

Dyslexia and Familial Cancer

an observational pilot study

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Developmental Dyslexia

A common, complex, neurodevelopmental learning disability

- thought to affect 5-10% of UK children
- involves unexpectedly poor reading relative to general intelligence (not explained by other factors like social background or gross neurological deficit)
- complex **genetics** (heritability estimated at ~50%)
- differences in **brain structure and function**

Brain Differences

- Functional imaging shows reduced activity in visual motion areas, corresponding to higher psychophysical detection thresholds in dyslexics
- Temporal processing deficits have repeatedly been reported: visual (motion) and auditory (frequency modulation) thresholds both independently predict nonword reading
- Problems processing rapidly changing stimuli may be core deficit?
- PM brains: ectopias, microgyria and disrupted connectivity
- PM brains: average cell size reduction, disorder in LGN

Two Puzzles of Dyslexia

- “Traditional” picture of dyslexia:
 - a problem with reading and spelling
 - mediated by some kind of brain dysfunction
- As well as this, studies have found two puzzling features associated with dyslexia:
 - differences in **phospholipid metabolism**
 - differences in **immune function**
- Underlying mechanisms remain unclear

Phospholipid Metabolism

- Cell membranes are made of phospholipids, which contain ω -3 and ω -6 fatty acids (FAs) obtained from the diet. Their relative proportions affect membrane properties:
 - More ω -6 FAs ⌚ stiffer membrane, less efficient neurotransmission
 - More ω -3 FAs ⌚ more efficient signalling
- Typical Western diets heavily favour ω -6 FAs relative to ω -3s
- Some children and adults with dyslexia show signs of ω -3 fatty acid deficiency, relative to controls
- Treatment with ω -3 FAs seems to help their dyslexic symptoms
- The enzyme PLA2, which releases FAs from cell membranes, is raised in dyslexics compared to controls
- ω -6 FAs are pro-inflammatory; ω -3 FAs anti-inflammatory

Immune Function

- Galaburda et al have rat models with genetic immune dysfunction / environmental BBB damage which develop temporal processing deficits analogous to dyslexics'
- LD rates are significantly higher in children of mothers with SLE
- Dyslexia has been linked to immune disorders for decades, though definition problems mean research is controversial

Genetic Studies

- Repeated linkages have been found to an area on chromosome 6p21.3
- Other QTLs have been found on chromosomes 1, 15, 2, 18 and 7
- Huge variability in dyslexic phenotype
- Probably multifactorial at both the genetic and environmental levels

Dyslexia is Not Just Poor Reading

- Some puzzling features require explanation, including:
 - the Galaburda group's work linking immune dysfunction and structural brain abnormalities to temporal processing deficits
 - evidence that dyslexics are particularly deficient in omega-3 fatty acids, and that supplementation helps their symptoms
 - evidence that LD rates are significantly higher in children of mothers with SLE

History

- We had a database of dyslexic and nondyslexic children available
- So a study of family medical history was set up to investigate the prevalence of immune disorders in that cohort
- Meanwhile, I was searching for a theoretical explanation for these disparate observations ...

How do these observations relate?

Simplest case (Occam's razor): Look for a single mediator which can relate to all four domains:

- neural
- lipid biochemical
- immune
- genetic

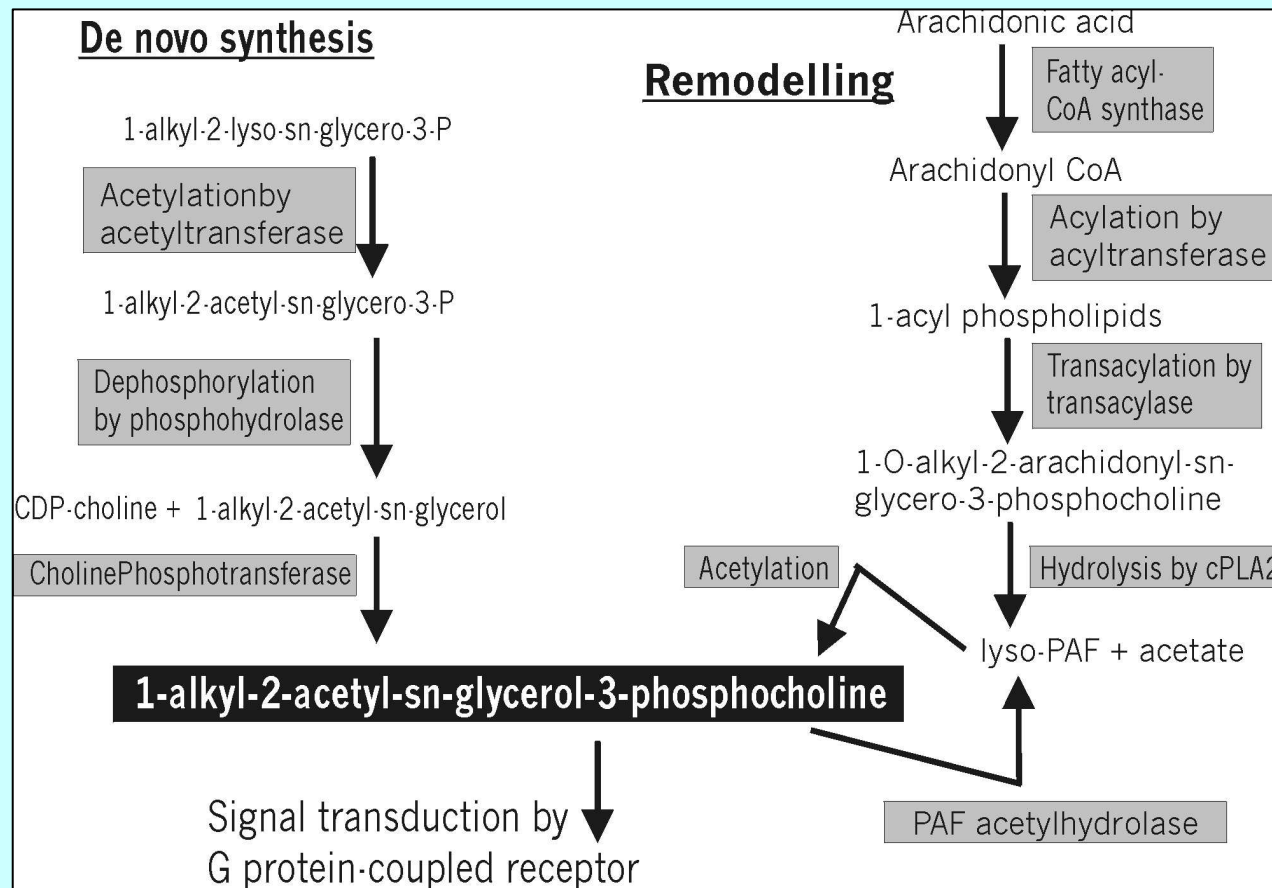
Hypothesis

- Excessive levels of **platelet-activating factor** (PAF), resulting from genetic mutations, environmental factors, or both could play a role in developmental dyslexia
- NB: PAF is part of a complex network of proinflammatory molecules; others, such as the proinflammatory cytokines and TNF- α , are probably also involved

Why PAF?

- involved in **long-term potentiation** and excitatory **synaptic transmission**
- **neurotoxic** at high (clinical physiological) concentrations
- a **vasopermeabiliser** which makes the blood brain barrier leaky and hence more vulnerable to penetration
- a marker of **inflammation** that is raised in numerous conditions including **lupus, stroke, multiple sclerosis, meningitis** and **HIV encephalopathy**
- a highly bioactive **phospholipid**
- **metabolism** tightly-regulated by PAFAH; mutations in genetic code for PAFAH give lissencephaly

Synthesis and metabolism of platelet-activating factor



PAF has many roles ...

- PAF is neurotoxic in excess
- PAF release is stimulated by NMDA receptor activation
- PAF increases BBB permeability
- PAF is pro-inflammatory
- PAF levels are reduced by ω -3 fatty acids
- PAF receptor is coded on Chr 1; PAFAH on Chr 6
- PAF-R and PAFAH interact with the cytoskeleton; excess PAF disrupts neuronal migration
- PAF is pro-apoptotic, activating NF- κ B

PAF and Apoptosis

- The study of family medical history asked about cancer as one of many “control” conditions
- BUT if PAF is pro-apoptotic, higher PAF levels ⌚ lower risk of cancer
- So dyslexics (predicted to have higher PAF levels) should be less likely to suffer from cancer than non-dyslexics

Predictions

- **POSITIVE ASSOCIATION** between dyslexia and disorders of excessive inflammation in which PAF levels are high (e.g. epilepsy, MS)
- **NEGATIVE ASSOCIATION** between dyslexia and disorders in which PAF levels may be low (e.g. cancer)
- **NO ASSOCIATION** between dyslexia and disorders in which PAF levels are not particularly relevant (e.g. diabetes)

Problems

- Relevant conditions (e.g. MS) mostly appear in adults
- Databases of adult dyslexics are hard to find and do not hold medical history info ... “it’s just a reading problem”
- Many high-PAF conditions are:
 - rare (e.g. lupus)
 - screened out at the selection stage (e.g. epilepsy)
 - medically ill-defined (e.g. asthma)
- Resource limitations prevented biochemical testing

Solution

- Genetics suggests that these associations may exist at the familial level
- So look at family medical history
- Look at common and medically well-defined conditions (i.e. low-PAF conditions): cancer
- Use diabetes (in which PAF is not thought to be central) as a control condition

Methods

- 163 dyslexic and 154 nondyslexic children from 202 families

Max(Similarities, Matrices) – Max(Reading, Spelling) > 2SD

- screened for gross neurological, visual or auditory problems
- parents did questionnaires about family medical history (FMH)
- children were grouped by FMH of cancer (C+/C-); and diabetes (D+/D-)

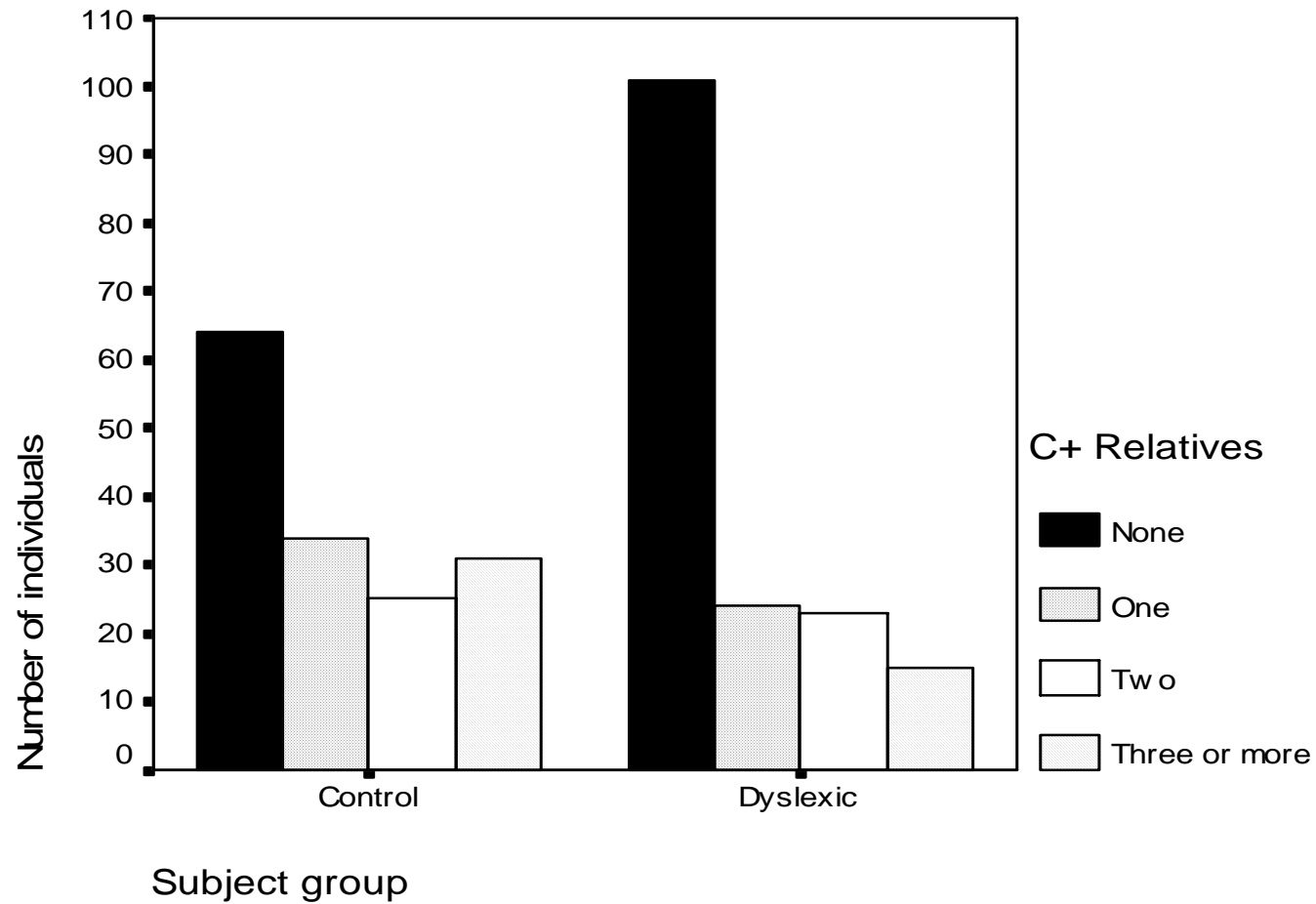
Statistics

- Dyslexic/control groups (Dx/Ct) compared on:
 - FMH disease ratios
 - logistic regression, controlling for sex, age, birth order, family size, parental age
- FMH groups (C+/C-; D+/D-) were compared on
 - Dx/Ct odds ratios
 - DxDisc: how far reading and spelling falls short of that predicted by general intelligence
- Additional analyses by sex, family, number of affected relatives showed similar results

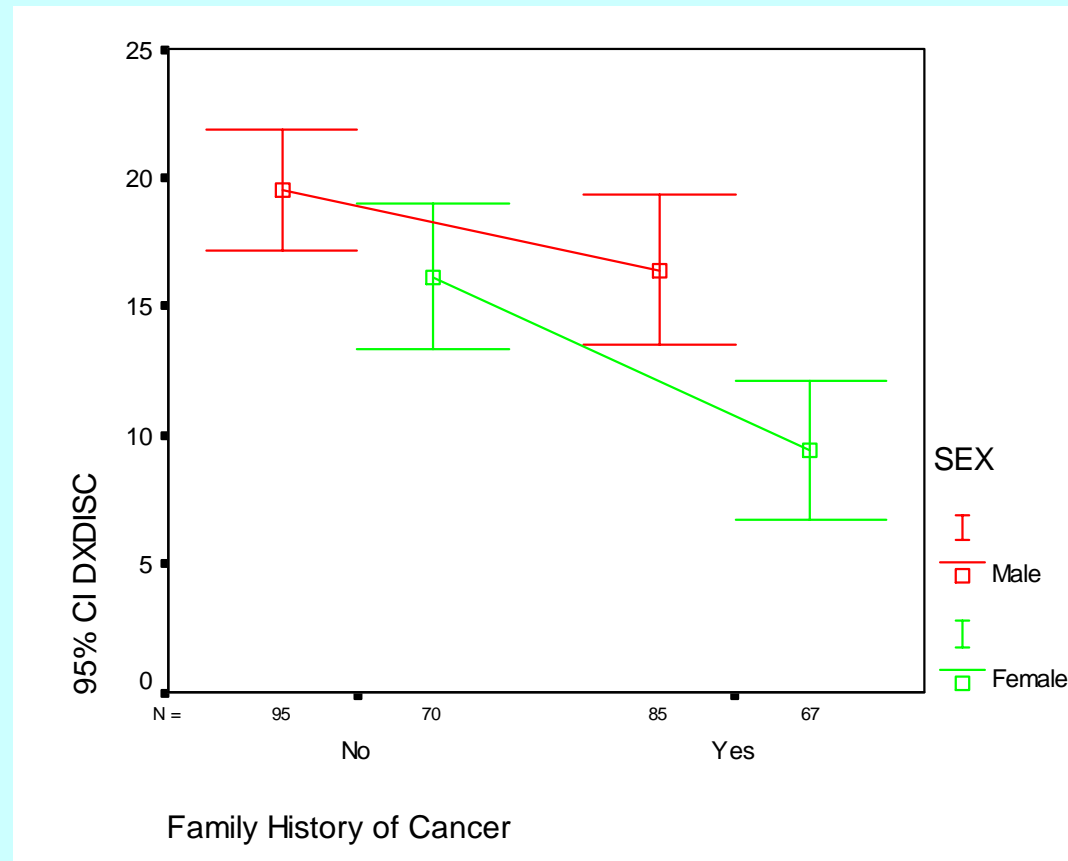
Results -- fewer Dx were C+

- Logistic regressions significant for Cancer ($p < 0.005$)
- Logistic regressions were nonsignificant for Diabetes (IDDM, NIDDM)
- There was some evidence of sex differences
- Odds ratios were:
 - **Cancer** 0.44
 - **Cancer (males)** 0.55
 - **Cancer (females)** 0.31
 - **IDDM** 0.84
 - **NIDDM** 0.60

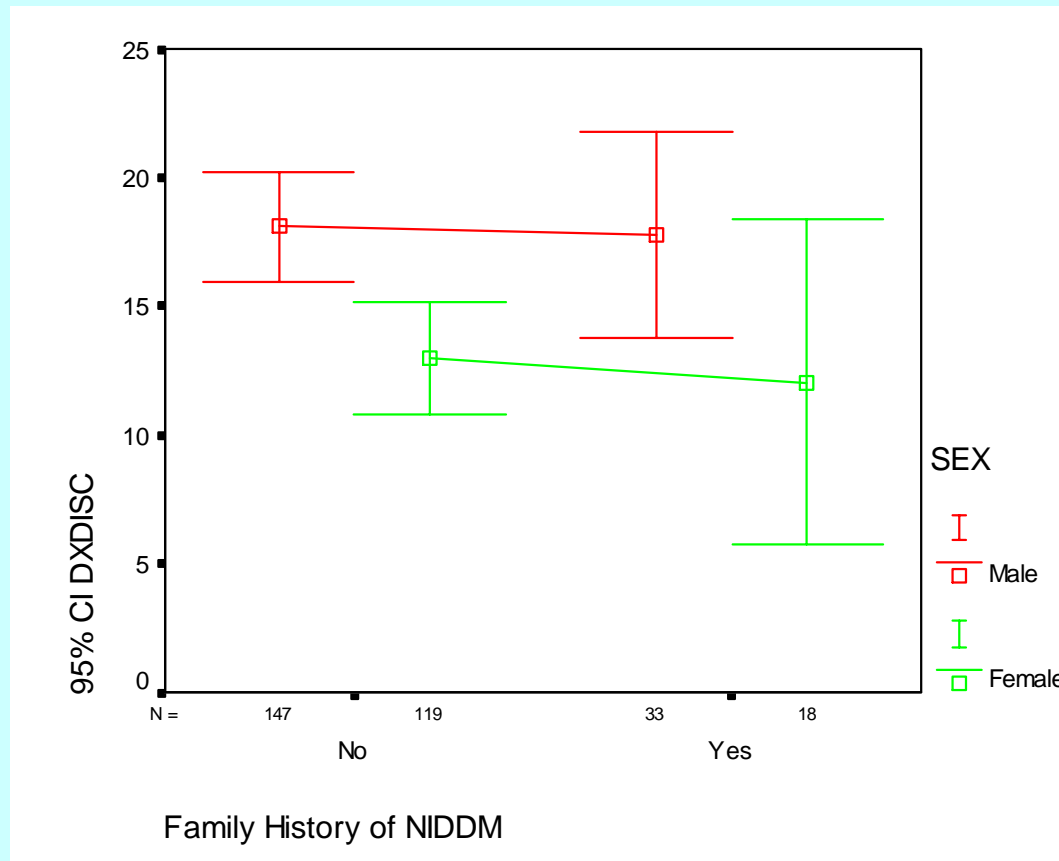
Number of relatives with cancer, for dyslexics and controls



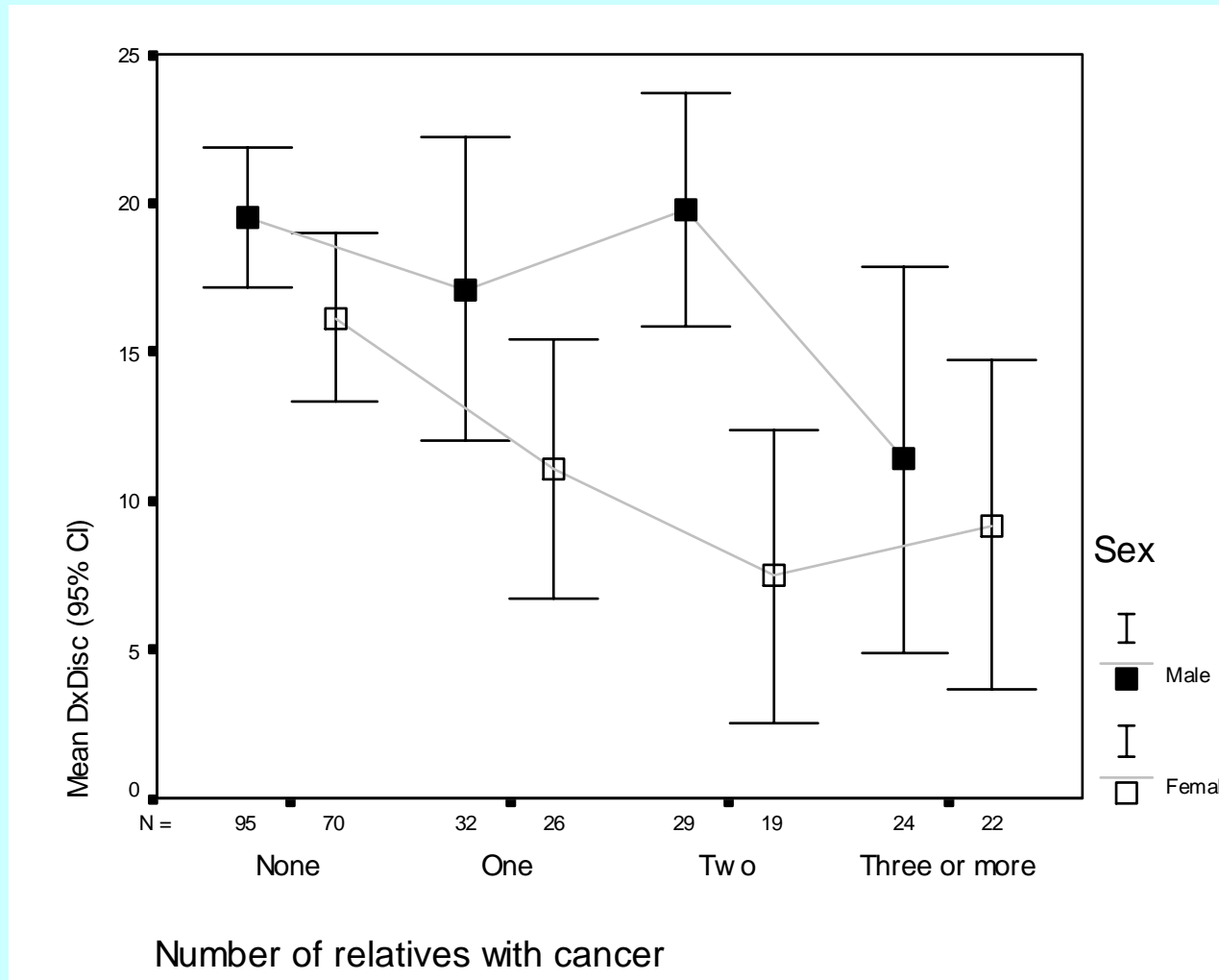
Sex differences



Comparison - NIDDM



Sex differences by number of relatives



Conclusions

- The PAF hypothesis of dyslexia offers a way to explain puzzling associations of dyslexia with fatty acid deficits and immune dysfunction
- It is a fruitful source of (often unexpected) predictions
- One of these is a negative association with cancer
- So far, resources only allow this to be tested at the familial level
- An initial study is consistent with the PAF hypothesis, but more work needs to be done

Further information

- All material is copyright Kathleen Taylor 2009
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- This presentation was given at Guys Hospital, London, in 2004