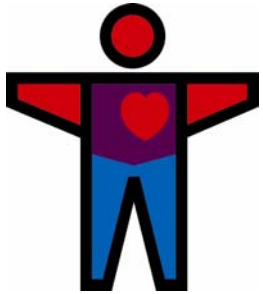
Celebrating 30 years of the MIDSPAN Studies



Phenotype and genotype studies across the generations

John Connell

Strengths of population

Parents

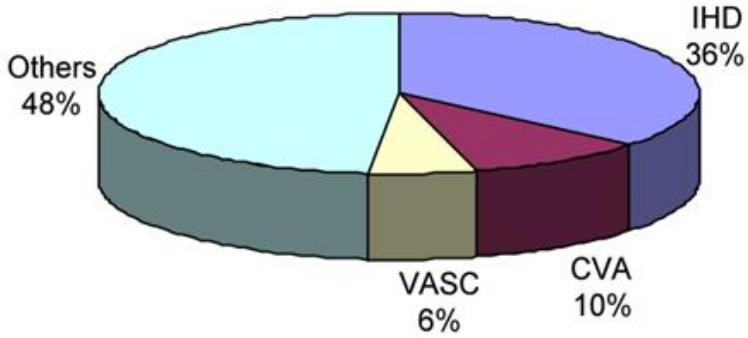
- **Long term follow up**
- **High event rate**
- **Excellent initial phenotyping**

Offspring

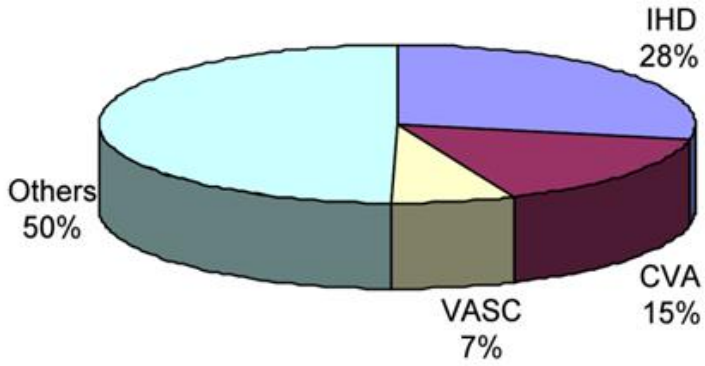
- **Detailed phenotyping**
- **Future recording of events**
- **Genetic material**

Renfrew Paisley - Mortality

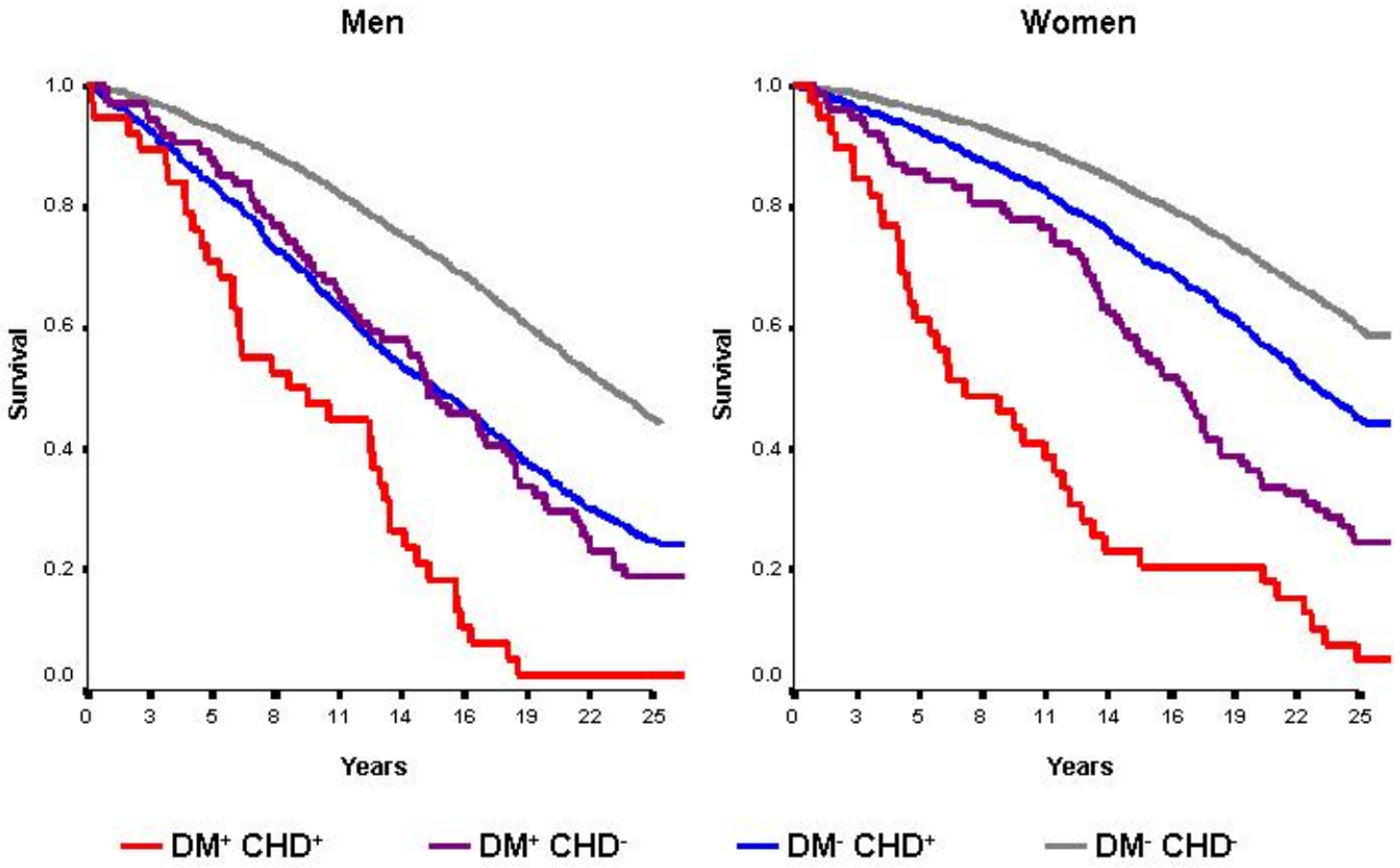
Male
n = 4267 (60%)



Female
n = 3746 (45%)



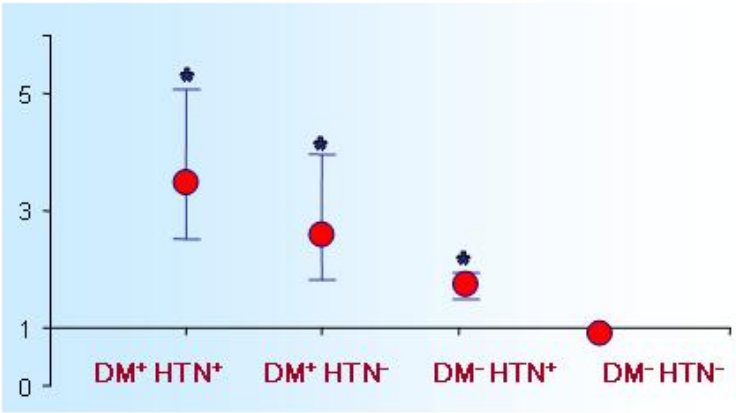
Diabetes mellitus confers increased CV risk in men and women



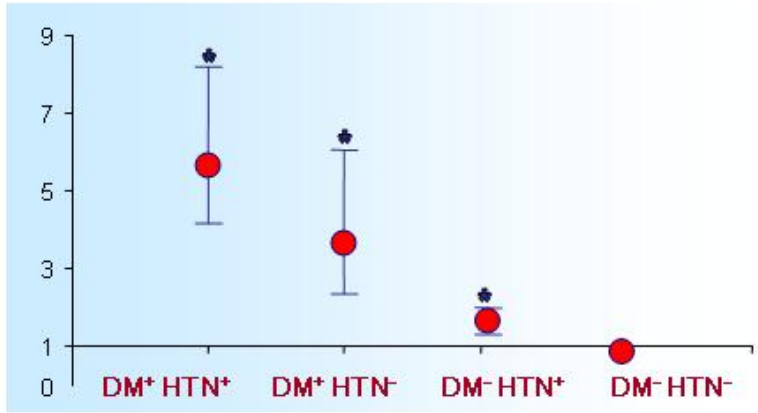
Hazard ratios:
Men – diabetes v CHD = 1.17
Women - diabetes v CHD = 1.97

Diabetes Care, 2005, 28, 1588

Diabetes and hypertension combine to increase CV risk



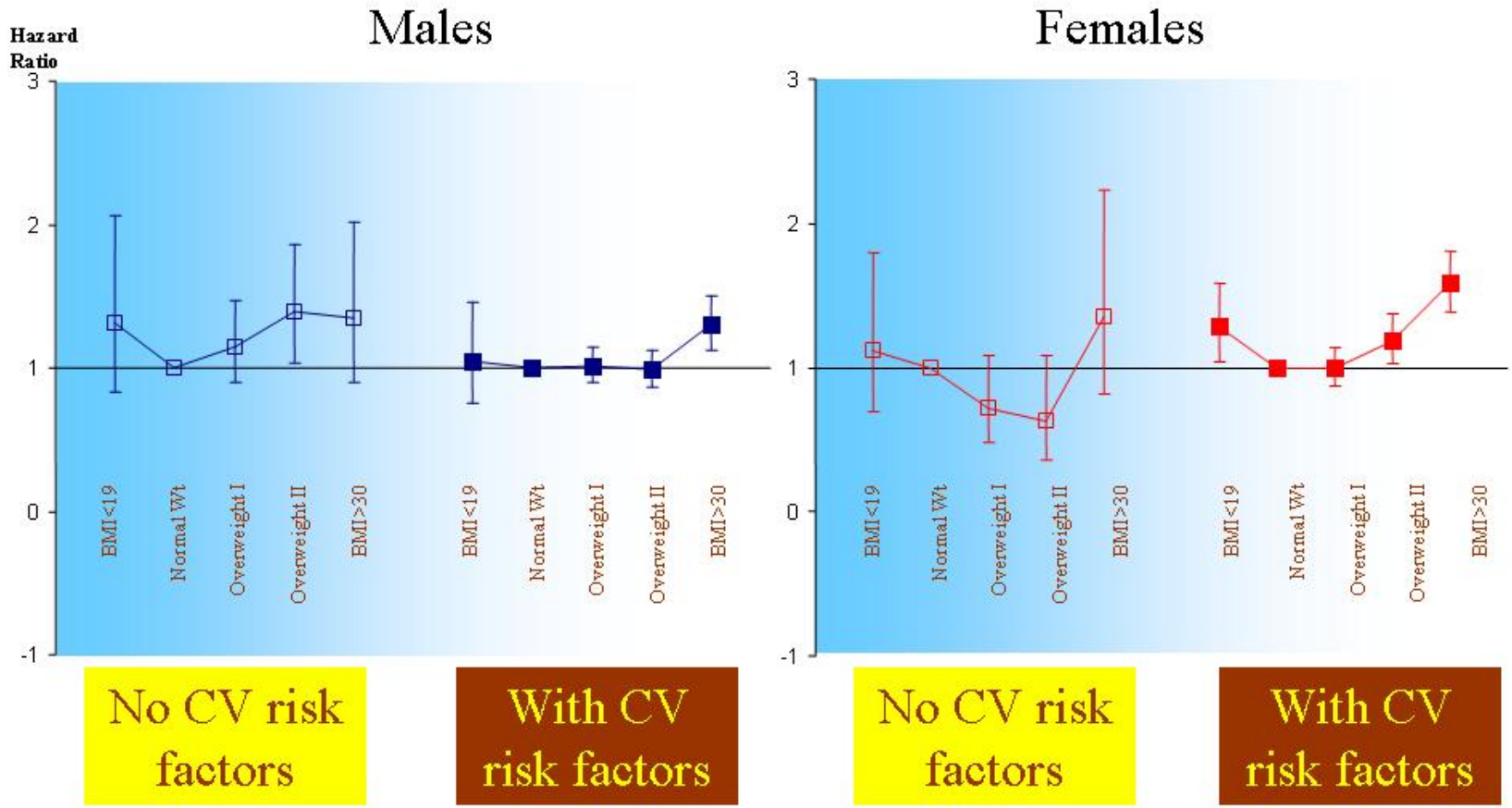
Male



Female

Adjusted for – Age, BMI, Smoking, Cholesterol, Social status

Impact of weight on CV mortality



Renfrew Paisley Studies

- **Complex interplay of cardiovascular risk factors**
- **Parental generation alone does not allow genetic contribution to be discerned**

↓

Development of offspring studies to allow:

- **Heritability estimates of key CV phenotypes**
- **Exploration of familial clustering of disease**
- **Studies of specific candidate genes**
- **Focus on specific CV risk factors – obesity; Blood pressure; ECG etc**

Heritability of key CV and ECG variables

Phenotype	Heritability
BMI	0.55±0.06*
Waist/Hip ratio	0.39±0.07*
Systolic BP	0.35±0.07
Diastolic BP	0.53±0.06*
ECG Phenotypes	
LVM (Rautaharju) gms	0.55 ± 0.07*
Cornell Voltage μV	0.32 ± 0.06*
Sokolow Lyon μV	0.32 ± 0.06*
12Lead μV	0.44 ± 0.06*
Sokolow Lyon product μV.s	0.28 ± 0.06*
Cornell Voltage product μV.s	0.28 ± 0.06*
12 Lead product μV.s	0.36 ± 0.07*

Good evidence from family approach that several variables are inherited

What are the key genes that lead to this?

Initial candidates studies focus on known pathways

renin/angiotensin/aldosterone system
adrenoreceptors
signalling pathways involved in CV regulation

Is one form of the gene inherited more often than another in relation to a particular cardiovascular risk factor ?

Studies on G-protein coupling; β-adrenoreceptor; angiotensin converting enzyme and aldosterone synthase

	GNB3		B1AR		ACE		SF1	
N / families[a]	610/244		645/245		703/283		610/244	
	Z	p	Z	p	Z	p	Z	p
Systolic BP	-0.61	0.54	-1.75	0.079	-1.03	0.30	-0.61	0.54
Diastolic BP	-0.62	0.53	-1.17	0.24	-0.67	0.49	-0.62	0.53
BMI	0.36	0.72	-1.23	0.22	0.07	0.94	0.36	0.71
LV mass	1.3	0.19	-0.72	0.47	-0.09	0.93	1.3	0.19
12Lead_V	-0.25	0.80	2.07	0.03	1.06	0.28	-0.25	0.80

No individual gene explains variation in measurements in population
? Combinations of genetic factors may be more informative

Future use of resource

- **Exploration of other candidate genes**
- **Better use of family structure and two generation design**
- **Alternative ways of analysing data – use of genetic information to stratify population**
- **Development of alternative phenotypes - eg; focus on central obesity**
- **Future utilisation of morbidity and mortality data**

Summary

- **Highly informative and well documented population**
- **Family structure allows social, environmental and genetic contributions to risk to be identified**
- **Genetic information needs to be fully exploited; very powerful tool for future research**

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