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Cohort Profile: The Whitehall II study

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How did the study come about?

The Whitehall studies have come to be closely associated with the investigation of socioeconomic differences in physical and mental illness and mortality: the social gradient.[1,2] That was not the initial purpose of the first Whitehall study. Donald Reid and Geoffrey Rose set up Whitehall, in the 1960s, as a kind of British Framingham:[3] 'Framingham' insofar as it was a longitudinal study of cardiorespiratory disease and diabetes, looking at individual risk factors for disease; 'British' in that it was done on the cheap—a simple screening examination with follow-up limited to deaths identified from the National Health Service Central Registry.

Socioeconomic differences were initially not on the agenda. In the 1970s there was a small group of researchers who continued the British tradition that went back to William Farr in the nineteenth century of examining social inequalities in health.[4] For the most part, within epidemiology, 'social class' was not an object of study but a control variable: a potential confounder that you got rid of in order to arrive at the 'correct' conclusion about the association between risk factor and disease. To the extent that there was a focus on inequalities in health, the general view was that poor people got diseases of material deprivation and rich people got heart disease and peptic ulcers. If this perception had been true,[5,6] Whitehall showed that it was no longer so. In a population of middle-aged men, all employed in stable jobs in the British Civil Service, there was an inverse social gradient in mortality: the lower the grade, the higher the risk of death. Ten-year follow-up showed that there was a steep inverse relation between grade of employment and death from all causes, from coronary heart disease (CHD), and from non-coronary causes.[7] The relative risk of death owing to CHD was 2.2 in clerical compared with senior administrative staff, and 1.6 for those in the intermediate professional and executive grade.

The first Whitehall study made clear that inequalities in health were not limited to the health consequences of poverty. Important as that issue remains, the Whitehall question was why there should be a social gradient in disease in people above the poverty threshold. When conventional risk factors were controlled for, two-thirds of the mortality risk differential between the clerical and administrative grades remained unexplained.[7,8] Mortality gradients in the study were in the same direction as national social class mortality data,[9] but larger. We hypothesized that psychosocial factors and aspects of nutrition other than those affecting plasma cholesterol (which was higher in high grades in Whitehall) might fill in the unexplained part of the social gradient in mortality.[7]

We therefore set up the Whitehall II study, a new longitudinal study of British civil servants, with the explicit intention of examining reasons for the social gradient in health and disease in men and extending the research to include women.

Who set Whitehall II up, and why, and how was it funded?

If research funding were organized in an imaginary world, the way to launch a new cohort study would be to write a proposal setting out the research questions, the long-term aims of the study, the mechanisms for enrolling the cohort, and the system of follow-up. One hopes for approval in the peer review process and a big grant, and off one goes. This bears little resemblance to how Whitehall II was funded. We had our research questions but did not dare to write the big grant application. Instead we funded the recruitment and baseline of the study with a series of small grants, each to fund a piece of the whole—except that without the pieces, there was no whole. The Medical Research Council (MRC) in the UK, the National Heart, Lung, and Blood Institute in the USA, and the UK Health and Safety Executive all provided small project grants. Once the cohort was assembled, we then secured programme support from the MRC, the British Heart Foundation, the National Institute of Aging, the National Heart, Lung, and Blood Institute, the MacArthur Foundation, and a variety of other sponsors (see Acknowledgements).

Although this method worked to establish the Whitehall II study, the major drawback is that the writing of grant applications becomes a major extra task. If one needs five grants to fund the next round of data collection and analysis, the burden is large. In our view it has been worth it. We wanted a study that was not done on the cheap. We planned regular contacts with the cohort to track changes in social and economic circumstances, psychological states, health behaviours, and biological pathways to clinical and subclinical disease. The variety of funding sources allowed this rich data collection to continue through seven phases of contact with the cohort, with Phases 8 and 9 planned.

What does Whitehall II cover and how has it changed?

The original broad research aim—to investigate social and occupational influences on health and illness—has been much elaborated but remains the central theme almost 20 years later. The theoretical perspective places wider determinants of health within the causal framework, adding material and psychosocial context to the narrower biomedical model that tended to underpin cohort studies of cardiovascular disease until the 1980s. The Seven Countries Study, for example, contributed

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profoundly to methodology and to epidemiological evidence for the population causes of CHD. These advances were achieved by studying the major dietary, lifestyle, and biological risk factors that we are now familiar with, without systematic reference to the nature of other differences between and within cultures at greatly differing risks of disease.

An early Whitehall II grant proposal (1986–89) that was funded by the US National Institutes of Health (NIH) outlines the original research agenda.

> We wish to determine the extent to which psychosocial factors at work and outside account for social class differences [in mortality and morbidity]. The overall aim is to study: a) the effect on health and disease of the work environment—psychological workload, control over work pacing and content, opportunity for use of skills, social support at work, b) the moderating effect on these relationships of social supports, and c) the interaction between these psychosocial factors and other established risk factors in the aetiology of chronic disease.

'Established risk factors' referred to included biological factors (blood pressure, cholesterol) and behavioural factors (smoking, alcohol consumption, physical activity). In addition to coronary outcomes, respiratory illness, 'neurotic disorder', and sickness absence were specified. Dietary assessments were added later, without specific funding.[10]

Eighteen years later our research aims continue to incorporate the original scientific question, extended to include the study of inequalities in health in our ageing population. Health-related quality of life is therefore an important addition to the focus on chronic disease. The 36-item Short Form Medical Outcomes Survey (SF-36) for physical, psychological, and social functioning has been administered five times since 1991, and tests of cognitive function have been completed three times. The strength of links between quality of life measures and social position is remarkable (Figure 1). This dimension of health inequalities research becomes increasingly significant in scientific and policy terms as the number of people surviving into old age and the dependency ratio rise.

A long-term aim is to determine the specific biological mechanisms that account for social inequalities in cardiovascular disease and diabetes. The purpose is to place the study of putative psychosocial processes on sound scientific foundations by opening the legendary black box of epidemiology that lies between 'exposure' and 'outcome'. By addressing mechanistic questions in our population-based study sample we seek to build evidence for specific explanations of disease occurrence and social inequalities in disease incidence. In Bradford Hill's terminology,[11] if biological plausibility can be complemented by coherence and time sequence, then evidence for causation rather than association has been generated.

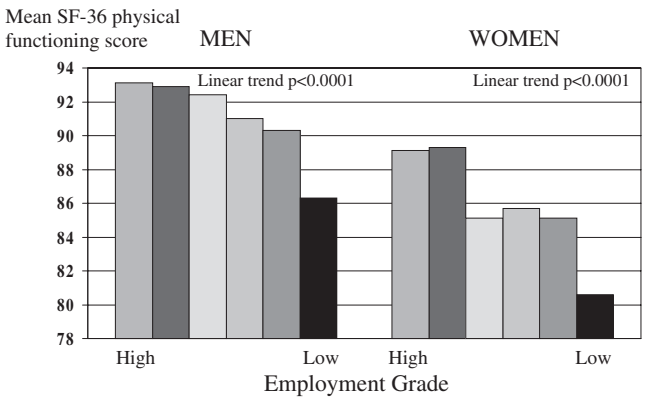

Figure 1 SF-36 physical functioning score by employment grade, men and women aged 40–59 years (Phase 3)

For example, the metabolic or insulin resistance syndrome is a precursor of diabetes and CHD. It is therefore useful to measure the component variables at successive 5-yearly examinations of the cohort in order to examine influences on emergence and remission of the syndrome and consequences for health. We showed that men with metabolic syndrome produce more urinary cortisol metabolites and normetanephrine and have a faster heart rate than healthy controls.[12] This nested case–control study is consistent with the psychosocial hypothesis that chronic stress leads to heart disease, and it adds to its biological plausibility. The cross-sectional evidence does not indicate whether the observed alterations in neuroendocrine and autonomic function were a cause or a consequence of the metabolic syndrome. Prospective studies in the whole cohort will shed light on the sequence of these processes.

The neuroendocrine substudy mentioned above illustrates a further added dimension of Whitehall II. Detailed mechanistic studies based on the collection of measurements that are not feasible in the entire cohort allow tests of biological hypotheses on a small scale. Intensive studies led by Andrew Steptoe investigate psychophysiological differences associated with social position. These studies utilize observational techniques such as ambulatory blood pressure monitoring and experimental psychological challenges among subjects stratified by grade. The work shows that delayed or impaired recovery in cardiovascular function after mental stress may be an early marker of the development of increased CHD risk among individuals of lower social status.[13]

Who is in the sample?

The target population for the Whitehall II study was all civil servants (men and women) aged 35–55 years working in the London offices of 20 Whitehall departments in 1985–88. The achieved sample size was 10 308 people: 3413 women and 6895 men. The participants, who were from clerical and office support grades, middle-ranking executive grades, and senior administrative grades, differ widely in salary (see Table 1). Some have remained in the civil service. Many have retired, and others have taken employment elsewhere; some are unemployed.

How often have participants been followed up?

The whole cohort is invited to the research clinic at 5-year intervals, and a postal questionnaire is sent to participants between clinic phases (Table 2). Home visits by nurses were offered for the first time to participants unwilling or unable to travel to the Phase 7 clinic. A brief telephone questionnaire is

Table 1 Salary range (1 August 1992) and sample size at baseline in the Whitehall II study

Civil Service employment grade	Salary range (£)	Whitehall II study grade	Sample size at baseline (Phase 1)		
			Men	Women	Total
Unified Grade 1–6	28 904–87 620	1	1015	118	1133
Unified Grade 7	25 330–36 019	2	1632	263	1895
Senior Executive Officer	18 082–25 554	3	1228	198	1426
Higher Executive Officer	14 456–20 850	4	1498	478	1976
Executive Officer	8 517–16 668	5	881	660	1541
Clerical and Support Staff, e.g. messengers, porters, telephonists, typists	7 387–11 917	6	641	1696	2337

Table 2 Phases of the Whitehall II study

Phase	Dates	Type	Participants
1	1985–1988	Screening/questionnaire	10308
2	1989–1990	Questionnaire	8133
3	1991–1993	Screening/questionnaire	8637
4	1995–1996	Questionnaire	8629
5	1997–1999	Screening/questionnaire	7830
6	2001	Questionnaire	7344
7	2003–2004	Screening/questionnaire	6914
8	*2006*	*Questionnaire*	*Planned*
9	*2008–2009*	*Screening/questionnaire*	*Planned*

administered to those who decline clinic and full questionnaire participation at each phase. Follow-up for mortality through the NHS Central Registry provides us with the date and cause of death (99.9% of participants flagged). Self-reported non-fatal coronary events and those identified by research clinic ECG are verified through primary care and hospital records. Cancer registry and NHS-Wide Clearing Service notifications provide further information on incident disease and hospital procedures.

Definitive tests of our hypotheses depend on the continuing accumulation of CHD events in the cohort. Collection of CHD outcomes, with validation through medical records, is a key but problematic activity. The struggle to gain access to records in the current research ethics climate, with its orientation towards individual rights rather than public health, could not have been imagined at the study baseline.

What has been measured?

Data collections are summarized in Tables 3 and 4.

Measurement error is problematic in epidemiological analyses, whether the aim is to estimate the unadjusted effect of a single risk factor or to account for such an effect using covariate adjustment. We address this issue in study design and analysis, as well as repeating measures throughout follow-up in order to characterize changing exposure levels. At each screening phase repeat measures are obtained on a subsample of participants, providing estimates of reliability. We have also developed and used better measures of important exposures. For example, physical activity was initially measured with simple questions on frequency and duration of mild, moderate, and vigorous activity, and estimates were correspondingly imprecise. We introduced a more detailed 20-item questionnaire at Phase 5 and have shown subtle effects with this measure of activity, including an association between a moderate level of activity and heart rate variability.[14]

What is attrition like?

In common with many cohort studies, loss of participants occurred between baseline and first follow-up (Table 2). Attrition at subsequent phases has been minimized by careful attention to the quality of all contacts with participants and diligence in tracing those lost to postal contact. In addition to the perceived benefit of receiving a free health check at 5-yearly intervals, participants appear to enjoy the process of being screened, which may contribute to the high response rates. Regular newsletters maintain contact between study phases. For participants who are absent from the screening and questionnaire surveys, health information is obtained from hospitalization records (from the NHS-Wide Clearing Service) and death certificates.

What has been found? Key findings and key publications

The main contribution of the Whitehall II study has been to test hypotheses to explain the social gradient in health. Recent analyses with over 15 years of data confirm the inverse relationship between socioeconomic position and validated CHD, diabetes, and metabolic syndrome. We provide further evidence for specific psychosocial, behavioural, and pathophysiological processes—including neuroendocrine, inflammatory, and haemostatic mechanisms—that contribute to health inequalities. For example, we show that job strain predicts CHD,[15] common mental disorder,[16] and sickness absence from work[17] and we demonstrate simultaneous links between the metabolic syndrome, urinary cortisol, normetanephrine, and heart rate variability.[12] In addition to psychosocial factors at work, we observe a role for psychosocial factors at home[18] and in the wider community[19] in disease development. Comparative studies in other populations produce similar findings that support the

Table 3 Summary of non-biological data collected in the Whitehall II study

Demographic data

Socioeconomic data

- Education
- Household composition
- Income
- Financial assets
- Work + work change (retirement)

Area-level indicators

- Deprivation
- Classification of area

Psychosocial/work exposure

- Effort–reward
- Demand–control
- Social support
- Social networks

Health behaviours

- Smoking
- Alcohol
- Diet—food frequency
- Physical activity

CVD

- WHO chest pain
- Details of cardiovascular disease (CVD) symptoms, investigations, and treatment

General health (subjective)

- Self-rated health
- Well-being
- Longstanding illness
- Hospital admissions
- Medications
- Musculoskeletal conditions
- Quality of life (SF-36)

Mental health (subjective)

- General Health Questionnaire (GHQ) (anxiety, depression)
- Center for Epidemiologic Studies Depression Scale (CESD)
- SF-36, Activities of daily living (ADL), Instrumental ADL

Health outcomes (objective)

- Sickness absence
- Myocardial infarction and coronary surgery
- Stroke
- Clinical depression
- CVD/CHD mortality
- Other cause-specific mortality
- Mortality

generalizability of many Whitehall findings. A complete list of Whitehall II publications is on the web at www.ucl.ac.uk/WhitehallII/publications.html.

Repeat measures of social circumstances, risk factors, and health assembled over almost 20 years make possible detailed study of adult influences on health and the social gradient in health, including accumulation of advantage and disadvantage. Physical health and health-related functioning show evidence for such accumulation.[20] The structure of the data also allows analysis of the effects of change in risk factors such as obesity and of how the pattern of change influences health outcomes. Related to this, causal analysis using techniques such as structural equation modelling enables competing hypotheses to be compared, such as health selection versus social causation.

Although early life determinants, life-course factors, and current circumstances all have effects on disease risk in older age, the preeminent determinants observed in the cohort are adult socioeconomic position and work-based determinants from mid-life. Social gradients in morbidity and functioning have become more marked as the population has aged and appear to be determined by factors operating during working life. The Whitehall II study is the model for occupational cohorts such as those in Helsinki and Japan,[21] and a plan for a 'Whitehall in Washington' study is being discussed by the National Institutes of Health. The Wellcome Trust-funded cohorts in Novosibirsk, Krakow, and Prague are population-based and are using many common protocols to study health inequalities in post-Soviet Siberia and Eastern Europe.

What are the main strengths and weaknesses?

The occupational hierarchy is probably more rigid in the Civil Service than in other large employers. This is simultaneously a strength and a weakness of the Whitehall II study. The study cannot be representative of the diversity of employment relations and conditions experienced in the workplace.[22] It does identify the health effects of working at different levels in a stratified organization and of organizational change,[23] and as such it provides 'proof of principle'. This has supported policy initiatives within the Civil Service[24] and across the UK by the Health and Safety Executive (http://www.hse.gov.uk/stress/manstandards.htm), following the Acheson recommendation[25] on psychosocial factors at work.

Whitehall II has demographic features that reflect the composition of the Civil Service at study baseline in the mid-1980s. Women make up one-third of the cohort and half of them were in the clerical and office support grade. This reduces power for examining the social gradient in women. There is also a lack of individuals from ethnic minority backgrounds in the higher grades. The absence of manual workers in the cohort, in common with many other white collar organizations, is an additional limitation. However, the trend in the labour market means that we are in a position to study an increasingly dominant section of the working population.

The particular strength of Whitehall II is its focus on the social gradient in health and disease. Health inequalities are examined from social, psychological, and biomedical perspectives at the same time. It has in this way generated evidence for the importance of the wider determinants of health that is of interest to a wide audience inside and outside medical research. Two major elements of the study that make this possible are the breadth of the information collected, derived from the interdisciplinary approach, and the loyalty of participants, who, based on their written comments, feel that they are making a worthwhile contribution to public health.

Table 4 Phases of medical examination in the Whitehall II study[a]

	Phase 1	Phase 3	Phase 5	Phase 7
Examination	Weight, height, BP	Weight, height, waist–hip ratio, BP	Weight, height, waist–hip ratio, BP	Weight, height, waist–hip ratio, BP, walking speed, spirometry
Neuroendocrine	Blood pressure reactivity[b]		Heart rate variability[b] hypothalamic–pituitary–adrenal axis measurements[b]	Heart rate variability Salivary cortisol diurnal rhythm
Subclinical cardiovascular disease	ECG: Minnesota codes ECG left ventricular mass (LVM)	ECG: Minnesota codes ECG LVM	ECG: Minnesota codes ECG LVM Ultrasound (US) measures of endothelial dysfunction[b] Carotid artery wall thickness/distensibility[b] MRI (white matter lesions)[b]	ECG: Minnesota codes ECG LVM US measures of endothelial dysfunction[b] Carotid artery wall thickness/distensibility
Lipids	Total cholesterol, apoA1, and apoB[b]	Total + HDL cholesterol apoA1 and B, Lp(a) Triglycerides Cholesterol ester fatty acids[b]	Total + HDL cholesterol Triglycerides	Total + HDL cholesterol Triglycerides
Carbohydrate metabolism		Fasting and post-load glucose and insulin	Fasting and post-load glucose and insulin	HbA1c, fasting, and post-load glucose and insulin
Genotype		DNA isolation	APOE	CRP, TNF, UCP2, MAO further genotyping
Haemostatic and other	Fibrinogen[b] Factor VIIc[b]	Fibrinogen, IL-6, CRP Factor VIIc von Willebrand factor PAI − 1[b] plasma β-carotene	Fibrinogen, IL-6[b], CRP[b], SAA[b] Viscosity D-dimer[b]	Fibrinogen, IL-6, CRP

[a] There is no medical examination for Phases 2, 4, and 6.

[b] Subsample.

Can I get hold of the data? Where can I find out more?

Our longitudinal dataset has great potential for secondary analysis. At present our arrangements are ad hoc, based on consideration of specific proposals from current and potential external collaborators. Data for the Change and Health Study, based on the privatization of the Property Services Agency in 1992, are available from the Economic and Social Research Council (ESRC) Data Archive (www.regard.ac.uk). Initial enquires with respect to the main dataset should be made to Miriam Harris (Project Director). One example of current off-site data sharing is that with the Fibrinogen Studies Collaboration. The MRC policymaking process will lead to an initiative on data sharing and preservation. The process has illuminated important questions, among them the ethical, scientific, technical, and cost implications of various approaches to data sharing. Data preservation relies on consolidation of all raw and derived data collected from Whitehall II participants into a single anonymized system that involves automated backups and off-site storage.

A booklet summarizing the Whitehall II study[24] is available at www.ucl.ac.uk/WhitehallII/Whitehallbooklet.pdf.

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References

[1] Marmot M. *Status Syndrome*. London: Bloomsbury, 2004.

[2] Brunner EJ, Marmot MG, Nanchahal K *et al*. Social inequality in coronary risk: central obesity and the metabolic syndrome. Evidence from the WII study. *Diabetologia* 1997;**40:**1341–49.

[3] Reid DD, Brett GZ, Hamilton PJ, Jarrett RJ, Keen H, Rose G. Cardiorespiratory disease and diabetes among middle aged male civil servants. *Lancet* 1974;**1:**469–73.

[4] Department of Health and Social Security. *Inequalities in Health: Report of a Research Working Group Chaired by Sir Douglas Black*. London: DHSS, 1980.

[5] Susser M, Stein Z. Civilisation and peptic ulcer. *Lancet* 1962;**1:**115–8.

[6] Marmot MG, Adelstein AM, Robinson N, Rose G. The changing social class distribution of heart disease. *Br Med J* 1978;**2:**1109–12.

[7] Marmot MG, Shipley MJ, Rose G. Inequalities in death—specific explanations of a general pattern. *Lancet* 1984;**323:**1003–6.

[8] van Rossum CTM, Shipley MJ, Van de Mheen H, Grobbee DE, Marmot MG. Employment grade differences in cause specific mortality. A 25 year follow up of civil servants from the first Whitehall study. *J Epidemiol Community Health* 2000;**54:**178–84.

[9] Marmot MG, McDowall ME. Mortality decline and widening social inequalities. *Lancet* 1986;**328:**274–76.

[10] Brunner EJ, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 day diet diary and food frequency questionnaire and validity against biomarkers. *Br J Nutr* 2001;**86:**405–14.

[11] Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;**58:**295–300.

[12] Brunner EJ, Hemingway H, Walker BR *et al*. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome. *Circulation* 2002;**106:**2659–65.

[13] Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsitivity and socioeconomic status. A mechanism for increased cardiovascular risk? *Eur Heart J* 2002;**23:**1757–63.

[14] Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am J Epidemiol* 2003;**158:**135–43.

[15] Kuper H, Marmot M. Job strain, job demands, decision latitude, and the risk of coronary heart disease within the Whitehall II study. *J Epidemiol Community Health* 2003;**57:**147–53.

[16] Stansfeld SA, Fuhrer R, Shipley MJ, Marmot MG. Work characteristics predict psychiatric disorder: prospective results from the Whitehall II study. *Occup Environ Med* 1999;**56:**302–7.

[17] Head J, Martikainen P, Kumari M, Kuper H, Marmot M. *Work Environment, Alcohol Consumption and Ill-Health: The Whitehall II Study*. Suffolk, UK: HSE Books, 2002.

[18] Chandola T, Kuper H, Singh-Manoux A, Bartley M, Marmot M. The effect of control at home on CHD events in the Whitehall II study: gender differences in psychosocial domestic pathways to social inequalities in CHD. *Soc Sci Med* 2004;**58:**1501–9.

[19] Stafford M, Bartley M, Mitchell R, Marmot M. Characteristics of individuals and characteristics of areas: investigating their influence on health in the Whitehall II study. *Health & Place* 2001;**7:**117–29.

[20] Singh-Manoux A, Ferrie JE, Chandola T, Marmot MG. Socioeconomic trajectories across the lifecourse and health outcomes in midlife: evidence for the accumulation hypothesis? *Int J Epidemiol* 2004;**33:**1–8.

[21] Martikainen P, Lahelma E, Marmot M, Sekine M, Nishi N, Kagamimori S. A comparison of socioeconomic differences in physical functioning and perceived health among male and female employees in Britain, Finland and Japan. *Soc Sci Med* 2004;**59:**1287–95.

[22] Goldthorpe J. The 'Goldthorpe' class schema: some observations on conceptual and operational issues in relation to the ESRC review of government social classifications. In: Rose D, O'Reilly K (eds). *Constructing Classes*. Swindon and London: ESRC/ONS, 1997, pp.40–48.

[23] Ferrie JE, Martikainen P, Shipley MJ, Marmot MG, Stansfeld SA, Davey Smith G. Employment status and health after privatisation in white collar civil servants: prospective cohort study. *Br Med J* 2001;**322:**647–51.

[24] Whitehall II Study team. *Work, Stress and Health: The Whitehall II Study*. London: PCSU, 2004.

[25] Acheson D. *Inequalities in Health: Report of An Independent Inquiry*. London: HMSO, 1998.