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DR as a Biomarker for Systemic Vascular Complications

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Disclosures

- Dr Wu has received lecture fees from
 - Bayer
 - Quantel Medical

Introduction

- DR is the most common and specific microvascular complication of DM
- DR's adverse impact on vision is well established
- The importance of retinopathy signs beyond visual impairment is less well recognized

DR and Mortality

Table 1
Selected studies on the relationship of diabetic retinopathy and mortality

Study	Population	Follow-up	Retinal status	Associations ^a	References
WESDR	1370 T2DM	16-year	NPDR PDR	+ ++	Klein et al. (1999a)
ETDRS	2267 T2DM	5-year	Moderate–severe NPDR Moderate–severe PDR	+ +++	Cusick et al. (2005)
Finnish	824 T2DM	18-year	NPDR in men NPDR in women PDR in men PDR in women	+ +++ ++ +++	Juutilainen et al. (2007)
WESDR	996 T1DM	16-year	Moderate NPDR or PDR	+ (NS)	Klein et al. (1999a)
ETDRS	1444 T1DM	6-year	Severe NPDR Moderate/severe PDR	+ (NS) + (NS)	Cusick et al. (2005)
EURODIAB	2237 T1DM	8-year	PDR	+++ (NS)	van Hecke et al. (2005)

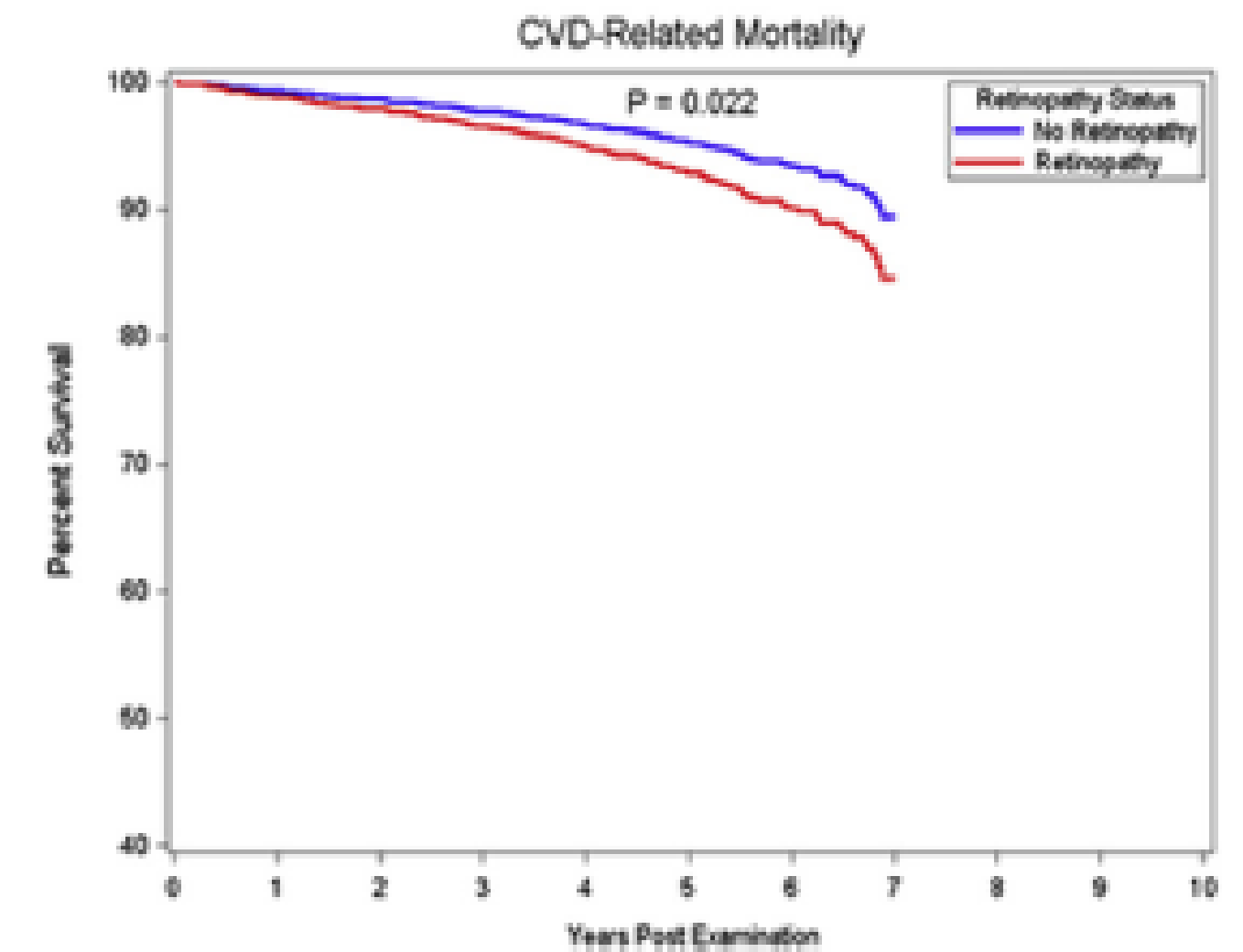
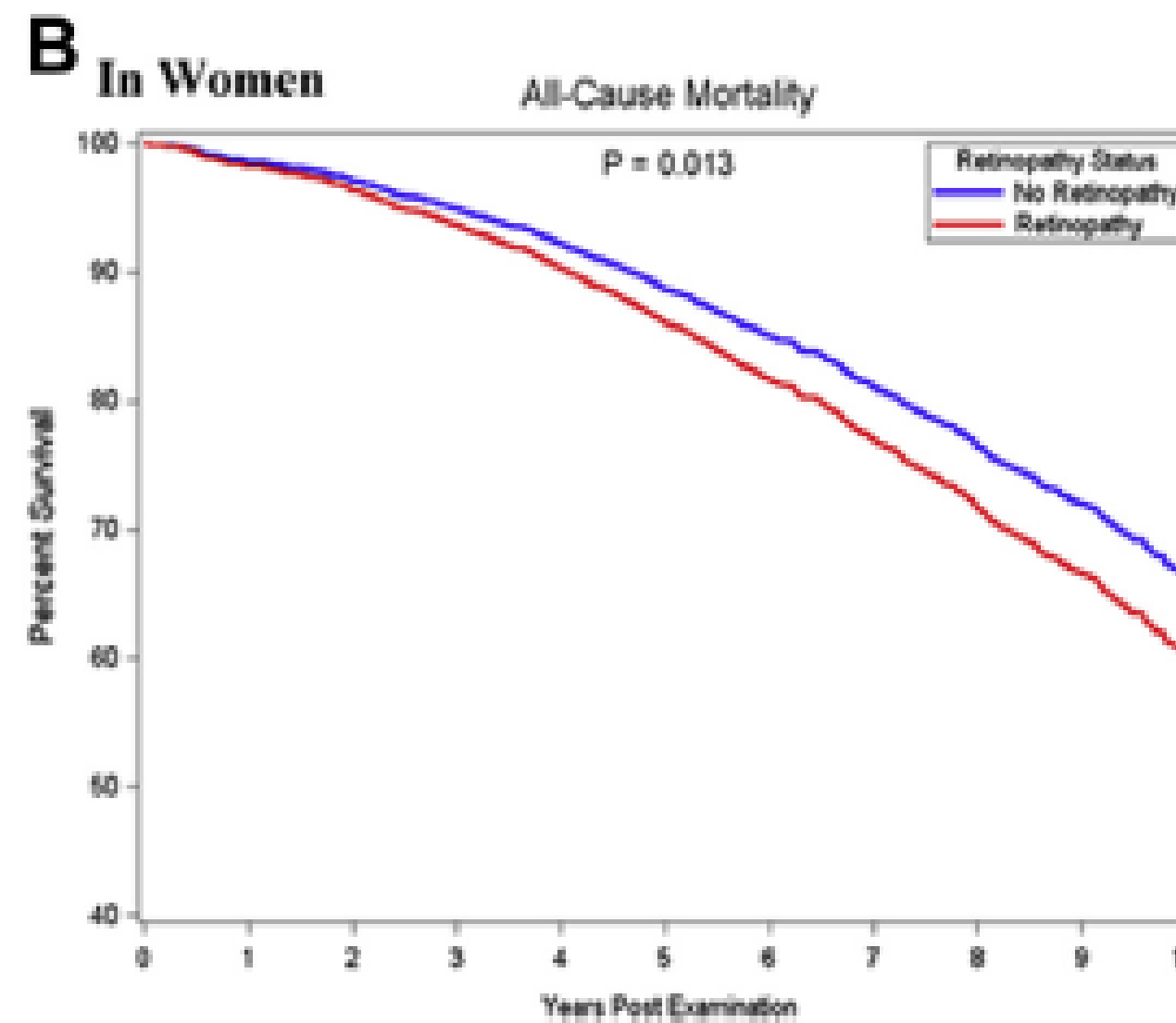
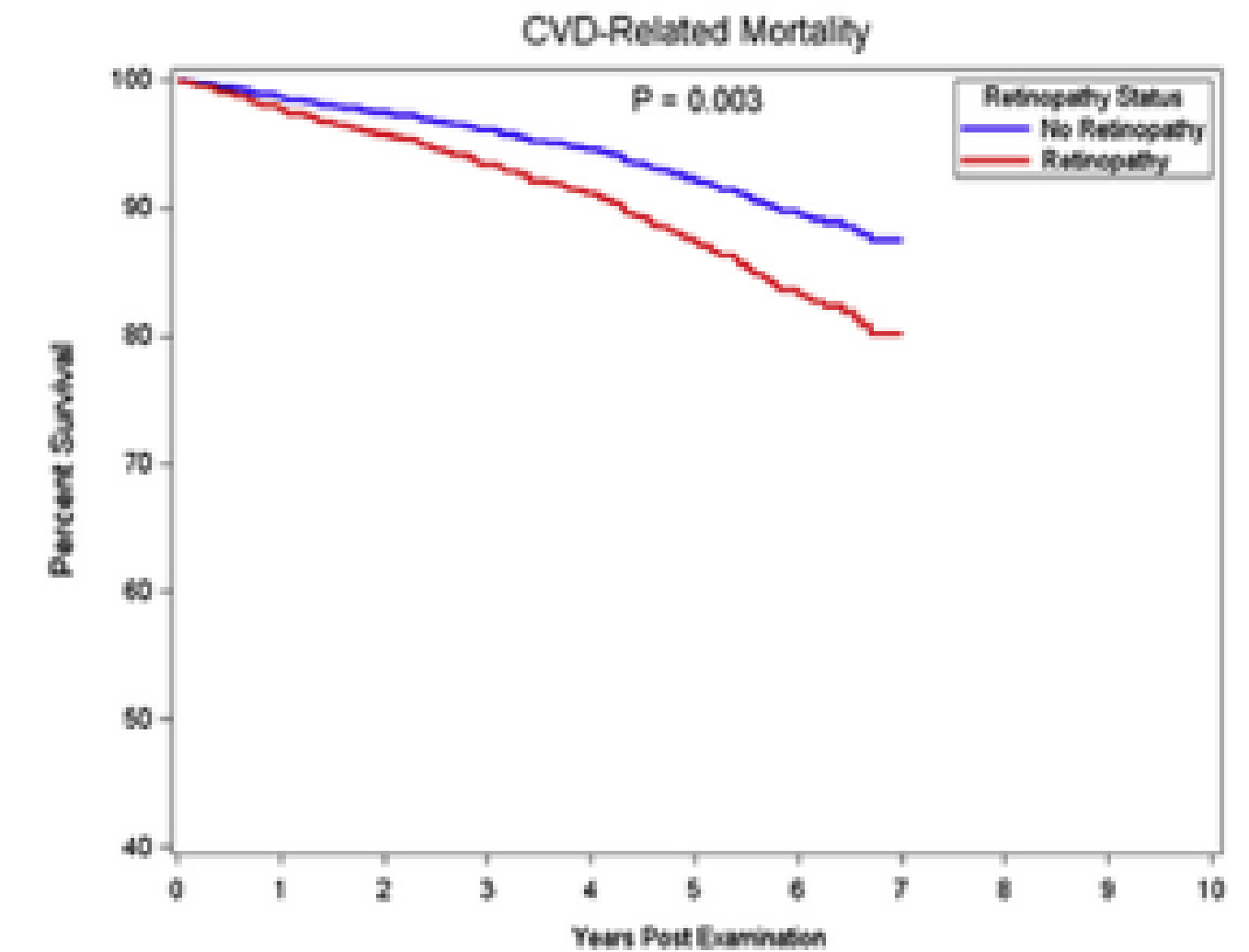
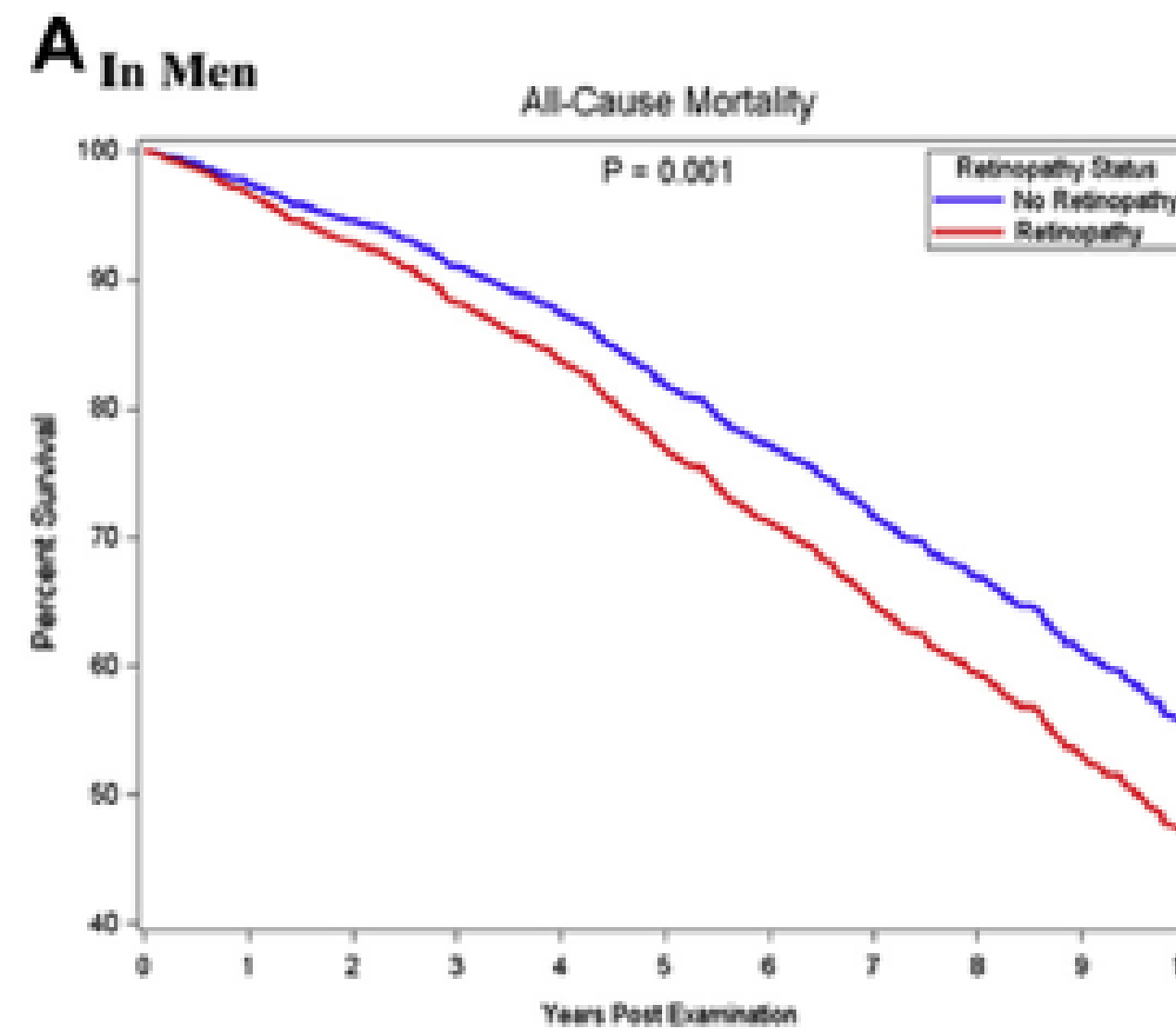
- This association more consistently seen in Type 2 than Type 1, reflecting older age and higher prevalence of CV risk factors in Type 2

Mortality in Older Persons with Retinopathy and Concomitant Health Conditions

The Age, Gene/Environment Susceptibility-Reykjavik Study

Diana E. Fisher, MA,¹ Fridbert Jonasson, MD,^{2,3} Ronald Klein, MD, MPH,⁴ Palmi V. Jonsson, MD,^{2,5} Gudny Eiriksdottir, MSc,⁶ Lenore J. Launer, PhD,⁷ Vilundur Gudnason, MD, PhD,^{2,6} Mary Frances Cotch, PhD¹

- Population based prospective cohort study of people ≥ 67 yrs old
- Even minimal retinopathy was a significant predictor of increased all cause and CV mortality (HR 1.26 and 1.57)
- Findings were more striking in men HR for all cause mortality 1.33 and 1.81 for CV mortality



Mortality in Older Persons with Retinopathy and Concomitant Health Conditions

The Age, Gene/Environment Susceptibility-Reykjavik Study



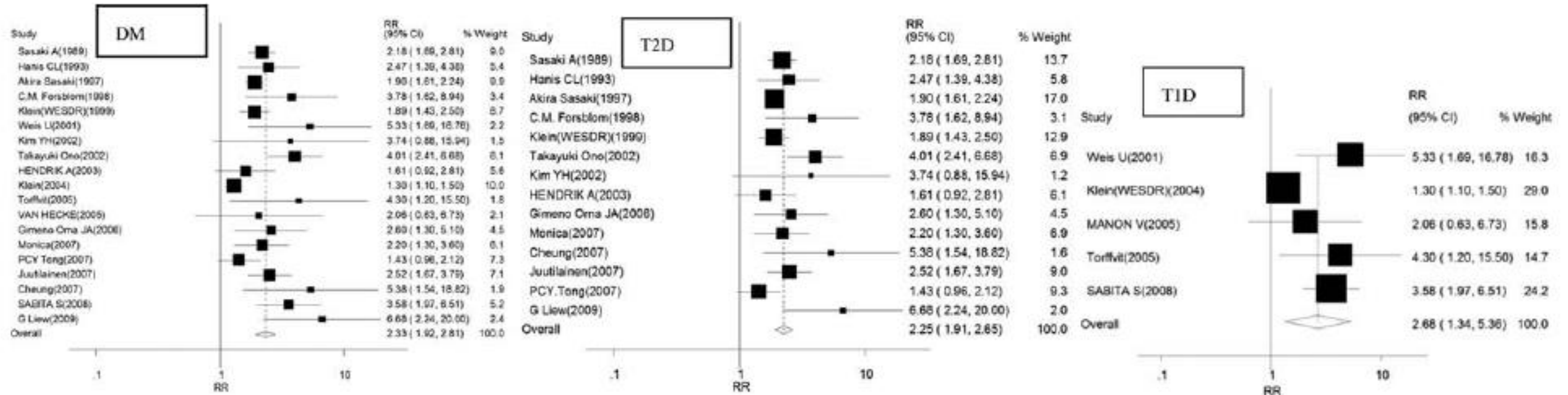
Diana E. Fisher, MA,¹ Fridbert Jonasson, MD,^{2,3} Ronald Klein, MD, MPH,⁴ Palmi V. Jonsson, MD,^{2,5}
Gudny Eiriksdottir, MSc,⁶ Lenore J. Launer, PhD,⁷ Vilundur Gudnason, MD, PhD,^{2,6} Mary Frances Cotch, PhD¹

- This association persisted despite adjustment for HTN, DM and other factors such as smoking
- Risk even higher if associated with microalbuminuria

Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure

Evidence from epidemiological observational studies

Xiao-Rong Zhu, MD^a, Yong-Peng Zhang, MD^b, Lu Bai, MD^c, Xue-Lian Zhang, MD^a, Jian-Bo Zhou, MD^{a,*}, Jin-Kui Yang, MD^{a,d,*}



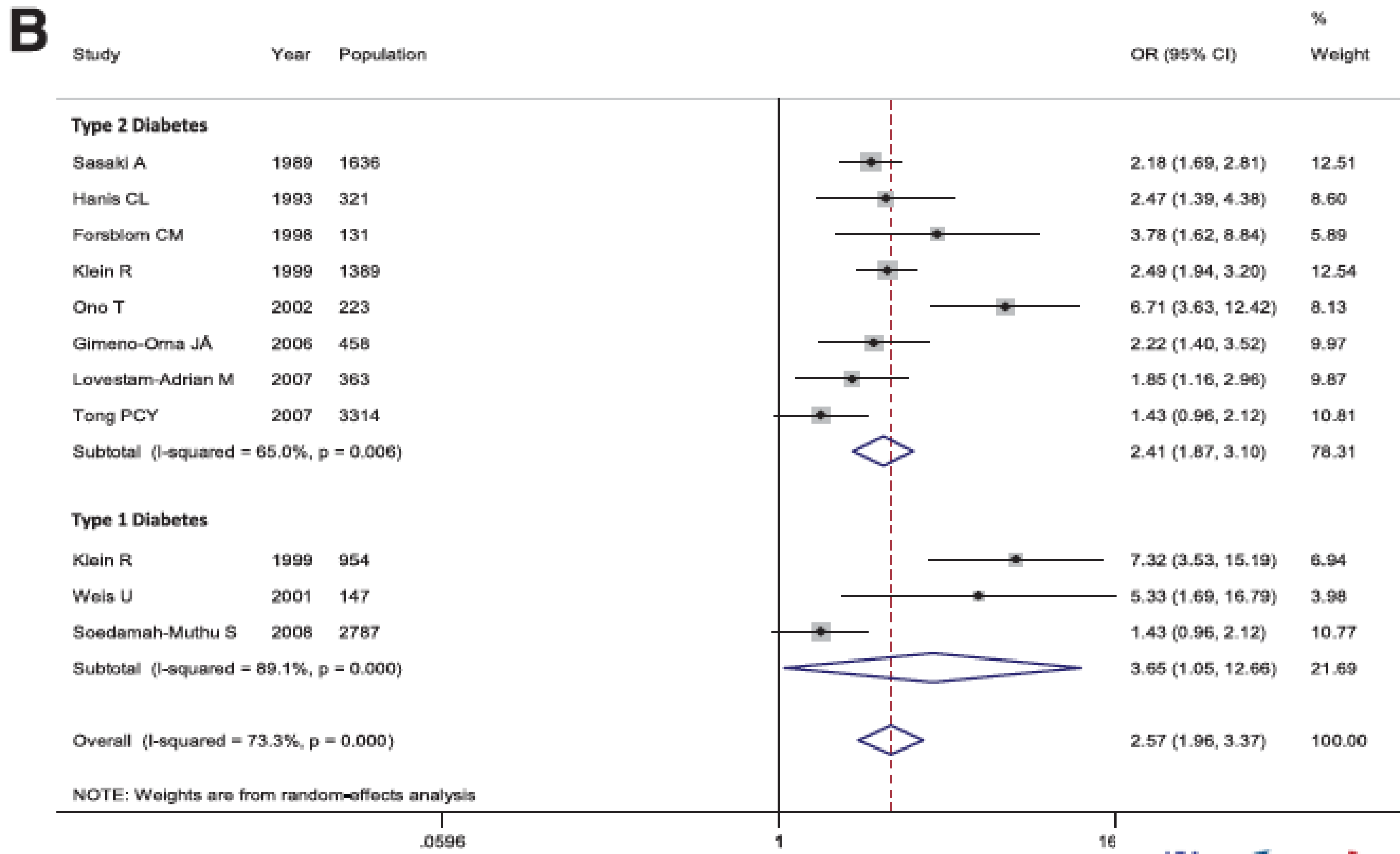
- 19 studies showed that the RR for all cause mortality with the presence of DR was 2.33 (95% CI 1.92-2.81)

Diabetic Retinopathy Predicts All-Cause Mortality and Cardiovascular Events in Both Type 1 and 2 Diabetes

CAROLINE K. KRAMER, MD, PHD
 TICIANA C. RODRIGUES, MD, PHD
 LUIS H. CANANI, MD, PHD

JORGE L. GROSS, MD, PHD
 MIRELA J. AZEVEDO, MD, PHD

Meta-analysis of observational studies



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- Presence of DR was associated with an increased risk of all cause mortality and CV events in both type 1 and 2 DM pts
- ***Focused on early stages of DR***
- ***Did not include DME***
- ***Did not have the ability to adjust for confounding effects of CV risk factors***

Association of Diabetic Macular Edema and Proliferative Diabetic Retinopathy With Cardiovascular Disease

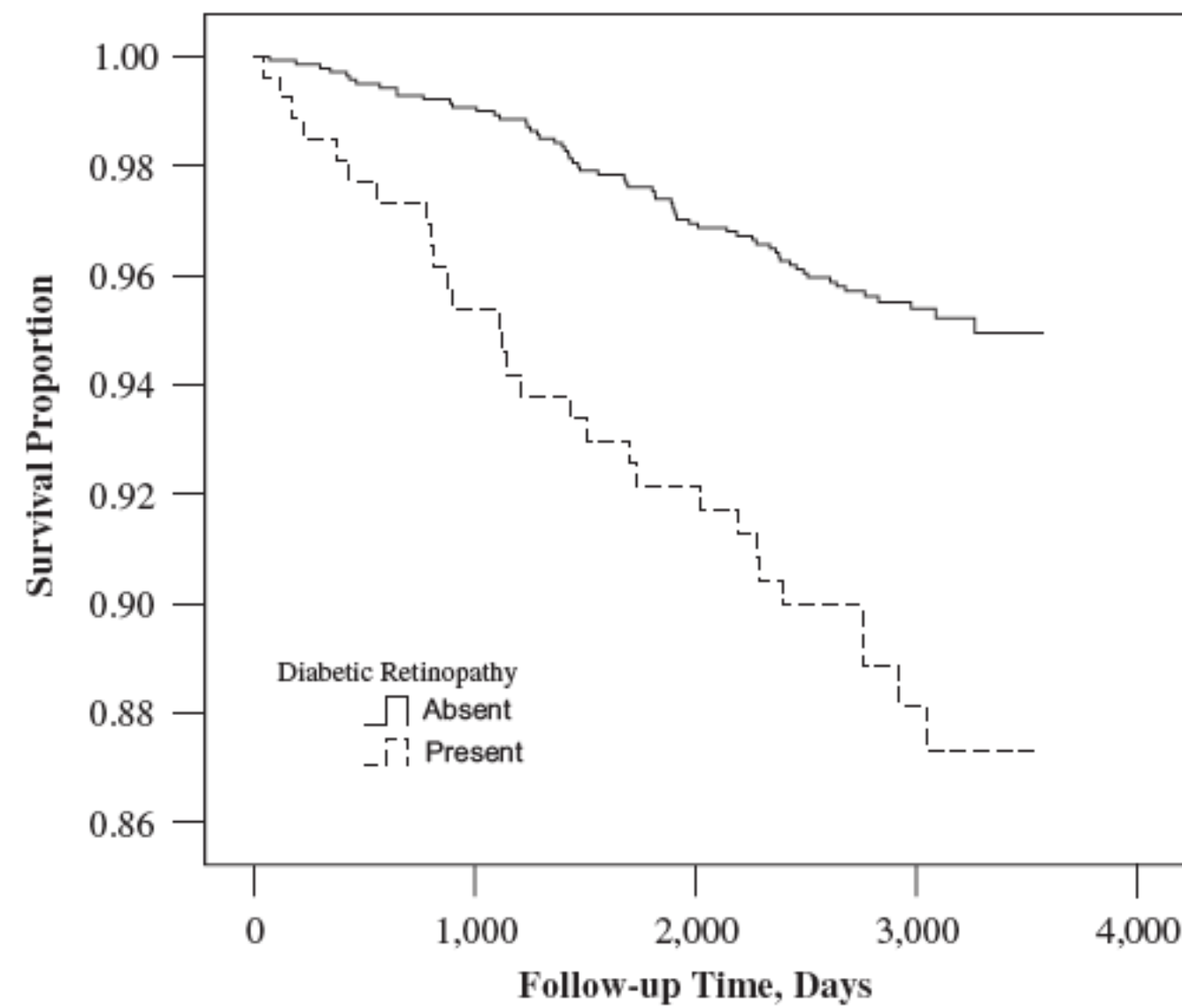
A Systematic Review and Meta-analysis



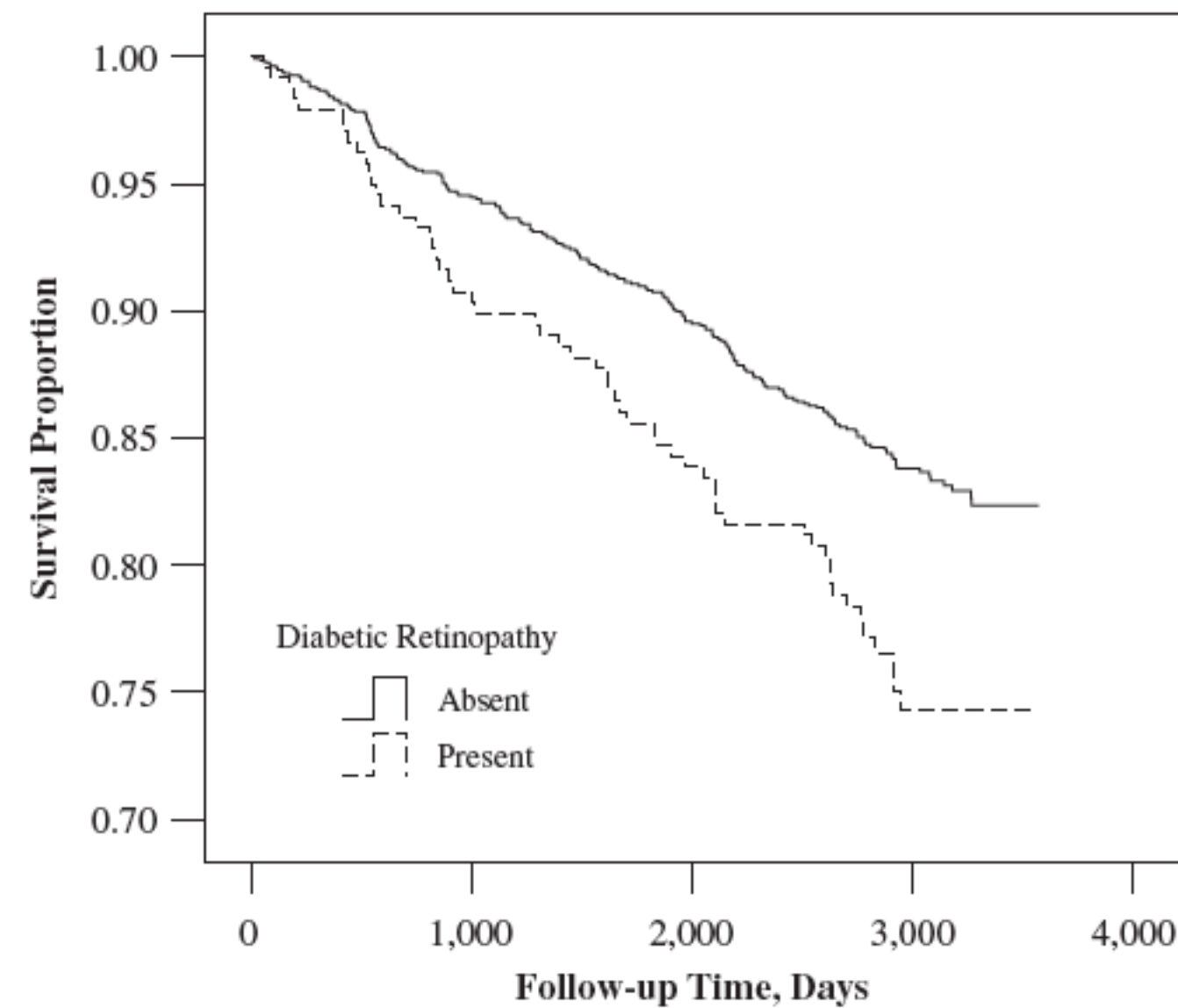
Jing Xie, PhD; M. Kamran Ikram, MD; Mary Frances Cotch, PhD; Barbara Klein, MD; Rohit Varma, MD, MPH;
Jonathan E. Shaw, MD; Ronald Klein, MD; Paul Mitchell, MD; Ecosse L. Lamoureux, PhD; Tien Yin Wong, MD, PhD

- Pts with DME or PDR were more likely to have incident CVD (IRR 1.39; 95% CI 1.16-1.67) and fatal CVD (IRR 2.33; 95% CI 1.49-3.67) compared to those without DME or PDR

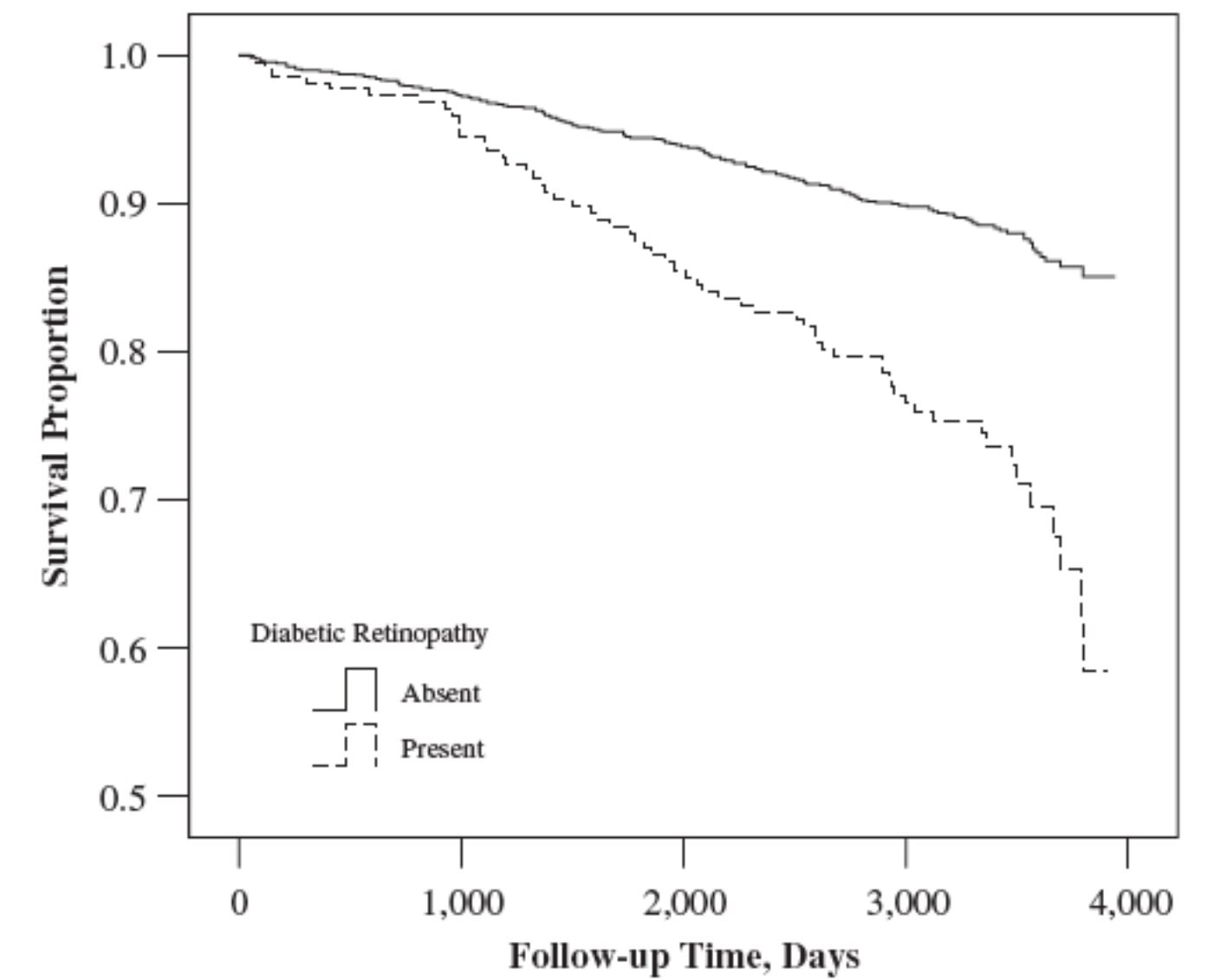
DR and Mortality



Stroke Free Survival



Coronary Heart Disease Free Survival



Heart Failure Free Survival

- Association of DR with mortality is mostly due to an increase in risk of CV disease in DM

DR and Cerebrovascular Disease

- Up to a third of symptomatic strokes can be attributed to disease of the small arteries/arterioles in the cerebral circulation
- Little is known about these small vessel pathologies due to the paucity of non-invasive methods to study the cerebral microcirculation
- Since retinal and cerebral vasculatures share similar embryological origins, anatomical features and physiological properties, vascular lesions seen in eyes with DR may mirror similar pathological disease processes in the cerebral circulation

DR and Cerebrovascular Disease

- Since the 1970's several investigators have reported the association of DR and stroke particularly in persons with HTN

Goto I et al. Stroke 1975;6:263-269

Nakayama T et al. Stroke 1997;28:45-52

Okada H et al. Stroke 1976;7:599-607

Petitti DB and Bhatt H. Stroke 1995;26:593-596

Schneider R et al. Stroke 1993;24:1874-1879

Svardsuud K et al. Acta Med Scand 1978;204:159-167

Tanaka H et al. Stroke 1985;16:773-780

DR and Cerebrovascular Disease

Table 2
Selected studies on the relationship of diabetic retinopathy and stroke

Study	Population	Follow-up	Retinal status	Associations ^a	References
WESDR	996 T1DM 1370 T2DM	4-year	PDR in T1DM PDR in T2DM	+++ +++	Klein et al. (1992)
WESDR	1370 T2DM	16-year	Mild NPDR PDR	+ (NS) ++	Klein et al. (1999a)
WESDR	996 T1DM	20-year	DR severity	++	Klein et al. (2004a)
ARIC	1617 T2DM	8-year	Any DR	++	Cheung et al. (2007c), Wong et al. (2002a)
WHO-MSVDD	1126 T1DM 3179 T2DM	12-year	DR in T1DM men DR in T1DM women DR in T2DM men DR in T2DM women	+ (NS) + (NS) +++ +++	Fuller et al. (2001)

WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; ARIC, Atherosclerosis Risk in Communities Study; WHO-MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetes; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

^aAdjusted hazard rate or relative risk <1.5 (+), 1.5–2.0 (++), >2.0 (+++); (NS), not statistically significant.

- DR is associated to both clinical and subclinical stroke independent of cerebrovascular risk factors

Is Diabetic Retinopathy an Independent Risk Factor For Ischemic Stroke?



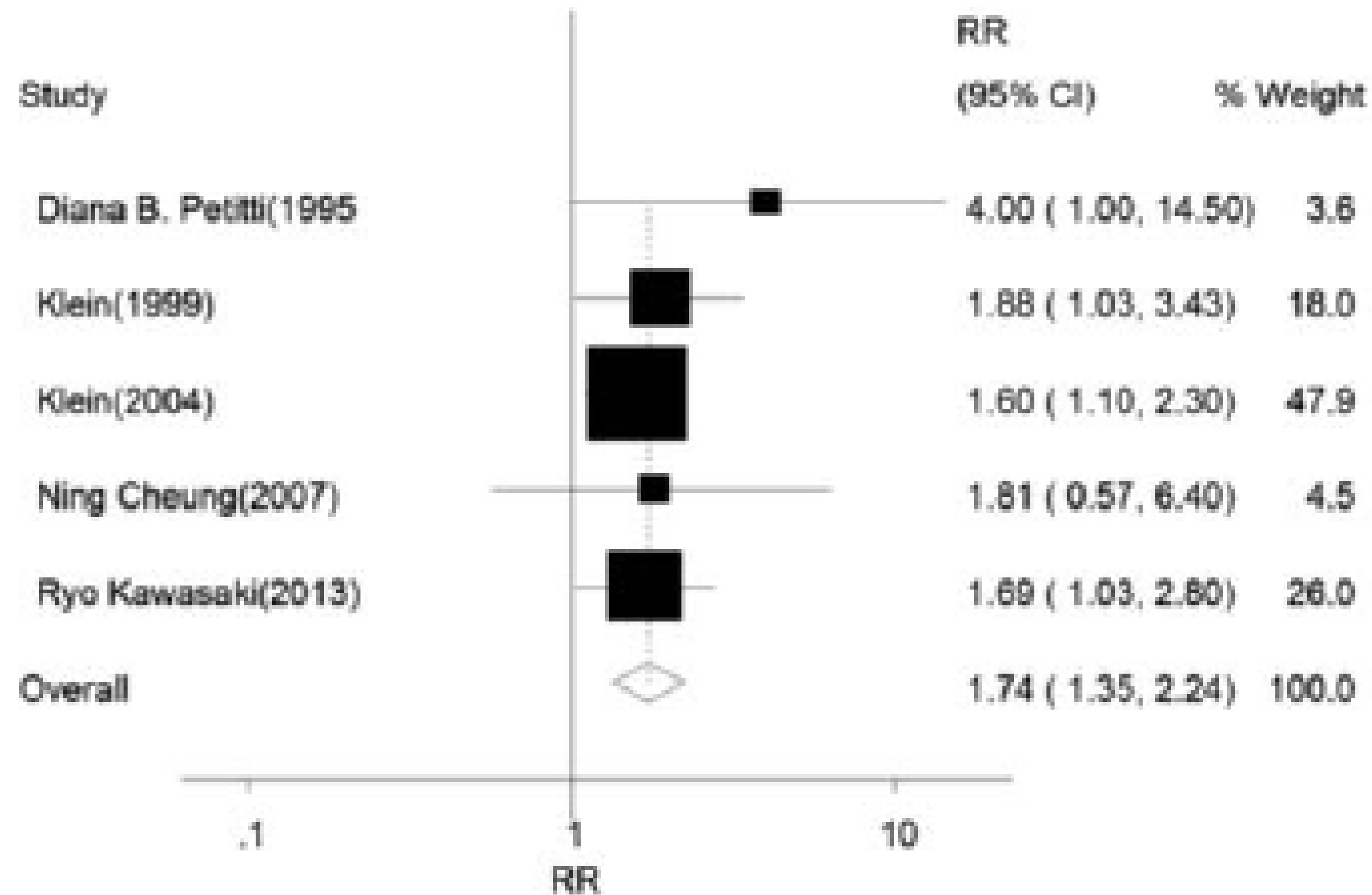
Ning Cheung, MBBS; Sophie Rogers, Mepi; David J. Couper, PhD; Ronald Klein, MD, MPH;
A. Richey Sharrett, MD, DrPH; Tien Y. Wong, MD, PhD

- Population based prospective cohort study of 1617 middle aged pts with DM
- DR identified via retinal photographs and incident ischemic stroke events were prospectively identified
- DR was associated with an increased risk of ischemic stroke (hazard ratio, 2.34; 95% CI 1.13-4.86)
- DR predicts incident ischemic stroke in diabetic pts independent of other risk factors

Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure

Evidence from epidemiological observational studies

Xiao-Rong Zhu, MD^a, Yong-Peng Zhang, MD^b, Lu Bai, MD^c, Xue-Lian Zhang, MD^a, Jian-Bo Zhou, MD^{a,*}, Jin-Kui Yang, MD^{a,d,*}



DR of DM and stroke

DR and Cerebrovascular Disease

- Apart from stroke, DR has also been linked to
 - cognitive decline
 - MRI detected cerebral atrophy
 - cognitive dysfunction and dementia

DR and Heart Disease

- Microvascular dysfunction has emerged as an important pathogenic factor in the development of diabetic heart disease
- No simple and non-invasive techniques for the assessment of coronary microcirculation

DR and Heart Disease

- Retinopathy signs may reflect a generalized microangiopathic process that affects the myocardium in people with DM
- Retinopathy has been linked to ischemic T wave on EKG, severity of coronary stenosis on coronary angiography, histologic evidence of microvascular disease in the myocardium and incident clinical coronary heart disease events

Hiller R et al. Am J Epidemiol 1988;128:402-409

Breslin DJ et al. Circulation 1966;33:87-97

Breslin DJ et al JAMA 1966;195:335-338

Michelson EL et al. Arch Int Med 1979;1139-1141

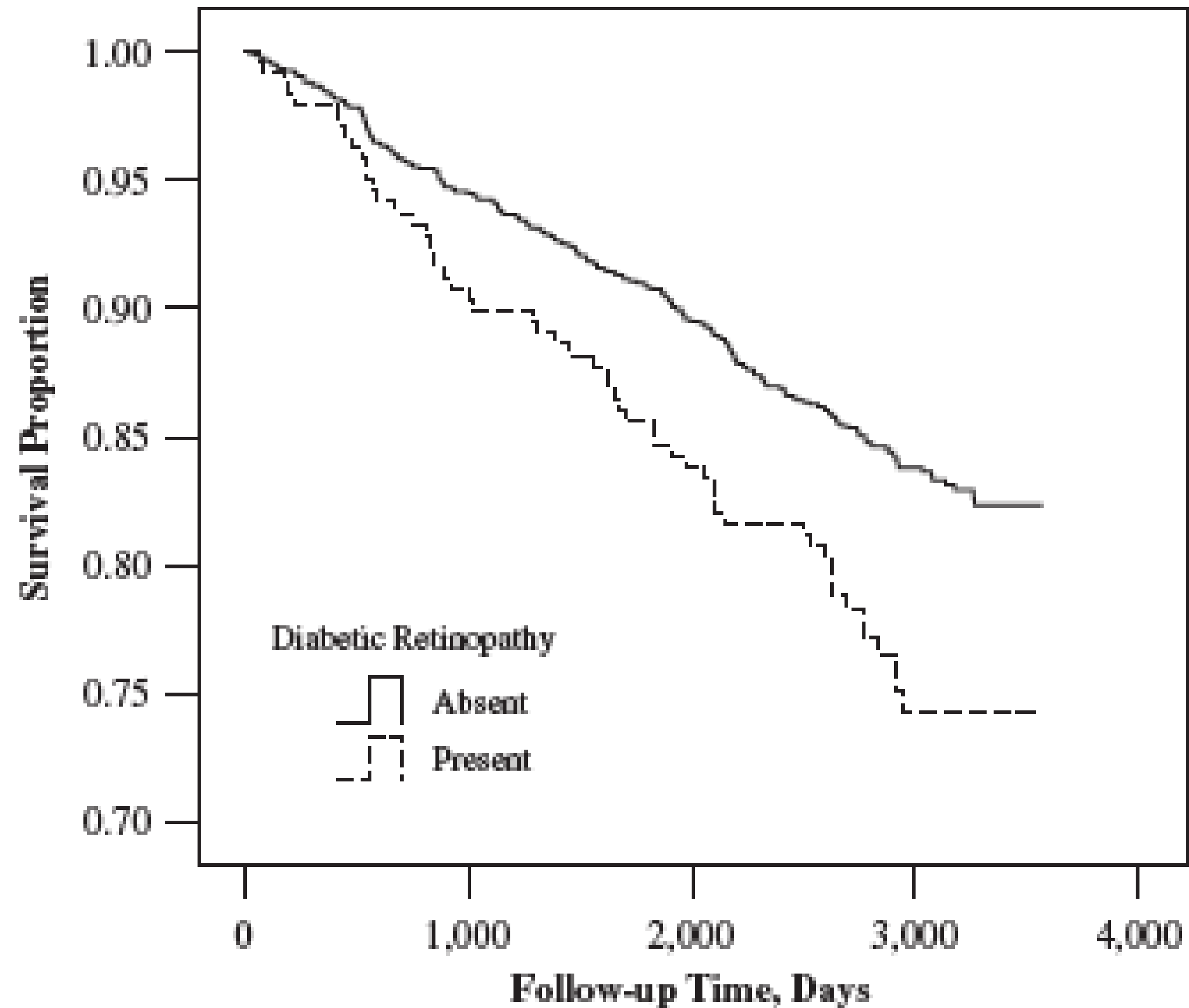
Factor SM et al. N Engl J Med 1980;302:384-388

Duncan BB et al. Br J Ophthalmol 2002;86:1002-1006

DR and Heart Disease

- Population based studies using retinal photographs have confirmed these prior observations
- Now clear that diabetic retinopathy signs are associated with an increased risk of MI and coronary heart disease and heart failure

DR and Heart Disease



- Coronary heart disease free survival in pts with and without DR

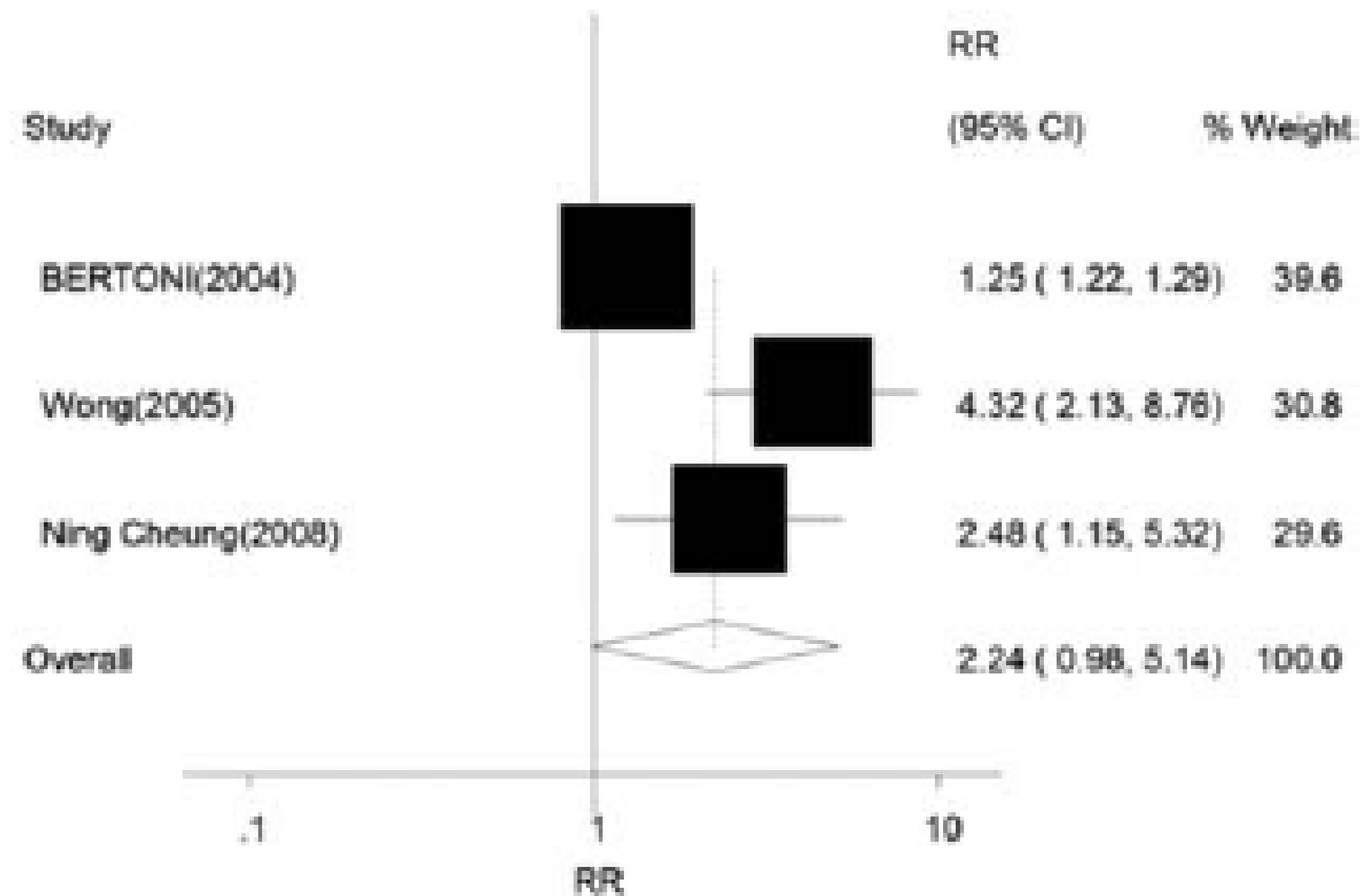
DR and Heart Disease

- Atherosclerosis Risk In Community (ARIC) Study
 - Large prospective cohort of 1617 middle aged white and African American with type 2 DM
 - Presence of retinopathy was associated with a two-fold higher risk of incident coronary heart disease (and MI), three-fold higher risk of fatal coronary heart disease and four-fold higher risk of congestive heart failure independent of diabetes duration, glycemic control, smoking, lipid profile and other risk factors

Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure

Evidence from epidemiological observational studies

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DR of DM and heart failure

DR and Heart Disease

- There is a graded, dose dependent association of increasing diabetic retinopathy severity with increasing coronary heart disease risk

Cheung N et al. Diabetes Care 2007;30:1742-1746

Fuller JH et al. Diabetologia 2001;44 (S2):S54-S64

Faglia E et al. Diabetes Care 2002;25:2032-2036

Juutilainen A et al. Diabetes Care 2007;30:292-299

Miettinen H et al. Diabetes Care 1996;19:1445-1448

DR and Heart Disease

- Clinical studies suggest that the presence of retinopathy can be used as an indicator of silent myocardial ischemia
- May help guide investigative approaches in diabetic pts with suspected heart disease
- Retinopathy may be a valuable prognostic predictor for diabetic pts undergoing cardiac revascularization procedures
- Pts with retinopathy are more likely to sustain major cardiac adverse events or complications after percutaneous coronary intervention or coronary artery bypass graft even after correcting for other risk factors

DR and Heart Disease

- Association between DR and subclinical coronary micro and macrovascular pathology
- Pathological and radiological studies studies have shown that pts with retinopathy are more likely to have myocardial arteriolar abnormalities, coronary perfusion defects, poorer coronary flow reserve, lower coronary collateral score, higher degrees of coronary artery calcification and more diffuse/severe coronary artery stenosis on angiograms

Norgaz T et al. Int Heart J 2005;46:639-646

Wong TY et al. Am J Epidemiol 2007;

Yoshida M et al. Horm Met Res 1999;31:558-563

Celik T et al. Clin Cardiol 2005;28:384-388

DR and Nephropathy

- Diabetic nephropathy is the other major classic microvascular complication of diabetes
- Epidemiological studies have consistently demonstrated that DR is associated with microalbuminuria and clinical nephropathy

Relationship Between Retinal and Glomerular Lesions in IDDM Patients

BLANCHE M. CHAVERS, S. MICHAEL MAUER, ROBERT C. RAMSAY, AND MICHAEL W. STEFFES



- Studied the relationship between DR and quantitative measures of glomerular structure in type 1 DM
- Renal biopsies were evaluated using morphometric techniques and DR was assessed with color fundus photography
- High correlation between pathological changes in the retinal vasculature with those in the renal vasculature
- Discordance between retinopathy and nephropathy exists
 - Pts with normal urinary albumin excretion, normal glomerular structure measures AND advanced retinopathy

The Relationship of Diabetic Retinopathy to Preclinical Diabetic Glomerulopathy Lesions in Type 1 Diabetic Patients

The Renin-Angiotensin System Study

Ronald Klein,¹ Bernard Zinman,² Robert Gardiner,³ Samy Suissa,⁴ Sandra M. Donnelly,⁵ Alan R. Sinaiko,⁶ Michael S. Kramer,⁷ Paul Goodyer,⁸ Scot E. Moss,¹ Trudy Strand,⁶ and Michael Mauer⁸



- Severity of retinopathy was positively associated with biopsy proven renal anatomical features of preclinical diabetic glomerulopathy

The Relationship Between Diabetic Retinopathy and Diabetic Nephropathy in a Population-Based Study in Korea (KNHANES V-2, 3)



Won June Lee,¹ Lucia Sobrin,² Min Jeong Lee,³ Min Ho Kang,¹ Mincheol Seong,¹
and Heeyoon Cho^{1,2}

- PDR is associated with microalbuminuria
- Diabetic retinopathy is associated with overt nephropathy
- When an ophthalmologist finds the presence of DR or PDR, timely evaluation of the pt's renal status is imperative

DR and Neuropathy

- Few studies show that retinopathy may be related to neuropathy risk in people with diabetes

Risk Factors for Severity of Diabetic Polyneuropathy

Intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort

PETER JAMES DYCK, MD
JENNY L. DAVIES, BA
DAVID M. WILSON, MD

E. JOHN SERVICE, MD
L. JOSEPH MELTON III, MD
PETER C. O'BRIEN, PHD



- In a longitudinal study of 264 diabetic individuals, the presence of more severe microvascular disease including retinopathy was associated with more severe diabetic polyneuropathy

Is Peripheral Neuropathy Associated With Retinopathy and Albuminuria in Individuals With Impaired Glucose Metabolism?

The 1999–2000 AusDiab

ELIZABETH L.M. BARR, MPH¹
TIEN Y. WONG, MD, PHD^{1,2}
ROBYN J. TAPP, PHD¹
C. ALEX HARPER, MD²
PAUL Z. ZIMMET, MD, PHD¹

ROBERT ATKINS, MSc, MD³
JONATHAN E. SHAW, MD¹
ON BEHALF OF THE AUSDIAB STEERING
COMMITTEE



- Significant association between retinopathy and neuropathy in persons without clinical diabetes but with abnormal glucose metabolism

Epidemiology of Proliferative Diabetic Retinopathy

RONALD KLEIN, MD, MPH
BARBARA E.K. KLEIN, MD, MPH
SCOT E. MOSS, MA

The 14-Year Incidence of Lower-Extremity Amputations in a Diabetic Population

The Wisconsin Epidemiologic Study of Diabetic Retinopathy

SCOT E. MOSS, MA
RONALD KLEIN, MD
BARBARA E.K. KLEIN, MD

- In the WESDR, pts with severe NPDR or PDR when compared to pts with no or minimal retinopathy, had a higher risk of incident lower leg amputation (complication partly related to diabetic somatic neuropathy)

Summary

- DR should be viewed as a biomarker of underlying deleterious effects of hyperglycemia on the systemic microcirculation