Age-adjusted prevalence of risk factors in obese patients

Figure 2

NHANES III Age-Adjusted Prevalence of High Blood Pressure (HBP),* High Total Blood Cholesterol (TBC),† and Low-HDL‡ by Two BMI Categories



* Defined as mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90 mm Hg, or currently taking antihypertensive medication.

† Defined as ≥ 240 mg/dl.

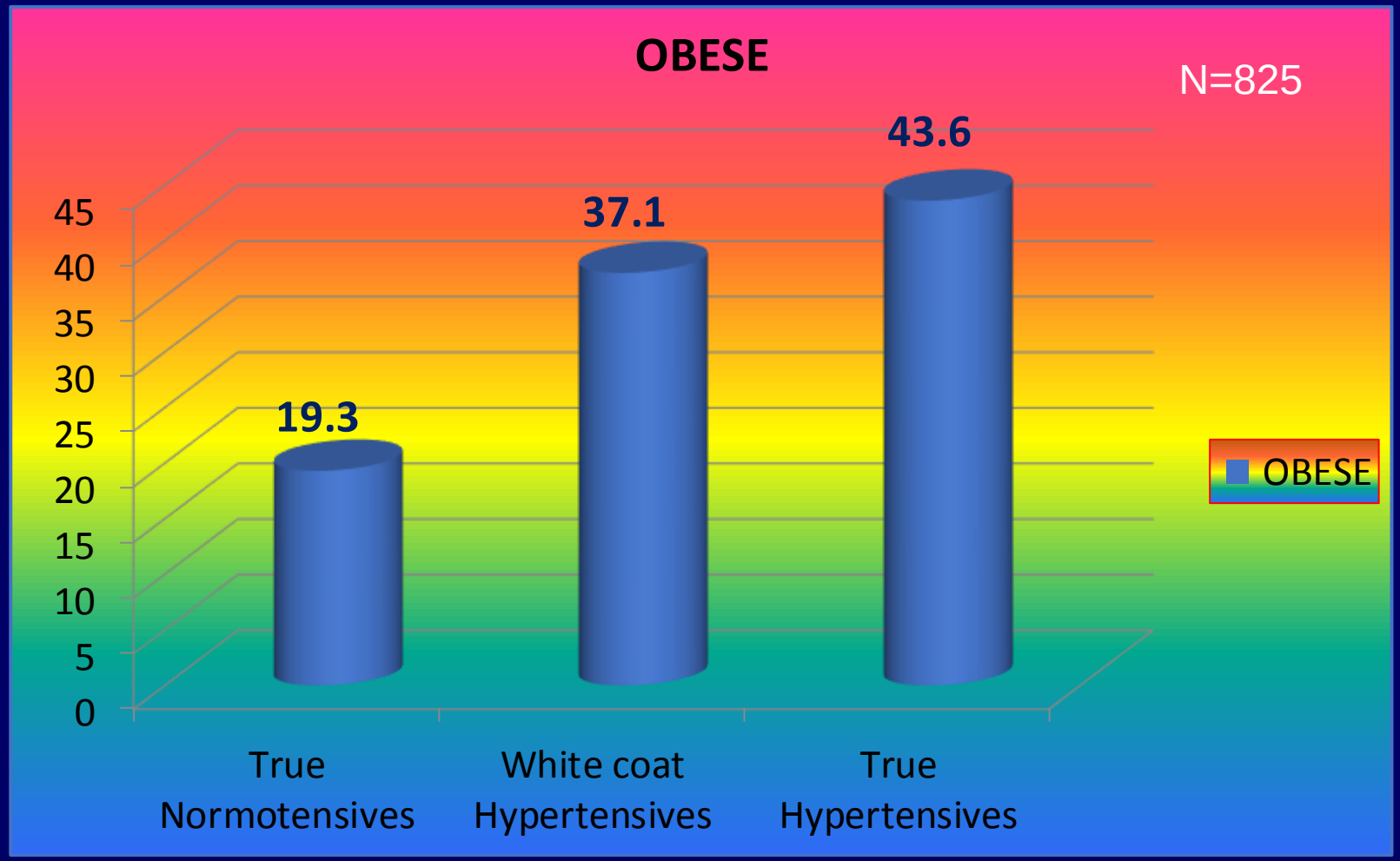
‡ Defined as < 35 mg/dl in men and < 45 mg/dl in women.

Source: Brown C. et al. Body mass index and the prevalence of hypertension and dyslipidemia (in press).

Adapted from the Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults , National institute of health, USA

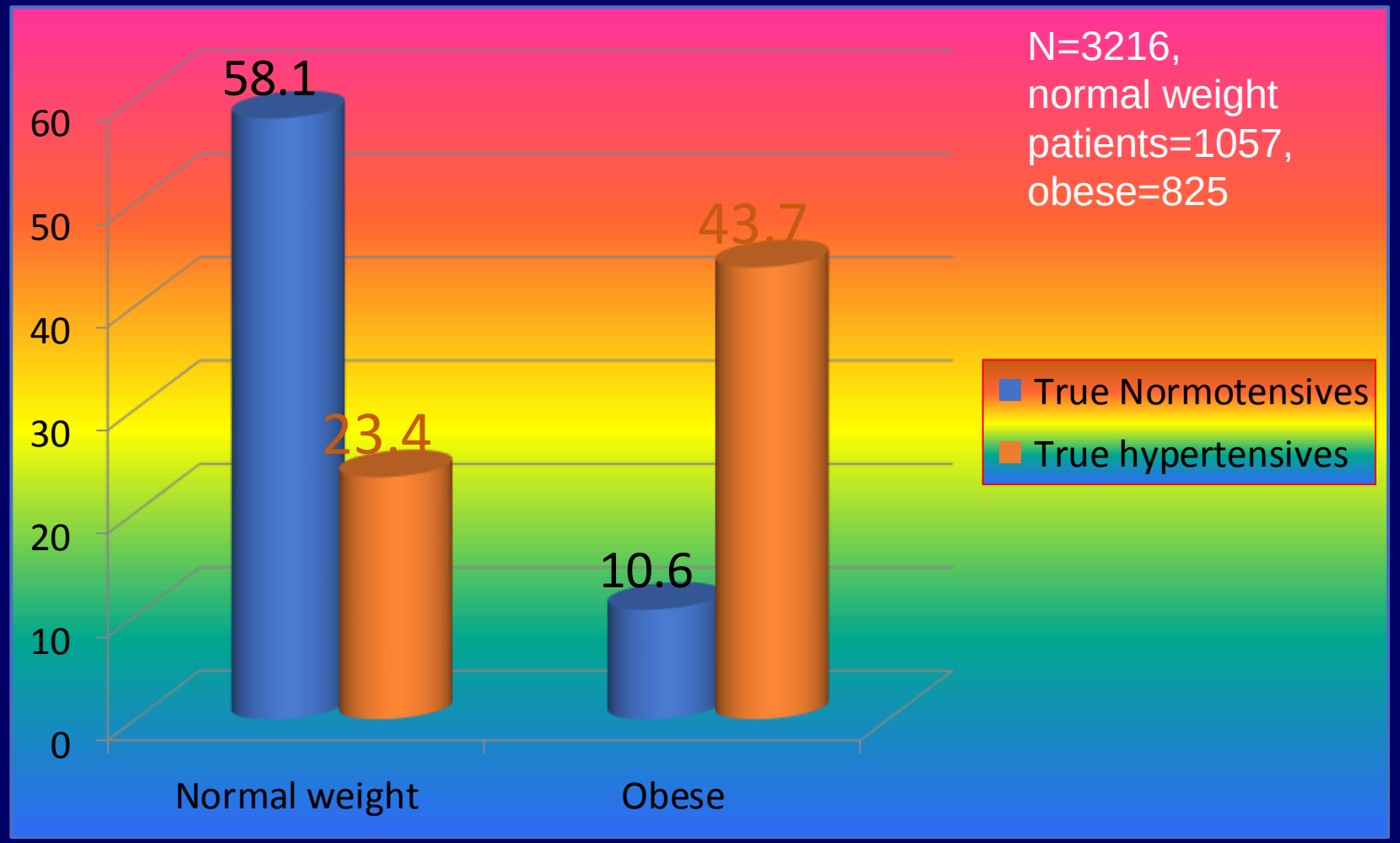
Obesity and hypertension

Obesity and hypertension prevalence confirmed with ABPM



V. Kotsis et al Hypertension 2005

Obesity and hypertension prevalence comparison to normal weight subjects



V. Kotsis et al Hypertension 2005: 45:602-607

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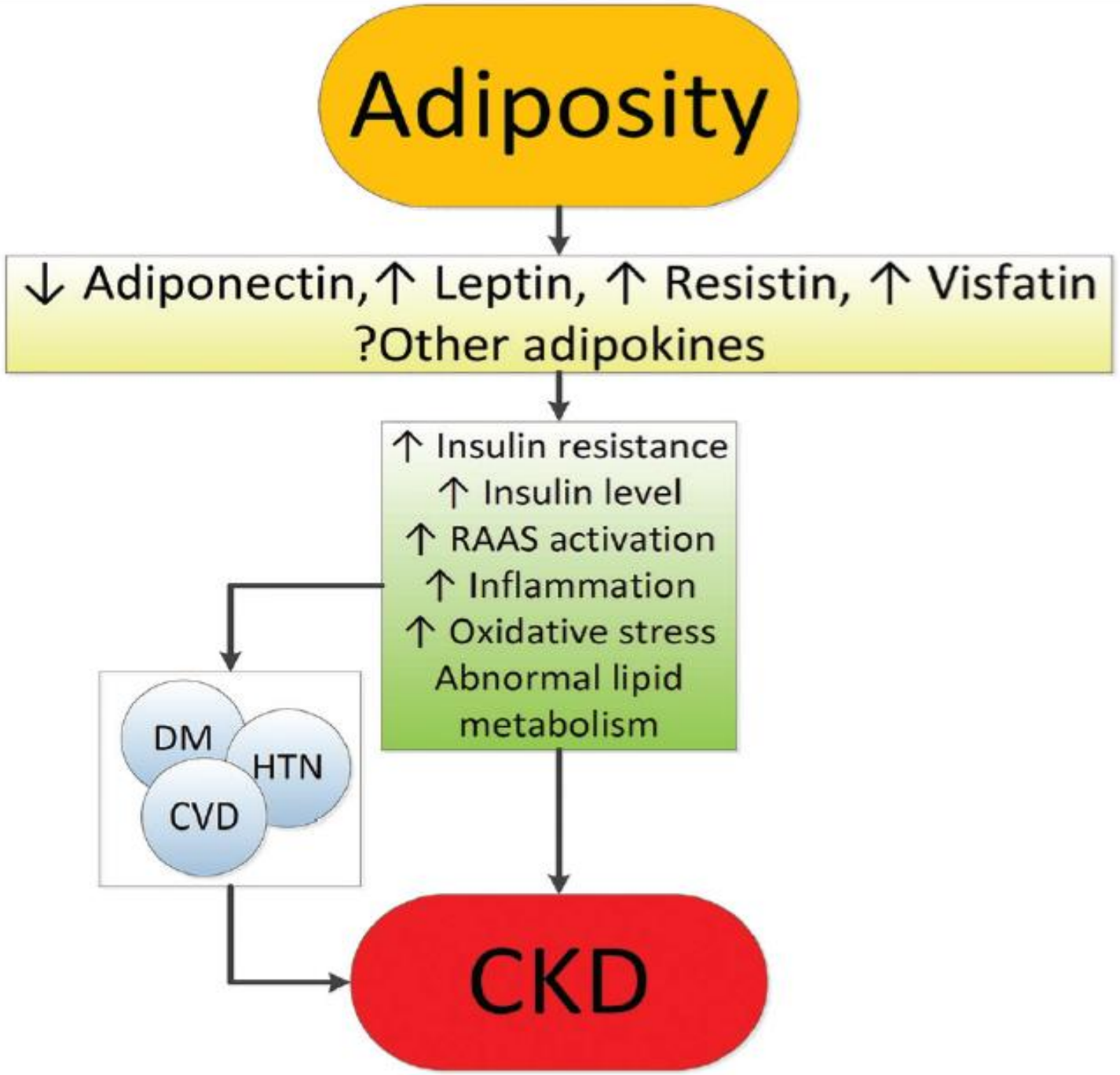


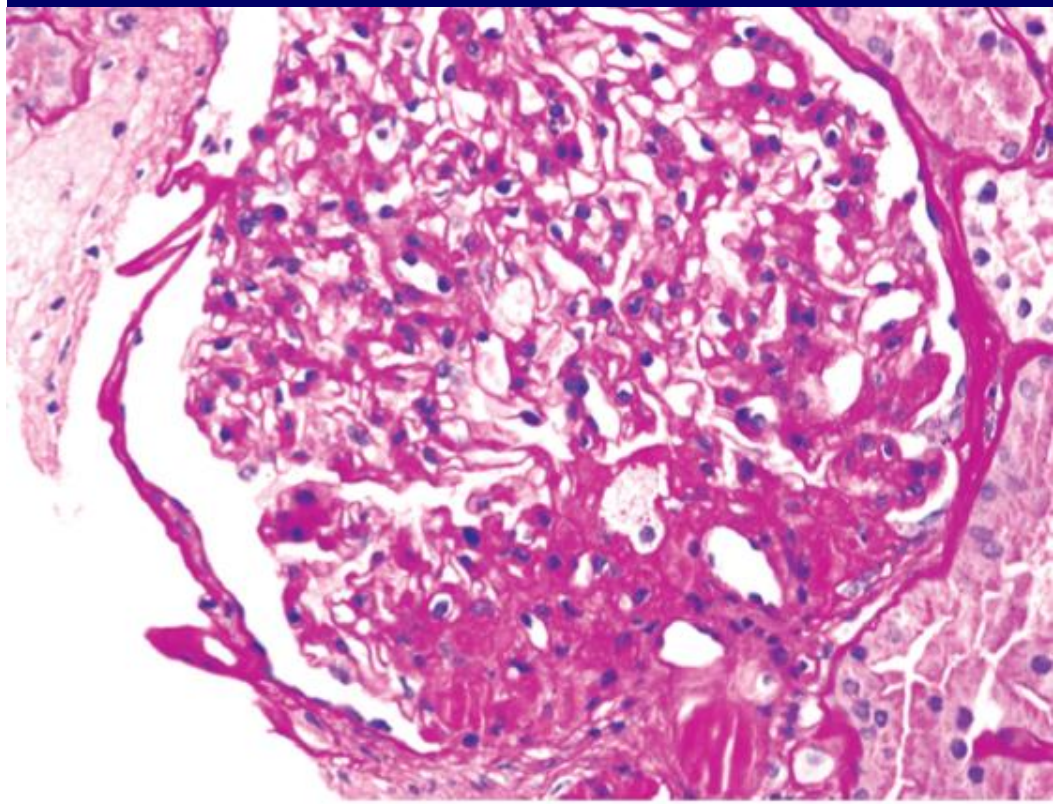


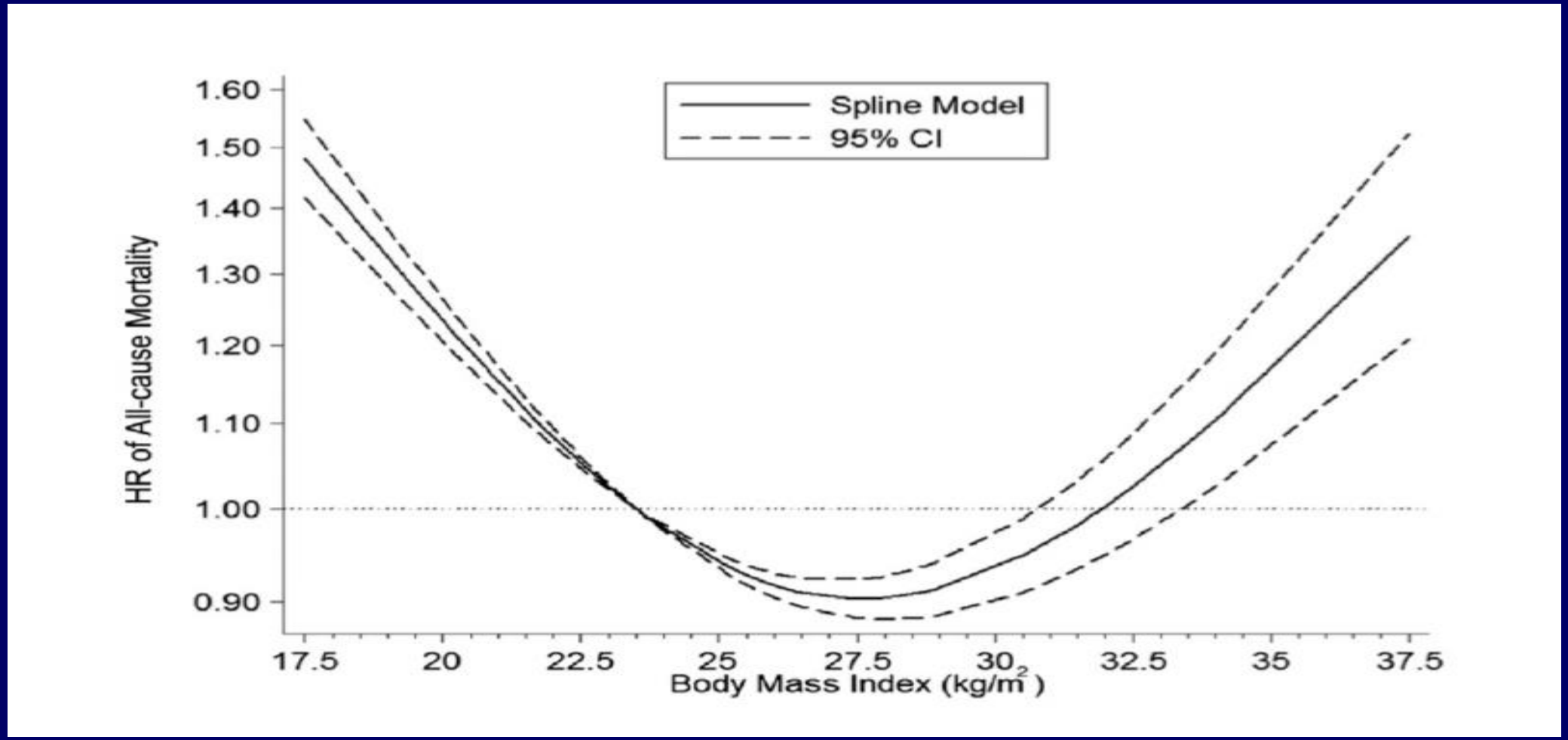
Figure 2. Obesity-related perihilar focal segmental glomerulosclerosis on a background of glomerulomegaly (periodic Acid-Schiff, × 400). Courtesy of Dr Patrick D Walker; Arkana Laboratories, Little Rock, AR.

Obesity paradox

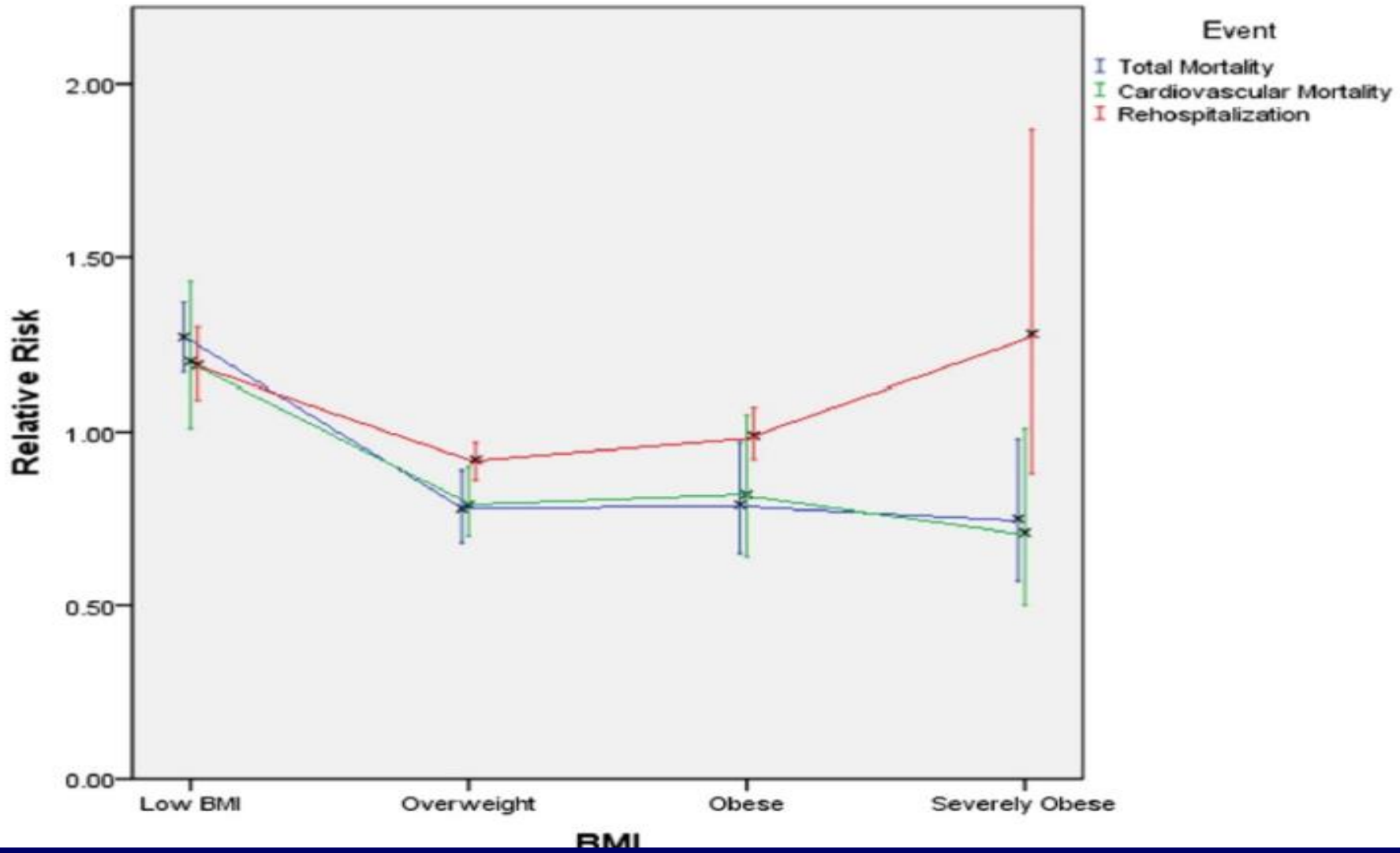
Has been observed in a variety of clinical settings including in patients suffering from:

- acquired immunodeficiency disease syndrome
- advanced chronic obstructive pulmonary disease
- chronic heart failure
- cancer
- End-stage renal disease (ESRD)

Reverse Epidemiology of BMI and Traditional Cardiovascular Risk Factors in the Geriatric Population



Total mortality, cardiac mortality, and hospitalization in a meta-analysis of outcomes in heart failure



Obesity Paradox in Advanced Kidney Disease

- Observational studies have found that obesity linked with improved survival in certain patient populations, including those with conditions marked by protein-energy wasting and dysmetabolism that lead to cachexia
- The latter observations have been reported in various clinical settings including ESRD and have been described as the “obesity paradox” or “reverse epidemiology

Cachexia

- Cachexia is a metabolic syndrome characterized by an imbalance in energy storage and expenditure which commonly manifests clinically as weight loss and loss of muscle and fat tissue
- Factors implicated in the pathogenesis of cachexia include anorexia, malnutrition, oxidative stress and inflammation
- Elevated resting energy expenditure is a major determinant in the development of energy wasting and consequently cachexia in patients at risk for this condition

Obesity Paradox in Advanced Kidney Disease

- Complications associated with cachexia cannot be overcome by nutritional supplementation and appetite stimulants
- Although the main tissues affected by cachexia are fat and skeletal muscle, several other organ systems including the liver, heart, and brain are also negatively impacted by this condition
- Cachexia leads to cardiomyopathy and thereby cardiac dysfunction and higher mortality

Obesity Paradox in Advanced Kidney Disease

- Patients with ESRD have an increased resting energy expenditure
- Risk factors of poor energy metabolism and cachexia in the CKD and ESRD population include inflammation, oxidative stress, insulin resistance and anorexia
- CKD and ESRD are associated with browning of white adipose tissue which has been implicated in the inefficient energy expenditure
- Browning of white adipose tissue observed in uremia is at least partly mediated by the secondary hyperparathyroidism
- Severe hyperparathyroidism in HD patients was associated with higher resting energy expenditure

Experimental models of cachexia in kidney disease

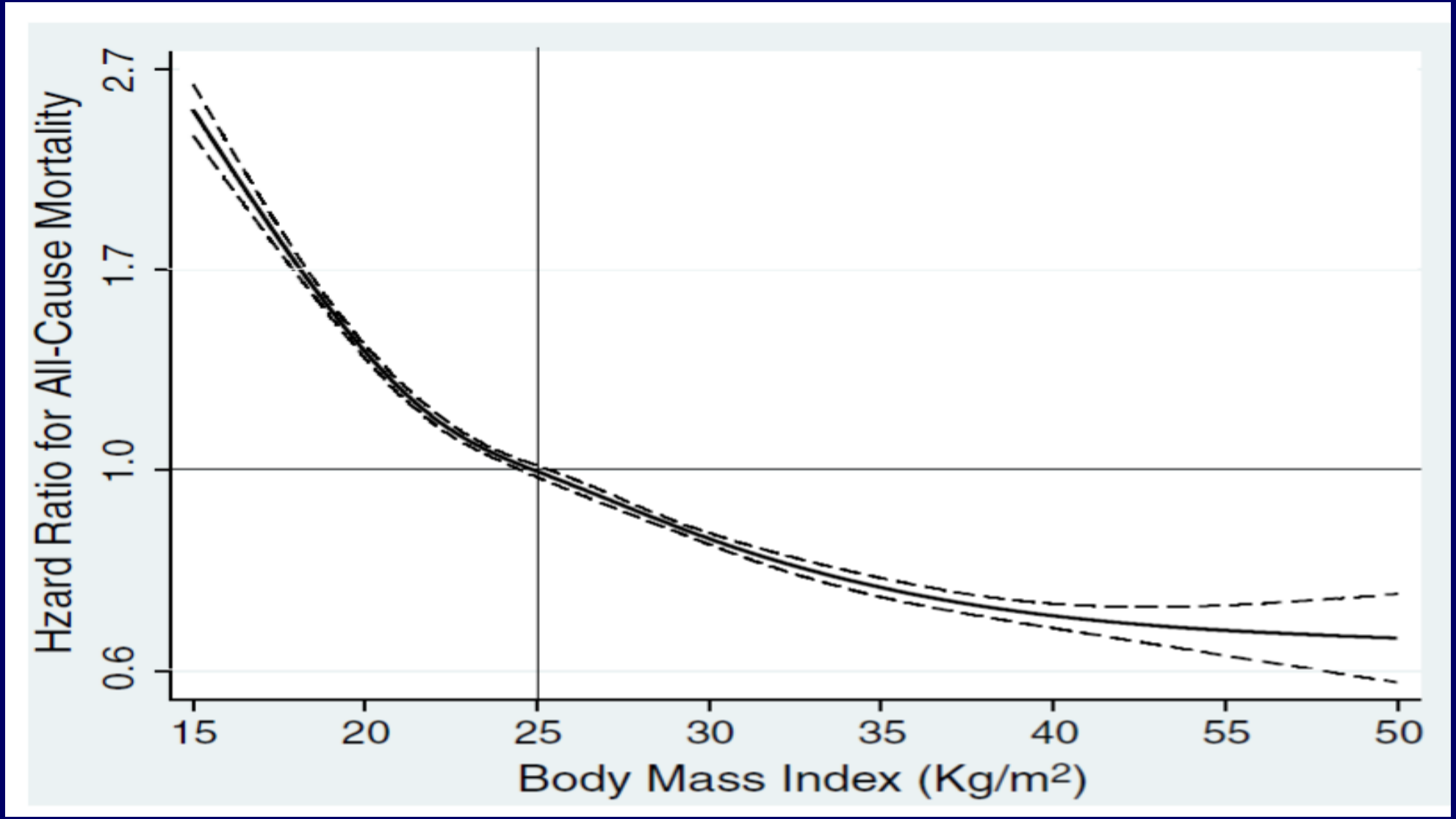
- Subtotally nephrectomized mice developed cachexia as indicated by an increased metabolic rate, loss of lean body mass, along with increased expression and abundance of uncoupling protein-1 (UCP1) in the fat tissue indicating a transition from energy preservation and storage to energy expenditure
- Pair-feeding the animals in order to restore their energy intake to the level of control mice did not improve weight gain in the uremic animals, further confirming the role of abnormally elevated energy expenditure rather than poor energy intake in uremia-associated cachexia.

Studies evaluating the association between BMI and mortality outcomes in CKD patients

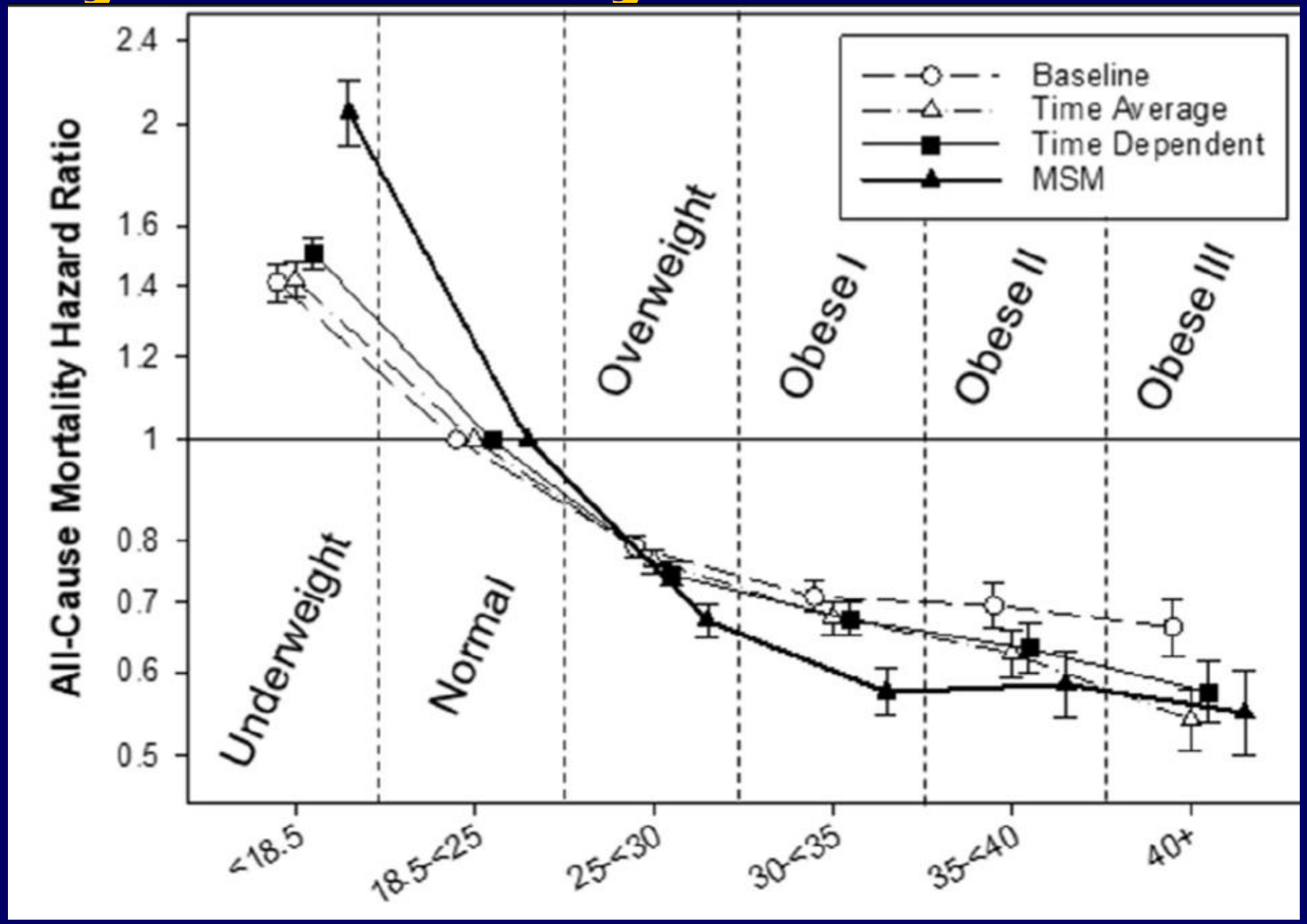
Study	Patients (n)	F/U* (y)	Results
Madero et al., 2007[80]	1759	10	No significant difference in all-cause mortality risk between higher BMI groups (BMI 25–>40) compared to normal weight group (BMI 18.5–24.9 kg/m^2)
Weiner et al., 2008[86]	1678	9	No significant association between increase in BMI (per 5 kg/m^2) and all-cause mortality
Elsayed et al., 2008[92]	13,324	up to 9.3	Each SD increase in BMI reduced the risk of the composite outcome (HR 0.94, 95% CI 0.90–0.99)
Obermayr et al., 2009[84]	49,398 (392 Moderate CKD)	5.5	Compared to the reference BMI of 25 kg/m^2, a higher risk of cardiovascular death in participants with BMI 20 kg/m^2 (HR, 1.35), BMI 30 kg/m^2 (HR, 1.37) and BMI 35 kg/m^2 (HR, 2.05)
Kramer et al., 2011[91]	5805	4	Every 1-kg/m^2 increase in BMI was related to a 3% reduction in mortality risk (95% CI, 0.94–0.99) and each 1-cm increase in WC was associated with a 2% higher mortality risk (95% CI, 1.01–1.04)
Dalrymple et al., 2011[81]	1268	9.7	BMI <18.5 kg/m^2 was associated with higher mortality, but higher BMI groups had similar mortality risk of the reference group (18.5–24.9 kg/m^2)
De Nicola et al., 2012[87]	1248	5.2	No significant association between BMI (continuous parameter) and mortality
Bello et al., 2013[83]	393,659 (54,403 CKD patients)	up to 30 days	Higher odds for 30-day mortality following an eligible procedure in obese CKD patients (BMI ≥ 35 kg/m^2 and eGFR < 60 ml/min/1.73 m^2) when compared to non-obese non-CKD patients in unadjusted and adjusted models (OR 5.51, 95% CI 4.48–6.79 and OR 1.49, 95%CI 1.18–1.87, respectively)
Babayev et al., 2013[88]	12,534	up to 8	BMI between 30 and 34.9 kg/m^2 was associated with improved survival (HR, 0.74) when compared to CKD patients with BMI < 30 kg/m^2
Ricardo et al., 2013[82]	2288	13	Participants with BMI 18.5–<22 kg/m^2 had a higher mortality hazard rate (HR, 1.3). In contrast higher BMI was not associated with a significantly different mortality risk when compared to BMI 22–<25 kg/m^2
Hanks et al., 2013[95]	4374	4.5	Metabolic healthy overweight (BMI 25–29.9 kg/m^2) CKD patients had lower all-cause mortality risk (HR, 0.74) in the fully adjusted model compared to metabolic healthy normal weight patients (BMI 18.5–24.9 kg/m^2)
Lu et al., 2014[89]	453,946	–	BMI had an U-shaped association (higher mortality in the lower and higher BMI groups) with all-cause mortality (BMI reference group 30–<35 kg/m^2)
Huang et al., 2015[90]	3320	2.9	Male participants with BMI < 22.5 kg/m^2 and BMI of 30.1–35 kg/m^2 had higher risk of all-cause mortality (BMI reference group: 27.6–30 kg/m^2) but not in females
Navaneethan et al., 2016[85]	54,506	3.7	CKD patients (mostly CKD stage III) with BMI 25-39.9kg/m^2 had lower risk of cardiovascular, malignancy, non-cardiovascular/non-malignancy related death compared to BMI of 18.5–24.9 kg/m^2
Sato et al., 2017[93]	27,978	up to 4	Increase of 1 SD in a body shape index associated with a higher risk for all-cause mortality in male CKD patients but not in females

* Duration of follow-up (F/U) in years (y) as reported by the authors. If not indicated mean or median reported.

Association of baseline BMI with mortality in 121,762 US HD patients over 5 years



Obesity and mortality in ESRD treated with HD



N. Naderi et al. / Progress in Cardiovascular Diseases 61 (2018) 168–181

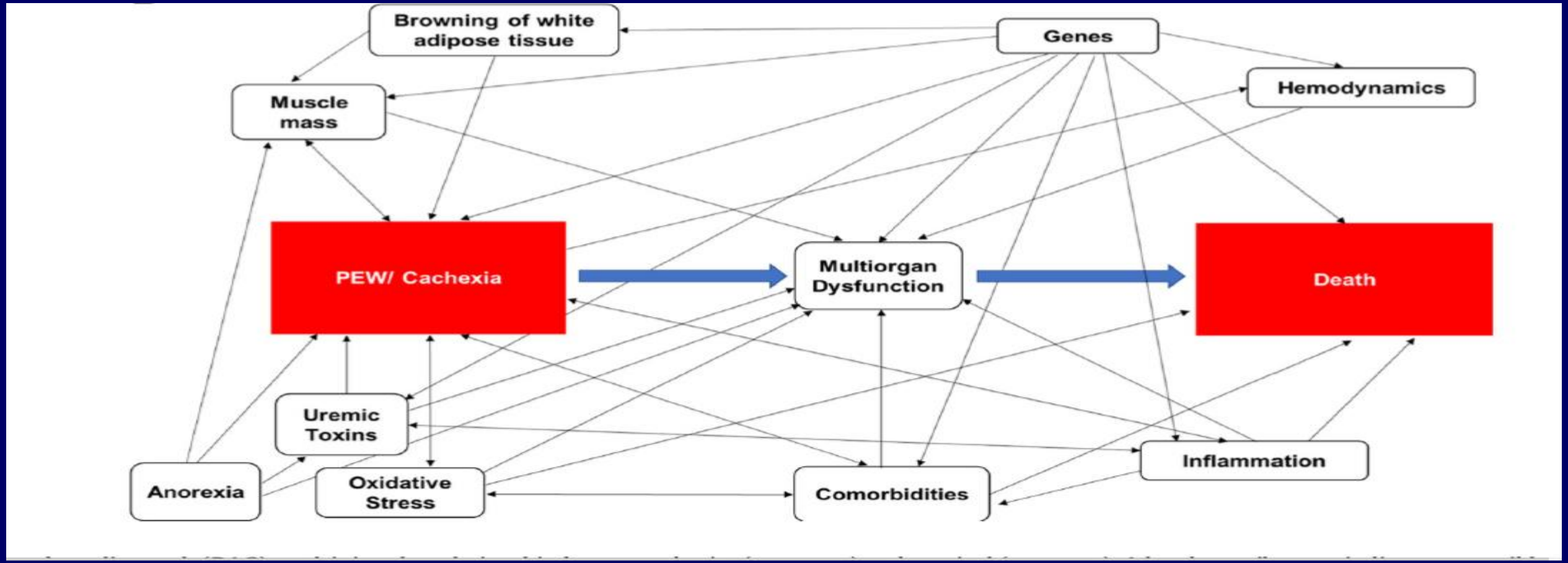
Summary of studies) evaluating the association between BMI and mortality outcomes in PD patients

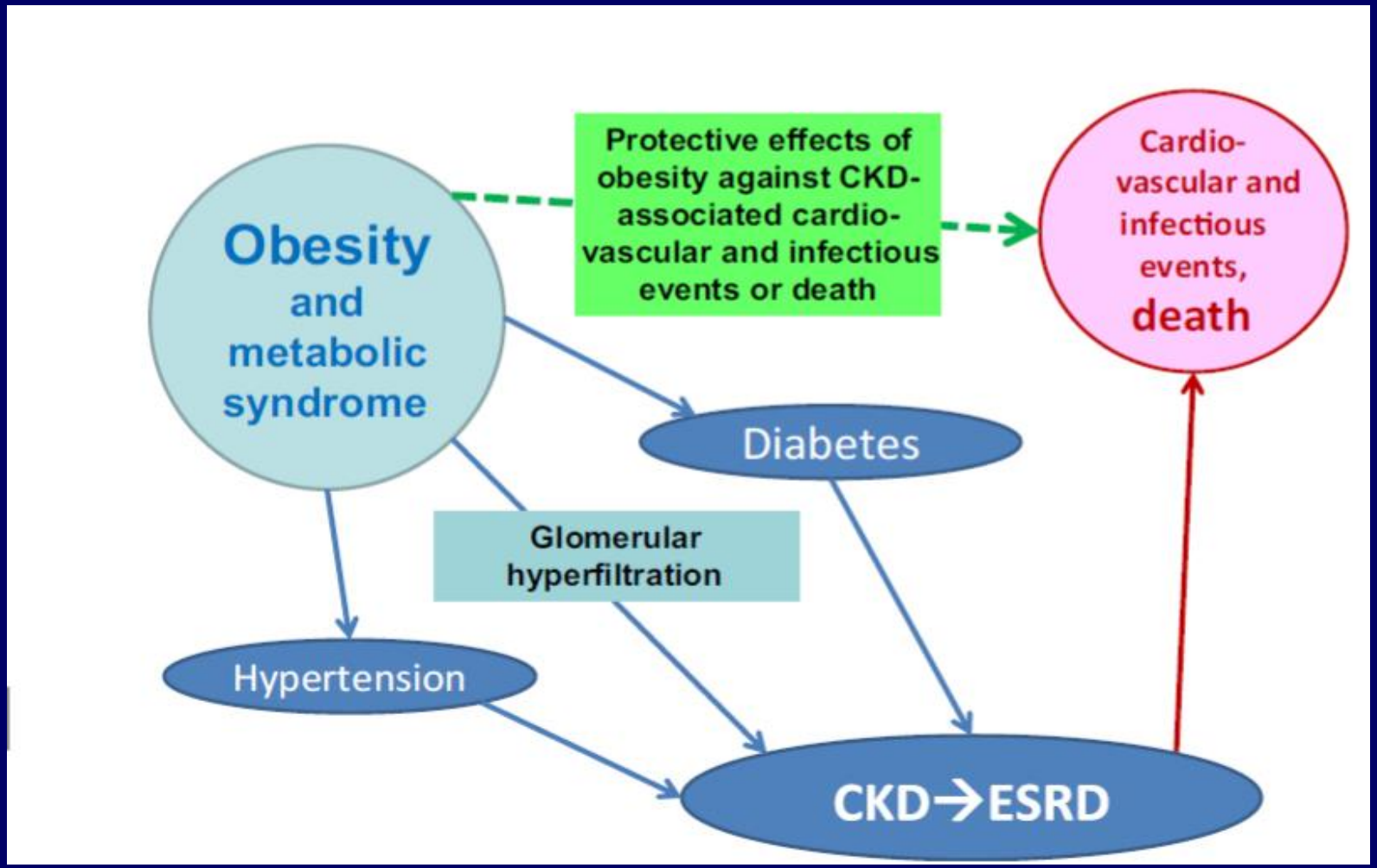
Study	Patients (n)	F/U* (y)	Results
McDonald et al., 2003[105]	9679	17,973 person-years	BMI ≥ 30 kg/m^2 was associated with higher mortality and technique failure; there was a J-shaped association between BMI and mortality with lowest mortality risk for patients with BMI close to 20 kg/m^2
Snyder et al., 2003[111]	41,197	up to 3	Overweight and obese participants had a survival benefit compared to those with lower BMI
Abbott et al., 2004[96]	1662	up to 5.8	BMI ≥ 30 kg/m^2 was not related to improved 5-year survival
Stack et al., 2004[97]	17,419	1	No survival advantage with higher BMI values
Ramkumar et al., 2005[114]	10,140	17,500 patient-years	Patients with a BMI ≥ 25 kg/m^2 and high muscle mass, had a 10% lower hazard ratio of all-cause mortality
Pliakogiannis et al., 2007[108]	4054	4.3	BMI > 30 kg/m^2 had neither higher nor lower mortality risk than the reference group (BMI 19–24.9 kg/m^2)
de Mutsert et al., 2009[109]	688	up to 5	BMI ≥ 30 kg/m^2 did not have statistically significant difference in mortality risk than normal BMI (18.5–25 kg/m^2)
Mehrotra et al., 2009[112]	66,381	up to 10	Higher BMI quartiles were related to lower mortality but higher technique failure (reference BMI: < 21.88 kg/m^2)
Fernandes et al., 2013[113]	1911	up to 2.8	BMI < 18.5 kg/m^2 had a higher death risk while a BMI > 30 kg/m^2 was associated with a survival benefit, also weight reduction in the first year of dialysis of <−3.1% was associated with significant higher mortality
Park et al., 2013[117]	10,896	5.9	Patients with serum creatinine levels ≥10 mg/dl had lower mortality risk compared to serum creatinine levels of 8–9.9 mg/dL, accordingly higher muscle mass might be associated with better survival
Kim et al., 2014[107]	900	2	Increased BMI was not associated with higher mortality
Badve et al., 2014[35]	6162	2.3	Survival advantage was seen only for patients with time-varying BMI between 28.1 and 31 kg/m^2 (reference group time-varying BMI: 25.1–28 kg/m^2)
Xiong et al., 2015[106]	1263	2.1	Obesity was associated with a higher cardiovascular mortality risk in multivariate analysis in Chinese patients and BMI decline >0.8% during the first year after PD initiation had higher cardiovascular and all-cause mortality hazard ratios (reference group: Δ −0.8% to 2.69%)
Obi et al., 2017[110]	15,573	up to 2	U-shaped association between BMI and mortality with best survival in the BMI 30–<35 kg/m^2 strata

* Duration of follow-up (F/U) in years (y) as reported by the authors. If not indicated mean or median reported.

Factor	Potential modification by obesity
Restricted Nutrition/ Diet contribute to cachexia and PEW	Obese patients may be more resistant to the impact of cachexia and PEW
Higher level of inflammation	Adipose tissue may sequester inflammatory cytokines
Intradialytic hemodynamics	Less intradialytic hypotension in obese patients
Browning of white AT	Obese patients may be more resistant to this effect
Body fat distribution	Less inclined to develop cachexia
Genetics	More likely to have underlying mechanisms preventing inefficient energy use

Relationship between PEW/cachexia (exposure) and death (outcome) in ESRD




Obesity
and
metabolic
syndrome
Protective effects of obesity against CKD-associated cardio-vascular and infectious events or death
Cardio-vascular and infectious events, death
Diabetes
Glomerular hyperfiltration
Hypertension
CKD→ESRD

Το παράδοξο της παχυσαρκίας στην προχωρημένη νεφρική νόσο

Η καχεξία συνδέεται με δυσμενή έκβαση συμπεριλαμβανόμενης της μυοκαρδιοπάθειας, αρρυθμίες και αιφνίδιο καρδιαγγειακό θάνατο

Το πλεονέκτημα επιβίωσης το οποίο παρατηρείται στους παχύσαρκους ασθενείς με τελικού σταδίου νεφρική νόσο μπορεί να προέρχεται από μηχανισμούς οι οποίοι τους προστατεύουν λόγω καλύτερης ικανότητας χρησιμοποίησης της ενέργειας (απορρόφηση και αποθήκες), καλύτερη διαχείριση με τον τρόπο αυτό της απώλειας ενέργειας από αποβολή πρωτεϊνών και την πρόληψη εμφάνισης καχεξίας

Έχοντας ως δεδομένο ότι σε τελικού σταδίου νεφροπαθείς η θεραπεία για κλασικούς καρδιαγγειακούς παράγοντες κινδύνου δεν έδωσε τα αναμένοντα αποτελέσματα επιβίωσης, η κατανόηση των μηχανισμών προστασίας στους παχύσαρκους ασθενείς μπορεί να βοηθήσει στην ανακάλυψη νέων θεραπειών που ίσως βοηθήσουν την επιβίωση των ασθενών αυτών όπως η χρήση αυξητικής ορμόνης ή της λεπτίνης για την βελτίωσή της καχεξίας