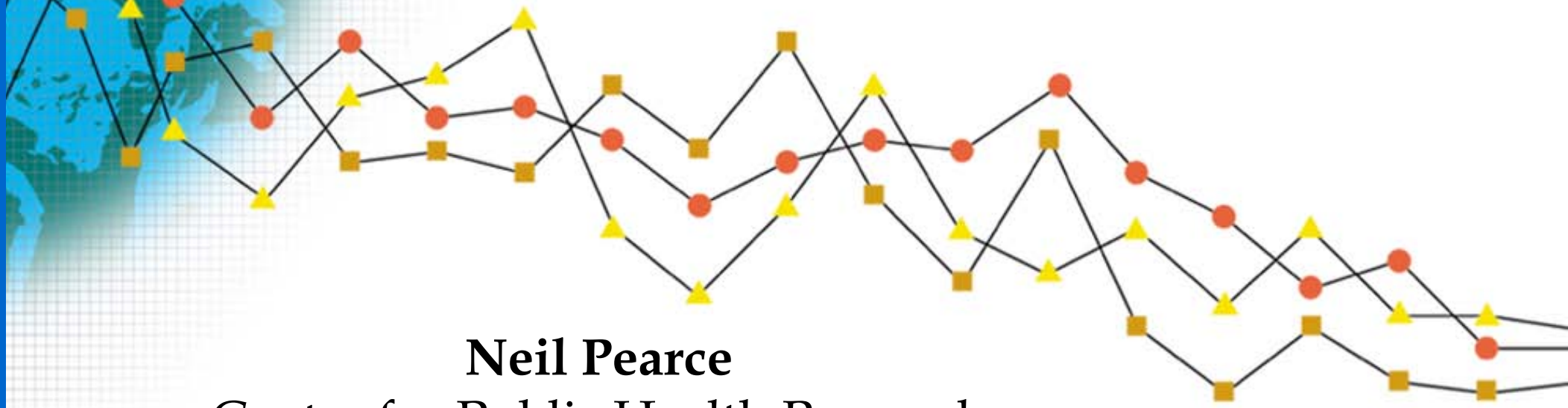
Genetics, environment and asthma



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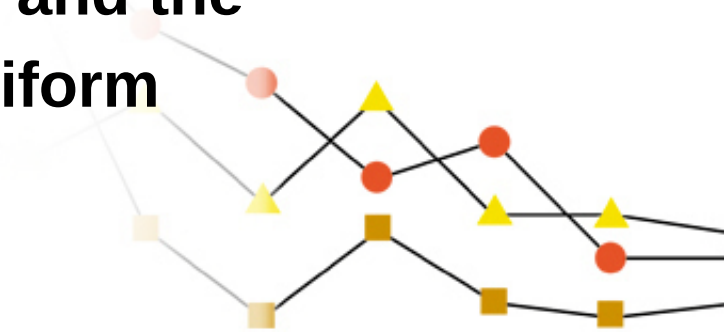
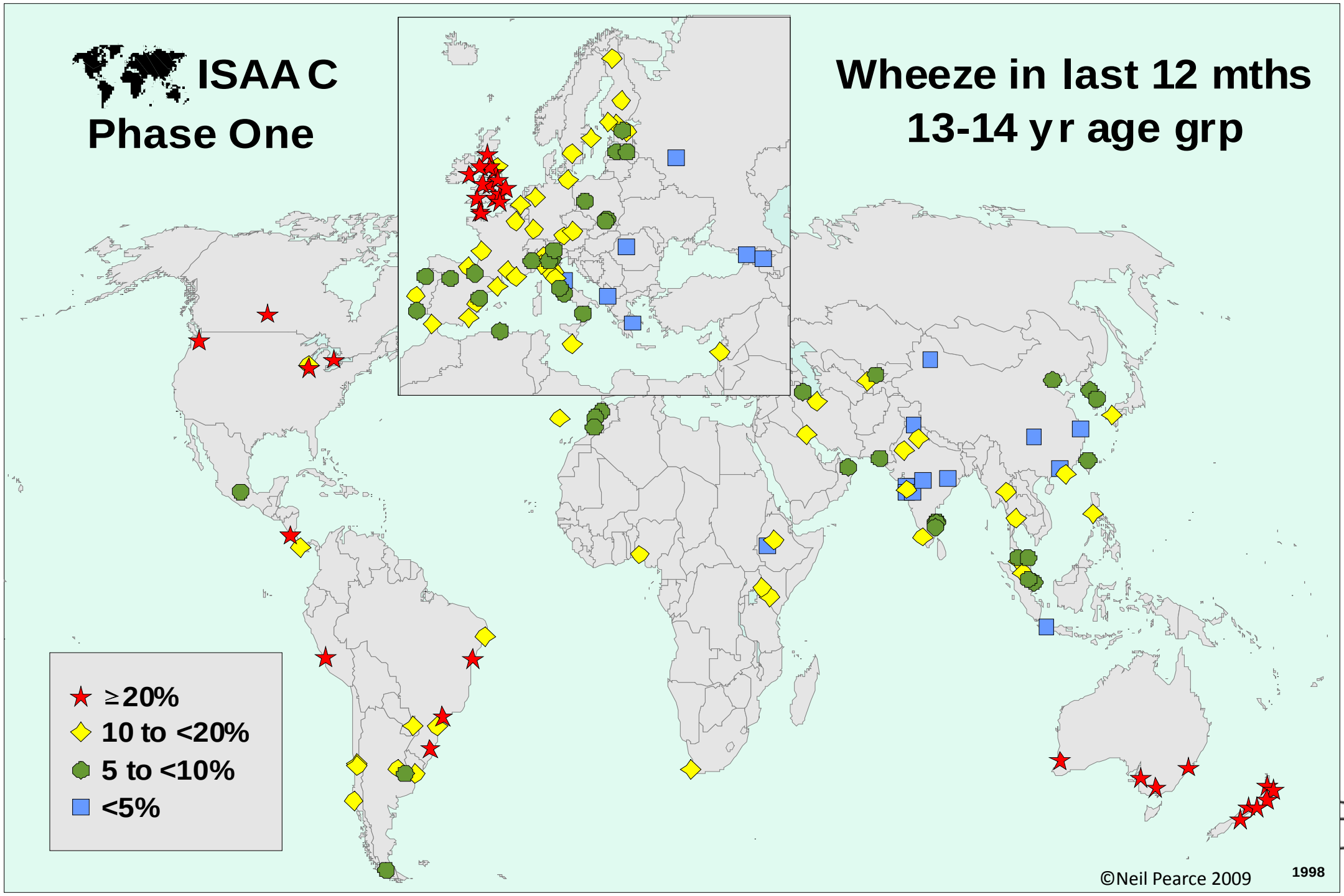
Rudolf Virchow (1821-1902)
published in 1859 the fundamental "Die Cellularpathologie"

However far man may advance in his understanding of physical and chemical processes occurring inside these elementary organisms, no research will, to my mind, ever lead us beyond considering the cell as the real essential basis of our medical understanding . For it it is in the cell that we find a uniform expression of the process of life, and the cell therefore seems the carrier of the uniform functions of life *(1867)*



ISAAC Phase One

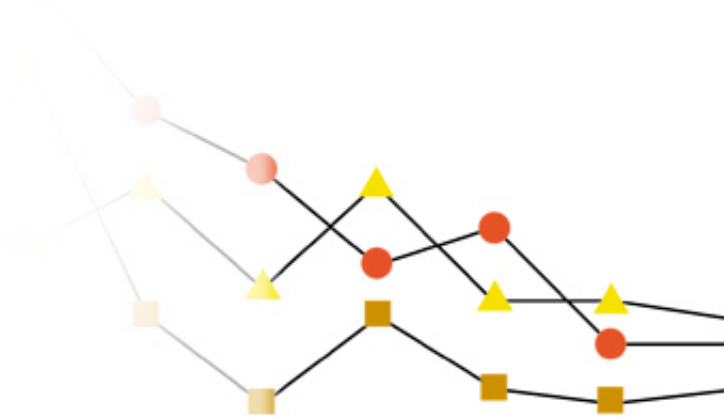
Wheeze in last 12 mths 13-14 yr age grp



1998

Evidence for the potential importance of genetic factors in asthma

- Candidate genes
- Heritability/family history
- Geographical/ethnic/race differences



Kaufmann F, and **the Post Genome Respiratory Epidemiology Group** (Anto J, Baur MP, Bickeboller H, Clayton D, Cookson WOC, Demenais F, Helms PJ, Humphrey-Smith I, Imbeaud S, Knoppers BM, Lathrop M, Little J, Pearce N, Schaid D, Silverman E, Weiss S, Wjst M). Post-genome respiratory epidemiology: a multidisciplinary challenge. Eur Respir J 2004; 24: 471-80.

- To date, asthma genetics has had limited success in explaining a significant proportion of asthma cases and even less success in explaining the population patterns.
- Those associations that have been found have rarely been replicated in other populations.
- This does not mean that the observed associations are invalid, but it does limit their usefulness in both **scientific and public health** terms.
- Genetics cannot account for the global asthma prevalence and time trends, although gene-environment interactions may be playing a secondary role.

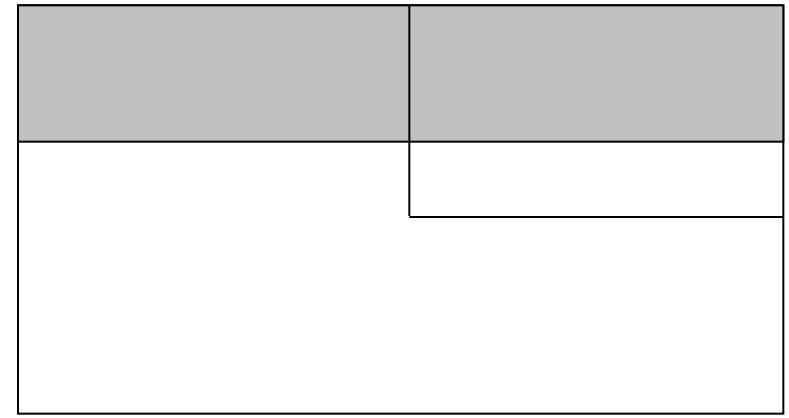
PKU gene

No Yes

Phenylalanine in the diet

High

Low



	% cases caused	% variance explained
High phenylalanine in the diet	100%	0%
PKU Gene	100%	100%

PKU gene

No Yes

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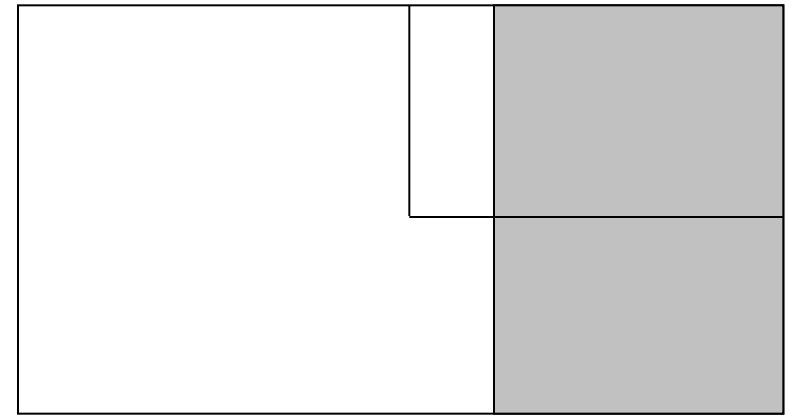

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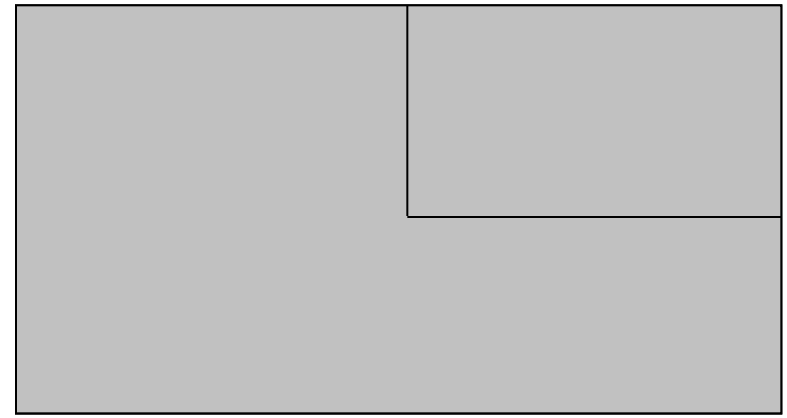
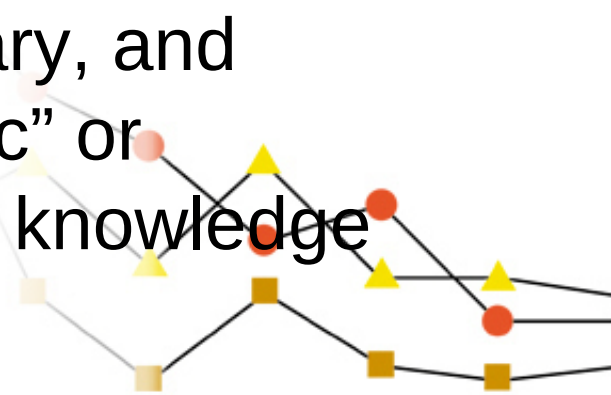


	% cases caused	% variance explained
High phenylalanine in the diet	100%	50%
PKU Gene	100%	50%

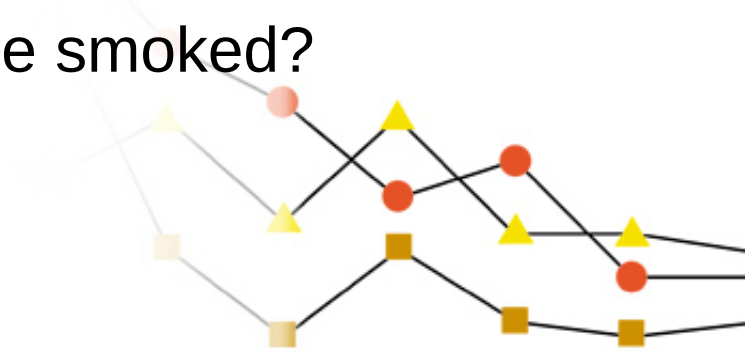
Genetic diseases

- When the environmental component is universal but the genetic component varies, then we say that the condition is entirely genetic
- When the genetic component is universal but the environmental component varies then we say that the disease is entirely environmental
- In most instances, presumably, both the genetic factors and the environmental factors vary, and whether we label the disease as “genetic” or “environmental” depends on our current knowledge



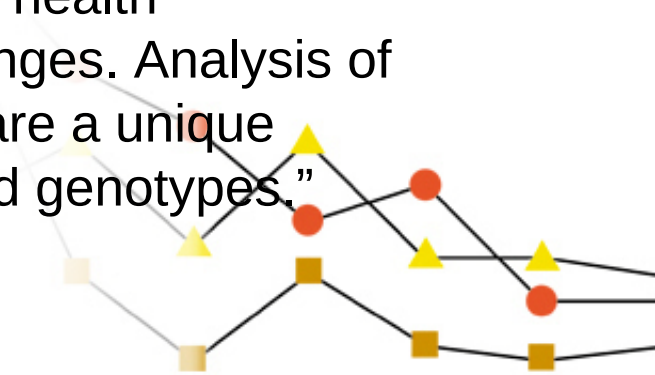
Genetics, heritability and the environment

- “Except for some cases of trauma, it is fair to say that virtually every human illness has a hereditary component.” Collins F. N Engl J Med 1999, 341: 28-37.
- Virtually every human illness also has an environmental component.
- Thus, virtually every human illness is 100% genetic and 100% environmental (e.g. PKU)
- What is the heritability of lung cancer? What would be the heritability in a population where everyone smoked?



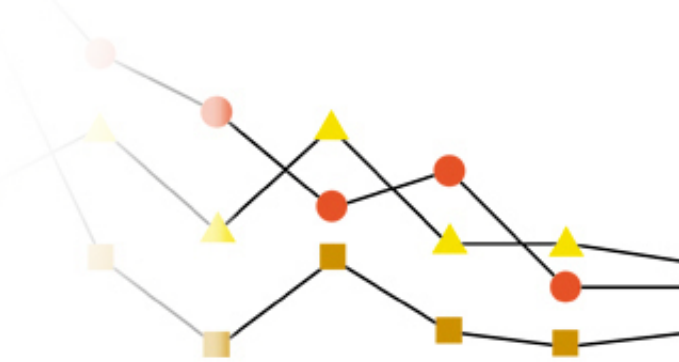
Lewontin RC. The analysis of variance and the analysis of causes. Am J Hum Genet 1974; 26: 400-11.

- "The difficulties in the early history of genetics embodied in the pseudo-question of 'nature versus nurture' arose precisely because it … supposed that the phenotype of an individual could be the result of *either* environment *or* genotype, whereas we understand the phenotype to be the result of *both*."
- "The analysis of causes in human genetics is meant to provide us with the basic knowledge we require for correct schemes of environmental modification and intervention. Together with a knowledge of the relative frequencies of different human genotypes, a knowledge of norms of reaction can also predict the demographic and public health consequences of certain massive environmental changes. Analysis of variance can do neither of these because its results are a unique function of the present distribution of environment and genotypes."



How much of the variation of (asthma) prevalence is explained by genetic variation?

- The “percentage of variation explained” by a risk factor (e.g. family history, genetic factors) is not a generalisable concept
- It does not make sense to say that “asthma is 40% genetic and 60% environmental”.
- Asthma must be 100% genetic and 100% environmental

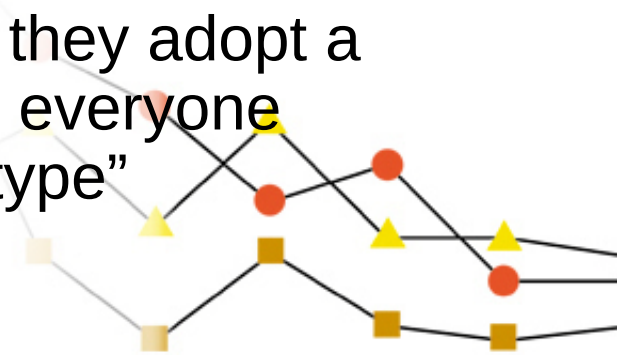


Pearce N, Foliaki S, Sporle A, Cunningham C.
Genetics, race, ethnicity and health.
Br Med J 2004; 328: 1070-2.

- Genetics
  - Heritability and the environment
- Race
  - Race and health
- Ethnicity
  - Ethnicity and health

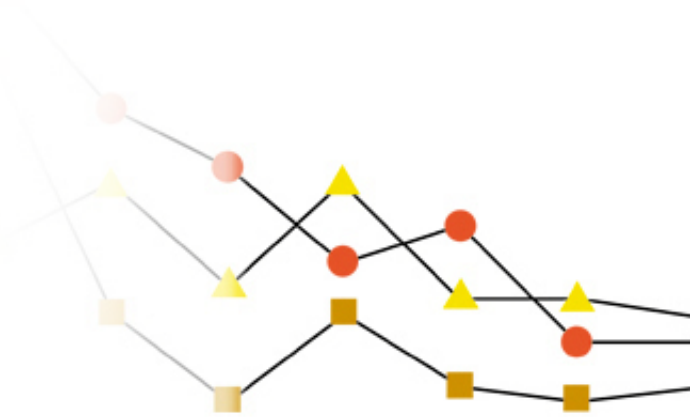
Genetics and the environment

- Genetic factors do have a major influence on health, but they are just part of a much larger picture; we are all continuously developing throughout our lives with a constant interaction between our genes and the environment
- Any discussion of genetic tendencies therefore makes assumptions about who is “normal” and what is a “normal environment”
- For example, many researchers have argued that Polynesians have a “thrifty genotype” with a greater tendency towards obesity and diabetes when they adopt a European diet, but it now appears that almost everyone except Europeans may have the “thrifty genotype”



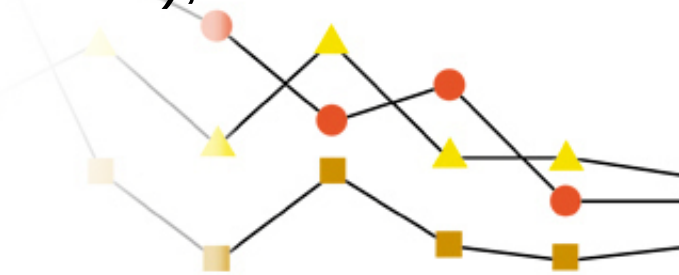
Genetics, heritability and the environment

- Few diseases are purely hereditary
- Diseases may “run in families” because of a common environment; e.g. pellagra was assumed to be a genetic disease until it was realised that it is a disease of poverty and malnutrition (which is inherited)
- Even for classic “genetic diseases” environmental factors usually also have an important role and are easier to modify



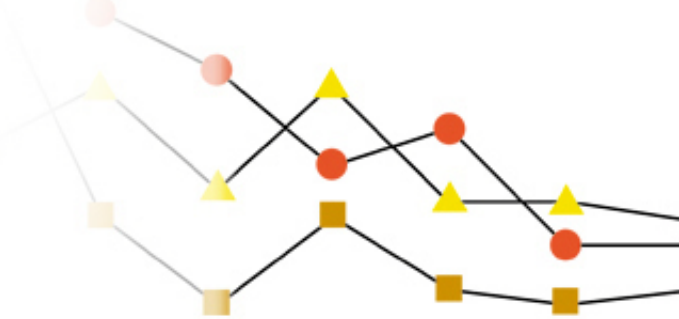
Race and health

- Genetics is important, but what does genetics have to do with race?
- Some researchers have attempted to define broad racial groupings (African, Caucasian, Pacific Islanders, Asian, Native American)
- Human races are not, and never were, pure; race is largely an artificial construct
- About 85% of all genetic variation is random and has no association with “race”; about 8% is between ethnic groups within the same “race” (e.g. Spanish, Irish, Italian), and about 7% is related to continental “race”



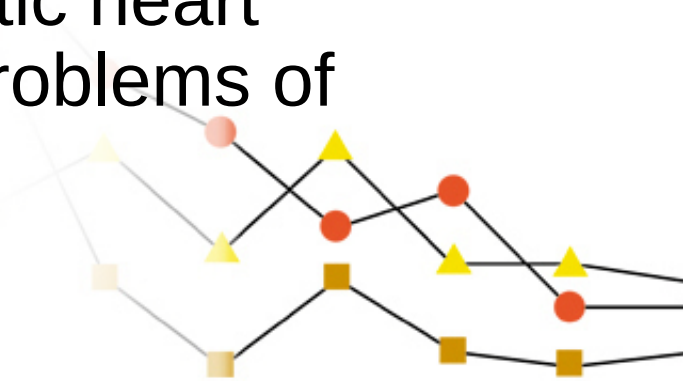
Ethnicity and health

- Ethnicity is a complex construct that includes biology, history, cultural orientation and practice, language, religion and lifestyle
- Ethnicity is only loosely related to “race” and very loosely related to genetics
- There are major ethnic differences in health
- These are predominantly due to differences in environment and lifestyle, as well as access to health care



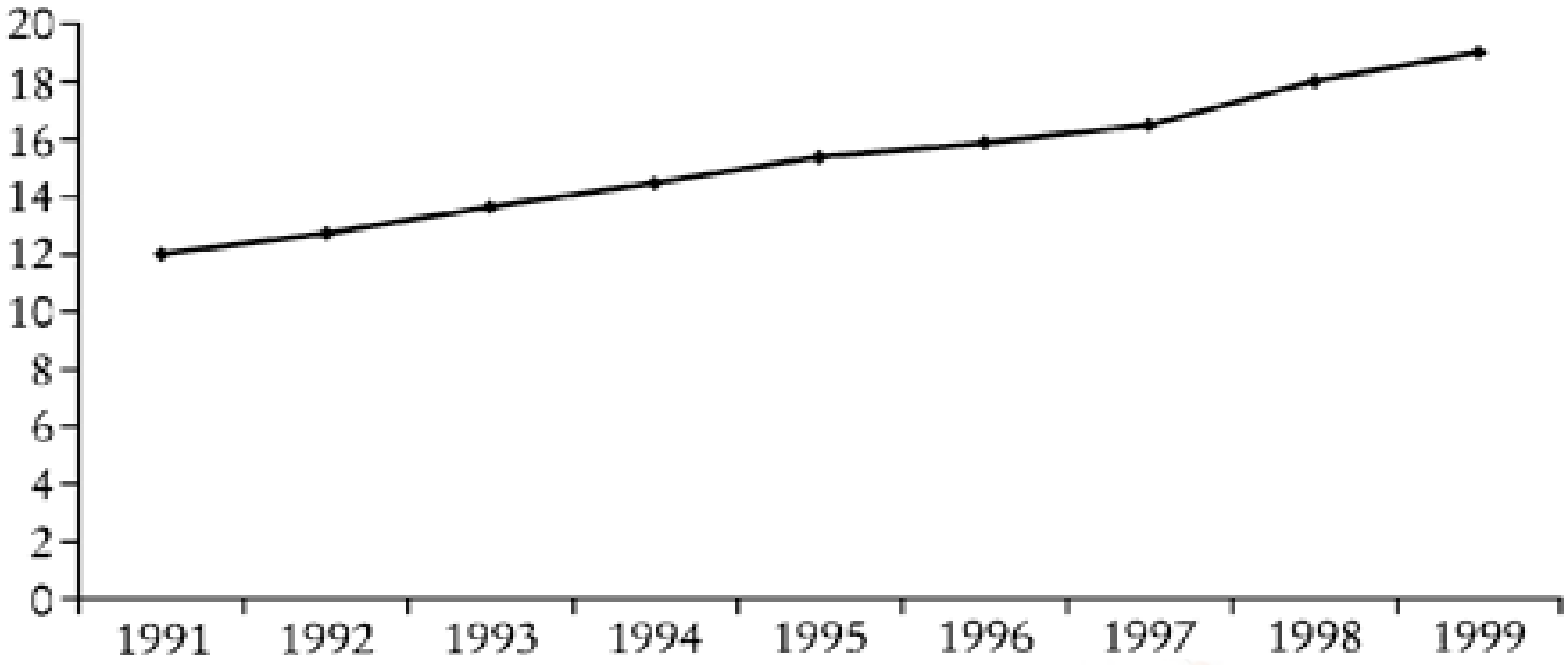
Ethnicity and health

- For example, the ADH2-2 gene, which protects against alcoholism, is more common in Maori than in European New Zealanders, but alcoholism is still more common in Maori because of socioeconomic factors
- Similarly, Maori experience high death rates from “non-fatal” diseases such as asthma, diabetes, bronchiectasis, tuberculosis, rheumatic heart disease; these are primarily due to problems of access to health care



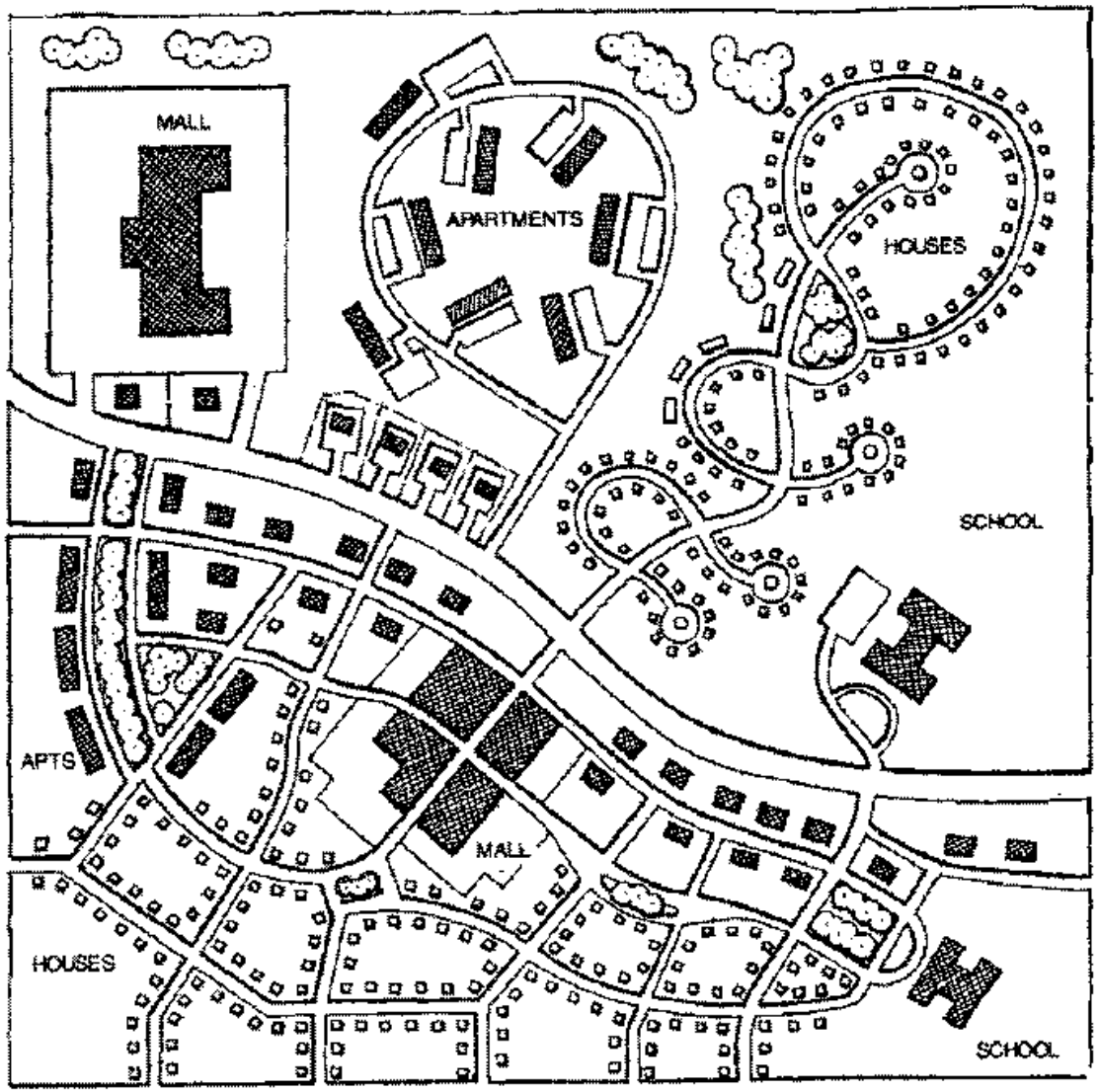
Race and health

- Few health-related genetic differences between “races” have been found
- Those that have been found are generally random mutations in subpopulations, or result from regional selection, and are not related to continental race.
- Thus your health may be influenced by who your ancestors were, but this depends on genetic factors specific to families, not “races”
- Genetic factors are unlikely to explain time trends in health, e.g. the increases in asthma in “Western countries” in the last few decades

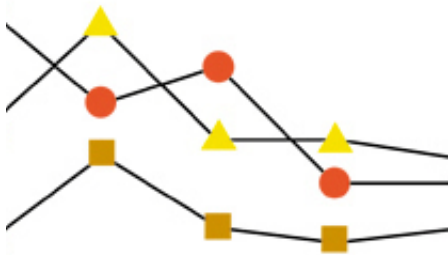


Prevalence of obesity in US adults from 1991-1999

Suburban Sprawl

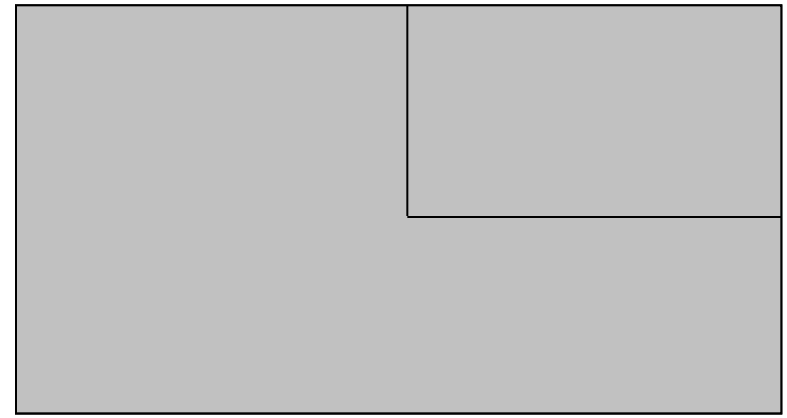


Traditional Neighborhood



Obesity genes

Exercise		No	Yes
	Low		
	High		



	% cases caused	% variance explained
High phenylalanine in the diet	100%	50%
PKU Gene	100%	50%

Obesity genes

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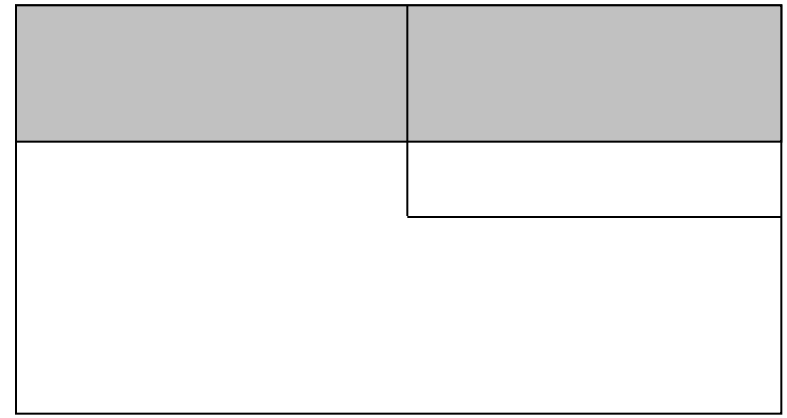
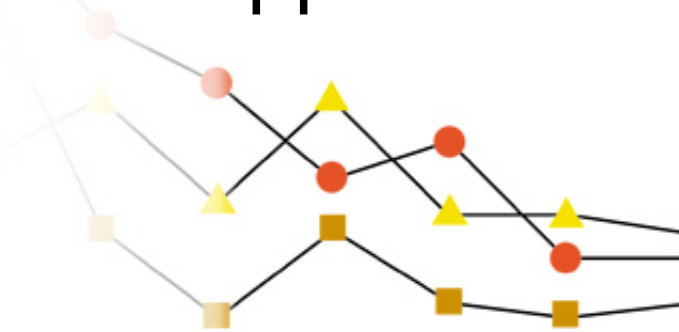


	% cases caused	% variance explained
High phenylalanine in the diet	100%	0%
PKU Gene	100%	100%

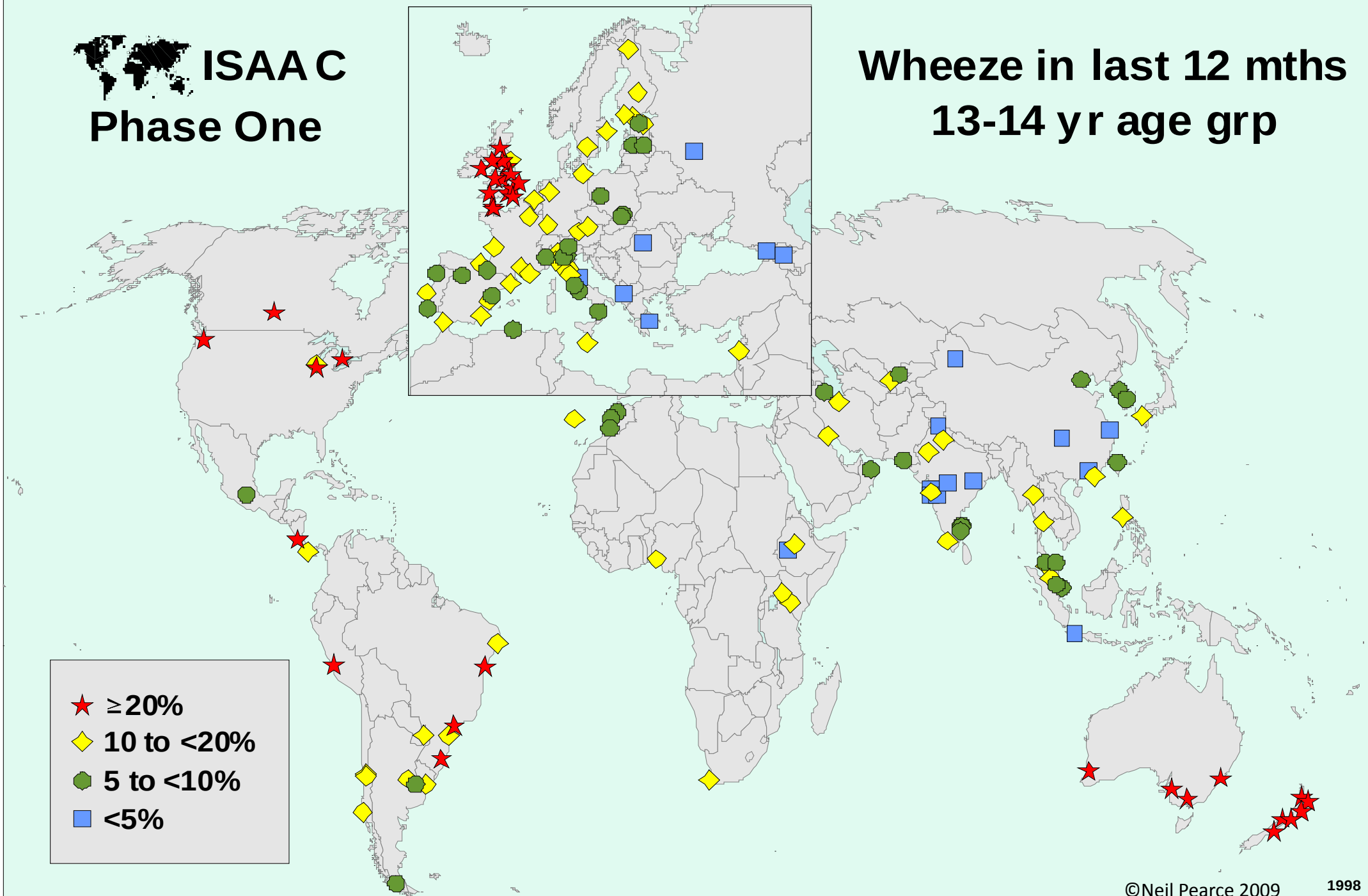
What causes obesity?

- Twin studies show high heritability
- Time trends show that environmental factors are of overwhelming importance
- Twin studies are perfectly matched on birth cohort – and thus on factors relating to secular trends – when there is no variation in the environment, then genetic factors appear to be relatively more important



ISAAC Phase One

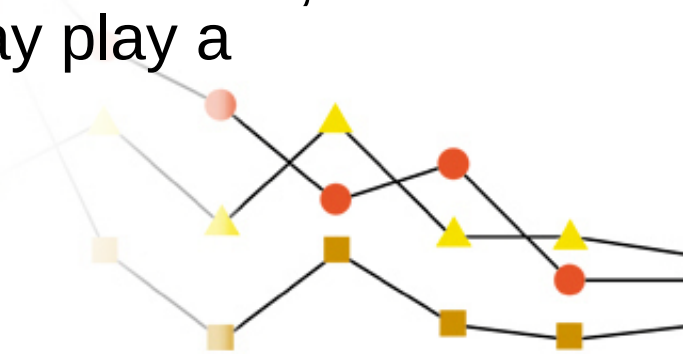
Wheeze in last 12 mths 13-14 yr age grp



1998

Do genetic factor explain the population patterns and time trends?

- There are large differences in asthma prevalence in the same ethnic group in different countries (e.g. Hong Kong/Guangzhou, Pacific children in the Pacific and in New Zealand)
- In the same country, the various ethnic groups often have similar asthma prevalence (e.g. Maori, Pacific and European children in New Zealand)
- Migration studies have shown changes in asthma prevalence with migration
- Genetic factors (alone) cannot explain the time trends, although gene-environment interactions may play a secondary role



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The greatest potential for population-based genetic interventions occurs when:

- the disease is known to occur through a single well-defined mechanism
- only a small number of genes are relevant to this mechanism
- there is little temporal or geographical variation.

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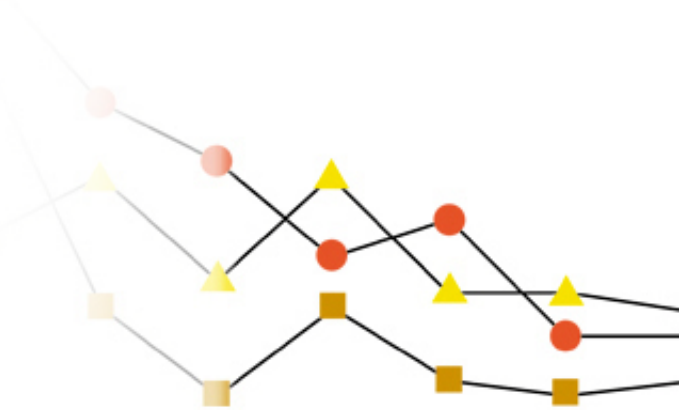
Asthma satisfies none of these conditions:

- it occurs through multiple mechanisms that are not well understood;
- many genes appear to be related to different aspects of the main (allergic) mechanism that has been studied to date;
- there is major temporal and geographical variation that cannot be explained by genetic factors.

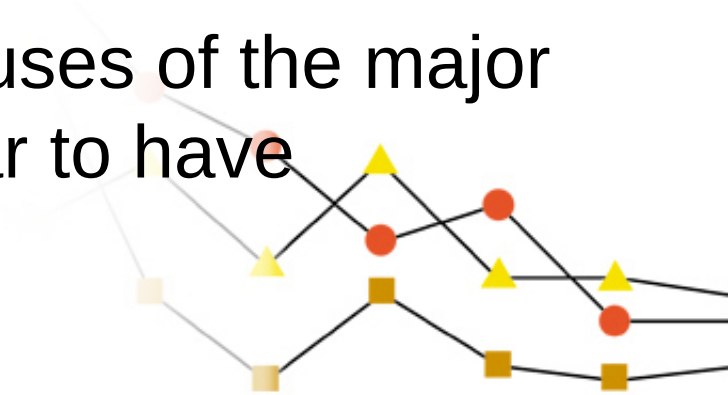
Asthma genetics

- Thus, to date asthma genetics has had limited success in explaining a significant proportion of asthma cases, and even less success in explaining the population patterns
- Those associations that have been found have often not been reproduced in other populations



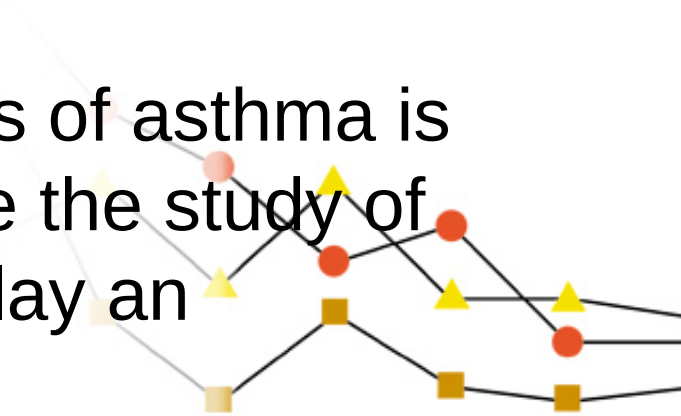
Asthma genetics

- It could be argued that the solution is to use narrower disease definitions and intermediate phenotypes
- However, the findings may then be generalisable to only a small proportion of asthma cases
- In particular, at most half of all asthma cases appear to occur through allergic mechanisms
- The major task is to identify the causes of the major increases in prevalence that appear to have occurred globally.

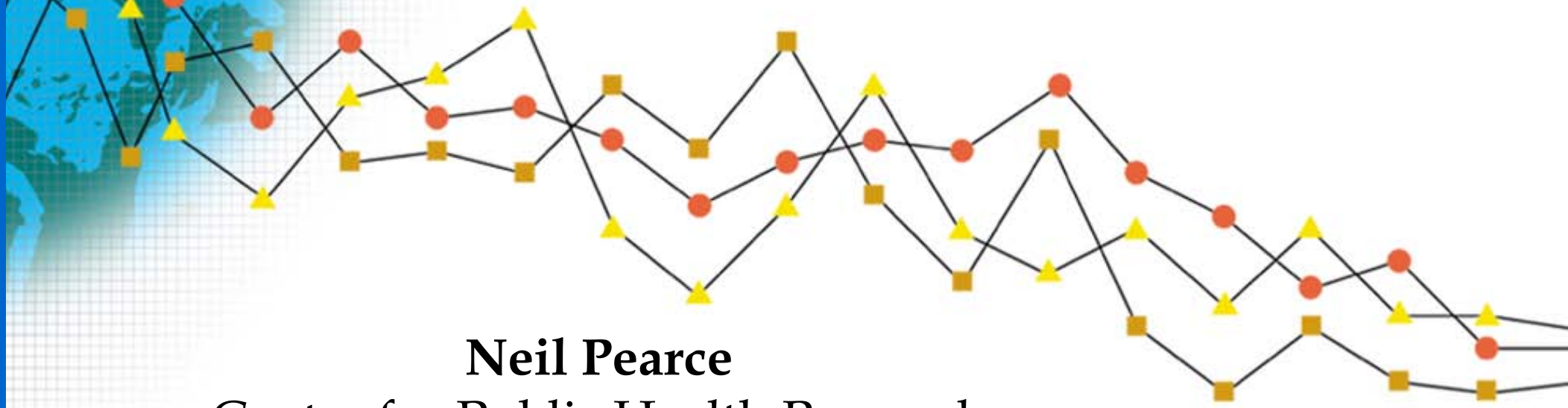


Asthma epidemiology

- Genetic factors cannot account for these increases, but gene-environment interactions may be important.
- In the past we have consistently overestimated the importance of genetic factors for health, and we have underestimated the ethical and practical problems in applying genetic knowledge to interventions
- The search for environmental causes of asthma is likely to continue to be primary, while the study of gene-environment interactions will play an important secondary role



Genetics, environment and asthma



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