Thank you. It is an honour to be invited to give the Lane Lecture.

My talk is about the exposome, an emerging concept that is relevant to identifying unknown causes of disease and by extension in tailoring interventions to reduce ill-health. I want to explore how the exposome is relevant to workplace exposures.

I will start with some traditional exposures, talk about how work is changing and how the exposures of concern are changing. I'll describe the exposome concept and how we can set about trying to measure it, and finish up with something about interventions.

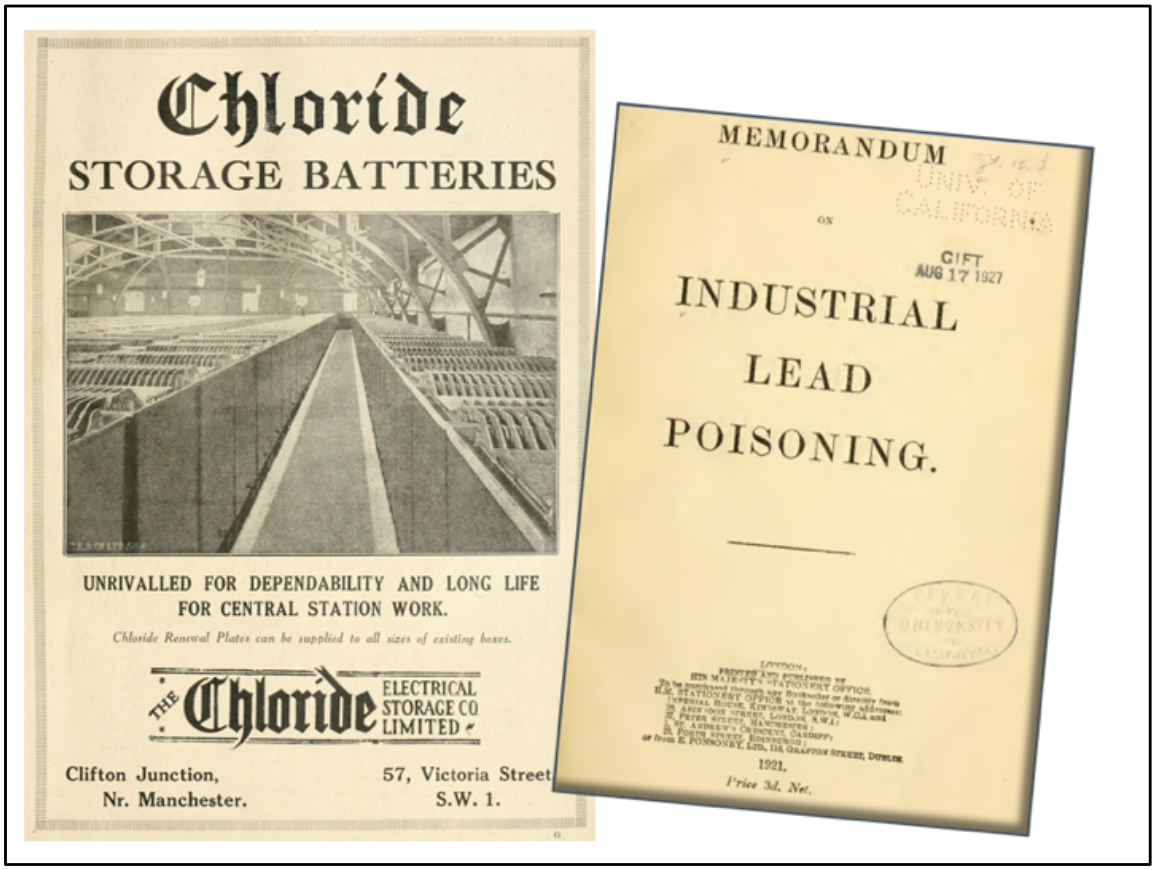
Prof Ronald Lane

- Pilot in the RAF
- Trained in medicine
- Became medical officer at the Chloride company
- Virtually eliminated lead poisoning at the company
- Founder member of the Society of Occupational Medicine
- Appointed Professor of Occupational Health at Manchester in 1945

IOM

I never met Ronald Lane but he seems like a formidable character. Flew in the RAF during the First World War, then trained in medicine before going to work for the Chloride Company. He is credited with putting in place measures that virtually eliminated lead poisoning in the company. He then switched and began an academic career here at the University of Manchester, where he held the chair in occupational health for 19 years.

We shouldn't underestimate the task that faced Lane. Around 1900 in Britain there were about 1000 new cases of lead poisoning diagnosed each year.

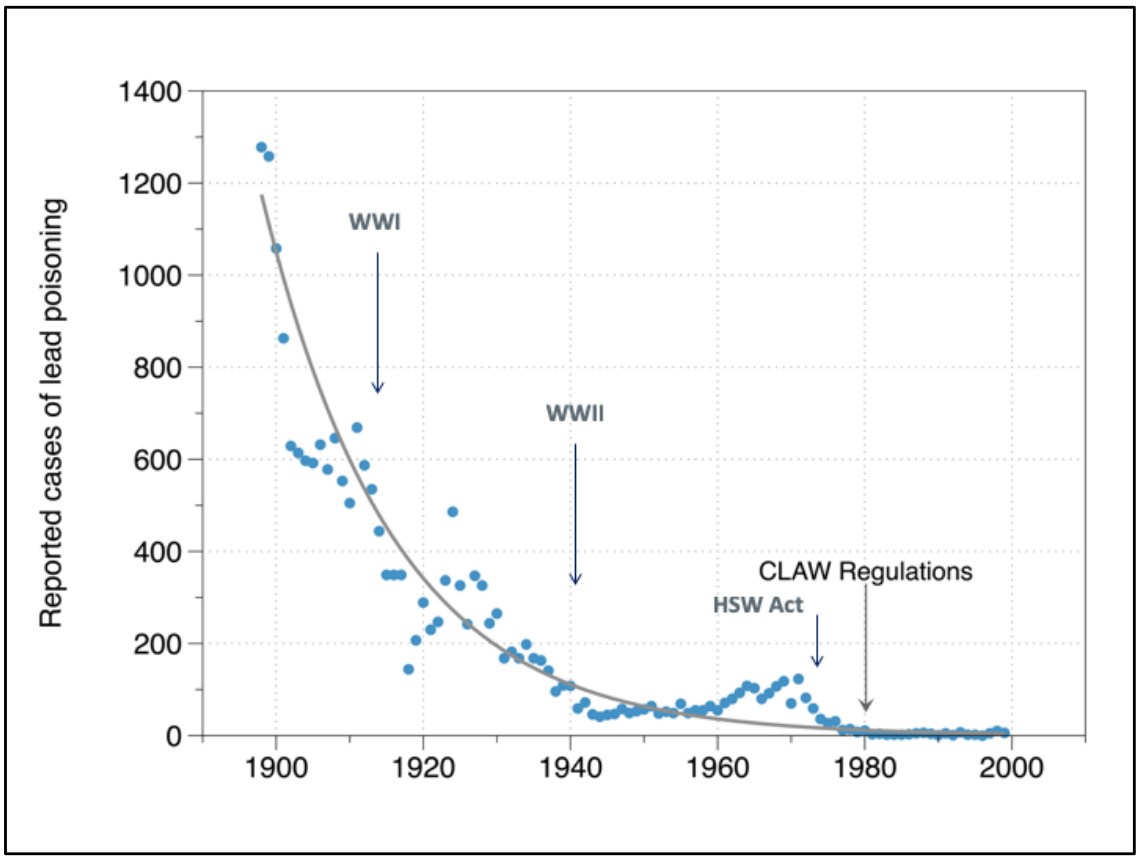


In 1921 a report from the Factory Department recommended medical surveillance, suspension of workers showing signs of poisoning, maintenance of health records, and interestingly the identification of a lowest inhaled dose of Pb that might result in chronic poisoning (2mg), a value that is very close to the current OEL.

The memorandum identified the battery industry as presenting the greatest risk.

Poster from the same year lauding the reliability of Chloride batteries.

Lane started with Chloride in 1925



Throughout the 20th Century we saw a remarkable decline in lead poisoning, which was mostly unaffected by wars or the passing of important health and safety legislation. The slight upturn in the 1960s is almost certainly due to a change to using blood lead determinations as part of the diagnostic criteria for lead poisoning. In 1980, when the problem was almost completely solved we introduced the Control of Lead at Work Regulations (CLAW).

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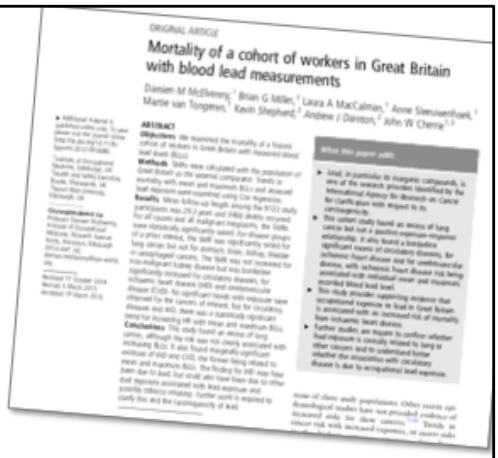
Lead…


ORIGINAL ARTICLE

Mortality of a cohort of workers in Great Britain with blood lead measurements

- Cohort of about 9,000 people for whom blood lead measurements were available
- An excess of lung cancer, but no exposure–response relationship
- Excess of ischaemic heart disease and cerebrovascular disease, with IHD risk associated with lead exposure

McElvenny *et al.* 2015. "Mortality of a Cohort of Workers in Great Britain with Blood Lead Measurements.." *Occupational and Environmental Medicine* 72 (9): 625–32.

With colleagues from eth IOM I have studied the mortality risks of workers exposed to Pb. Workers were identified in the later 1970s, when concentrations were relatively low. By the time of our study around 3500 had died.

The SMR for lung cancer = 142. However, we did not have smoking data so this makes the interpretation of causation more problematic.

Cerebrovascular SMR = 116
IHD SMR = 106

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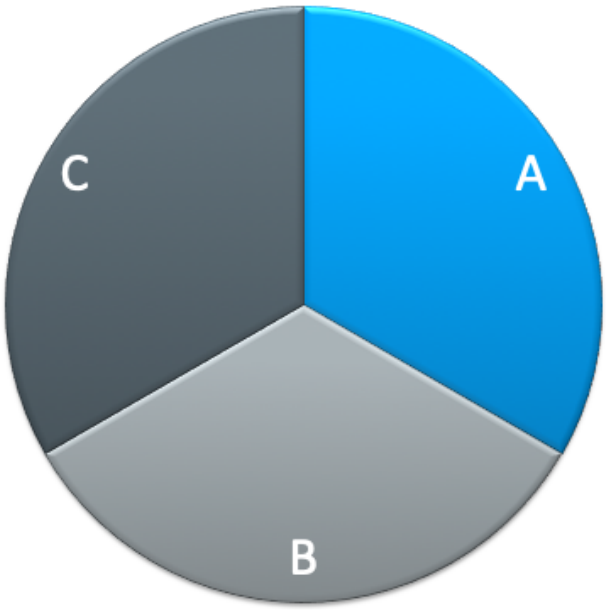
Causation…

A cause of a disease is an event, condition, characteristic, or combination of these factors that plays an important role in producing the disease



IOM

Most common diseases are multi-causal and may involve a number of contributing factors. We are interested in understanding causation so that we can design interventions to prevent disease.

One way to think about this is using these causal pies where the segments represent the contributing factors, with all needing to be present for the disease to arise. In this case we have two ways that the disease may be causes, but in both the factor A is necessary but not in its self sufficient to cause the disease. The model requires all the components to be present in the pie to be sufficient to cause the disease.

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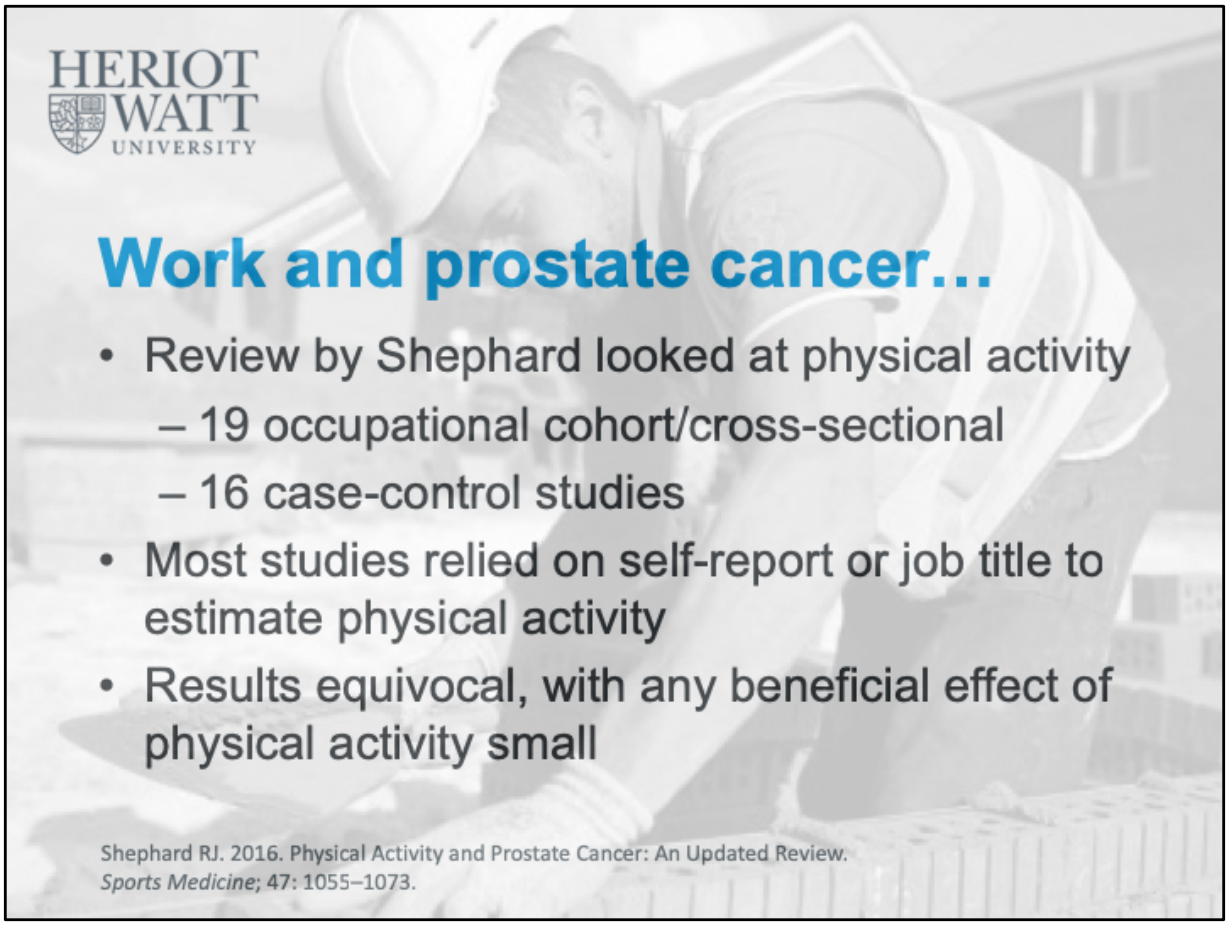
Causation…

A cause of a disease is an event, condition, characteristic, or combination of these factors that plays an important role in producing the disease

IOM

For example, lung cancer may result from a sufficient cause that includes smoking as a component cause. Smoking is not a sufficient cause by itself, however, because not all smokers develop lung cancer. Neither is smoking a necessary cause, because a small fraction of lung cancer victims have never smoked. Genes may be a necessary or contributing cause in this scheme.

Removing one element of the sufficient cause will prevent disease.



Recently I have been interested in the effect of work-based physical activity and prostate cancer. In 2016 there was a review of the published evidence undertaken by Shephard. He identified 19 cohort or cross-sectional studies and 16 case-control studies. Most of these studies relied on self-reports or job title as a way of assessing exposure to physical activity at work.

I think the results are equivocal, although Shepard is more upbeat suggesting that about half the studies were positive (with the other half negative)!

The Scandinavians have accumulated a great deal of data in registries. This study, just published, has almost a quarter of a million cases of prostate cancer and 1.2 million controls. They also relied on job title to assess physical activity using the NOCCA JEM. In their study they showed about a 5% reduction in risk of prostate cancer, which was statistically significant.

The point about this study and those in the Shephard review is that the exposure assessment is very crude. We need better ways of characterizing exposure in epidemiological studies.

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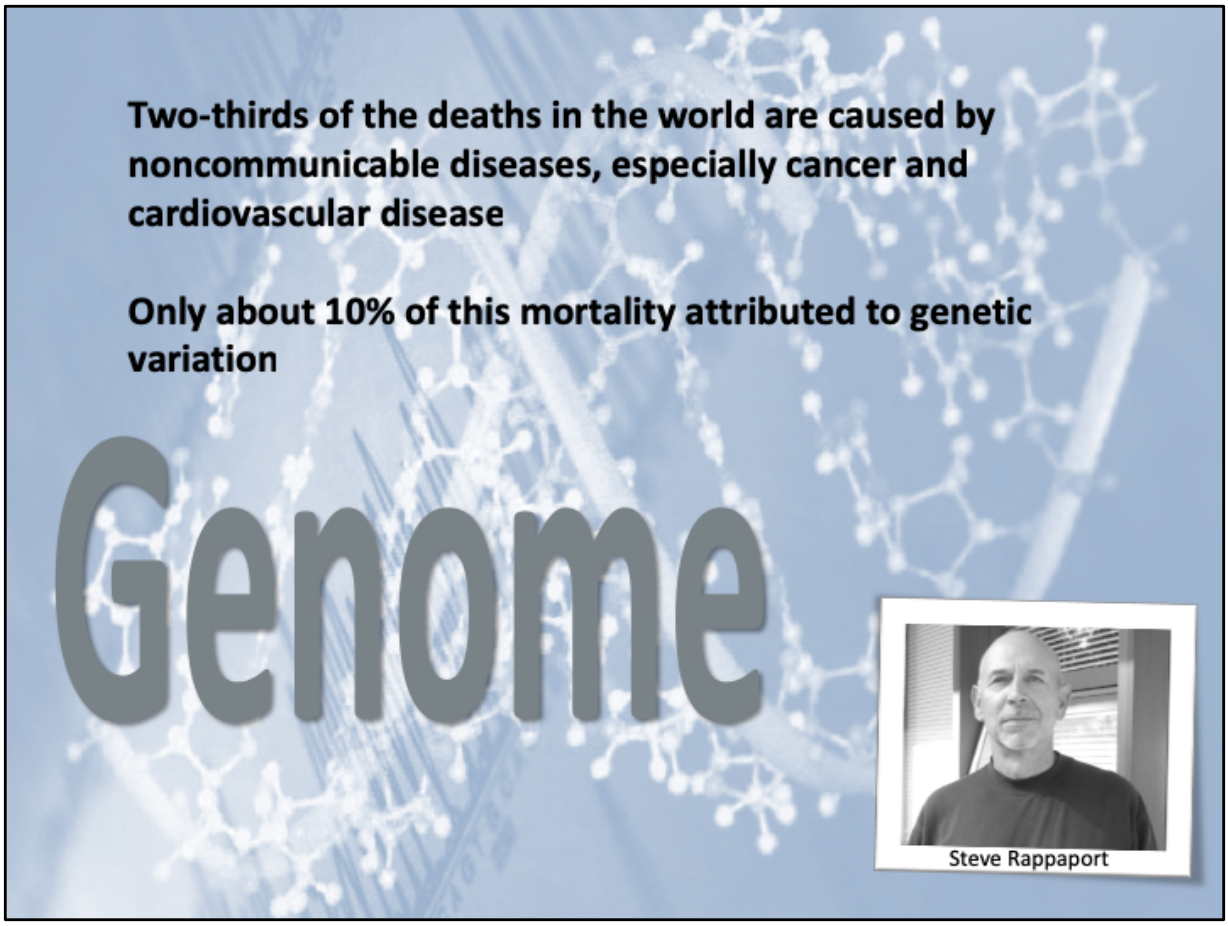
Work has changed…

- Exposures have generally decreased
- Transition to a service-based economy
- More frequent change in employment
- Work into older age
- Less job security
- Temporary migration for work more common
- Boundary between work and life blurred

IOM

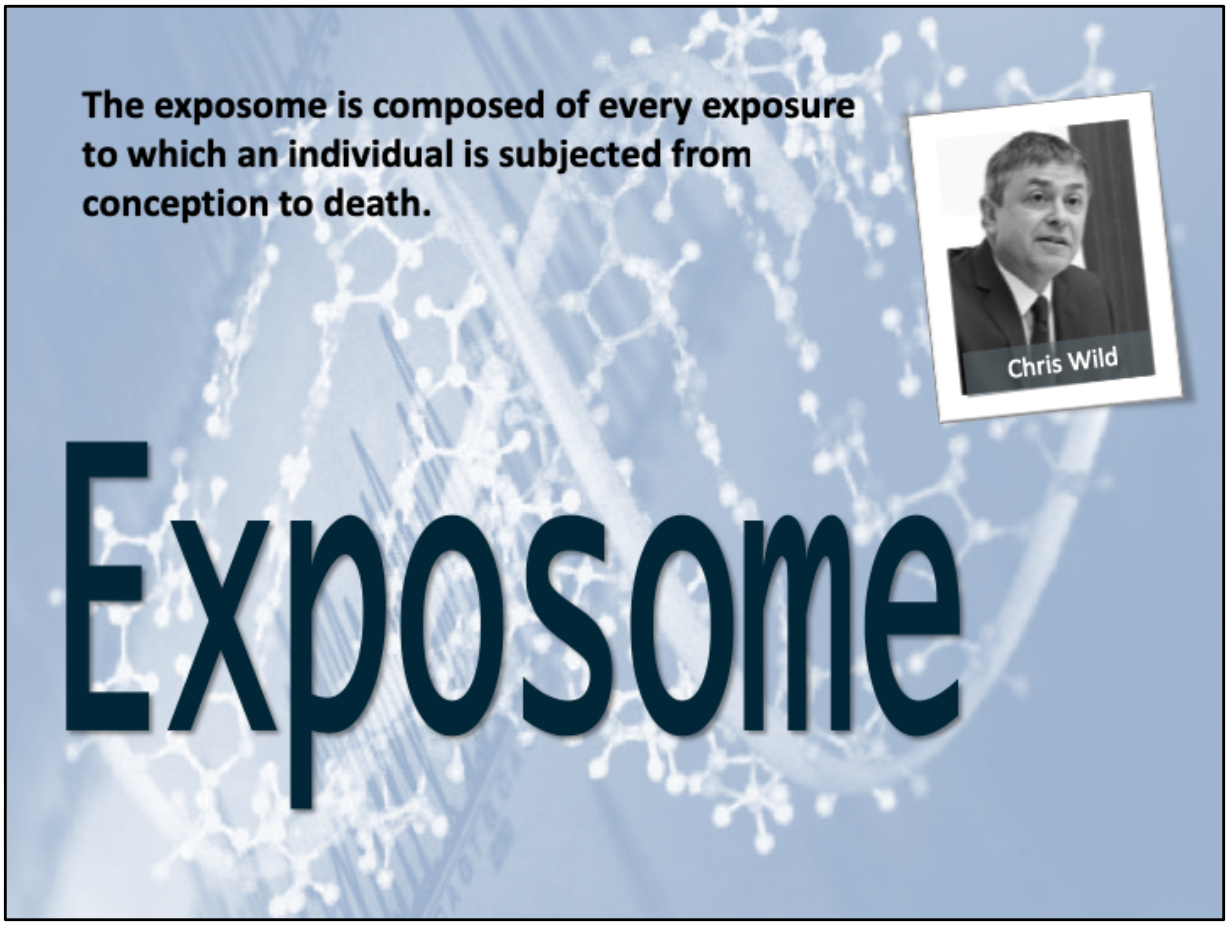
The world of work is changing. Occupational exposures have generally declined over time due to changes in the manufacturing processes and improvements in controlling exposures, and the hazardous agents involved in many jobs has changed. In addition, the number of industrial workers in Europe and North America has declined due translocation of manufacturing facilities to lower income countries and increased automation of manufacturing. Changes in the way we work means that, on the one hand, we work longer before we retire, but on the other hand we change jobs more often. In recent years the development of the 'gig' economy and temporary migration for work means that increasingly workers are seen as independent contractors or freelancers who work on short-term engagements, increasing the frequency of employment

changes.



There has been enormous effort invested in mapping out the human genome and much of this was motivated by the believe that by understanding our genetic makeup we would be better placed to prevent disease.

However, there is only about 10% of non-communicable disease that can be attributed to genetic variation. Of course the missing piece is the environment – the nurture part of nature and nurture.



Chris Wild, the Director of IARC, coined the term the exposome to try to conceptualize the measurements that we need to make to understand disease.

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The Exposome comprises…

- processes internal to the body such as metabolism, gut microflora, inflammation…
- external exposures including infectious agents, chemical contaminants, diet…
- social, economic and psychological influences.

IOM

Wild, C. P. (2012). The exposome: from concept to utility. *International Journal of Epidemiology, 41(1), 24–32.*

This is a very grand vision, at least as challenging as the scientific project to map the genome. It includes all teh elements described on the slide.

...and all this from cradel to grave.

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Bottom-up or Top-down

Or a more use a more integrated approach?

IOM

van Tongeren, M., & Cherrie, J. (2012). An Integrated Approach to the Exposome. *Environmental Health Perspectives, 120(3), a103–a104.*

There are two main approaches that are being pursued to try to quantify the exposome: one using sampling of the internal body fluids using very sophisticated untargeted chemical analysis to characterise metabolites, proteins and other biological molecules, and continuously monitoring of the environment using low-cost electronic sensors.

And of course the biological samples can be used to characterise the subjects genome.

We have argued that in addition there needs to be a more integrated approach to this characterisation using a wider range of data, for example records of supermarket purchases, logs of journeys taken on

public transport using smart cards.

The other main challenge is obtaining data for a whole life, and at the moment we are unable to get this continuously and so the main strategy is to intensively study subjects periodically throughout their lives, collecting and biobanking samples of blood, urine and other biological media, and to track their external exposures using sensors.

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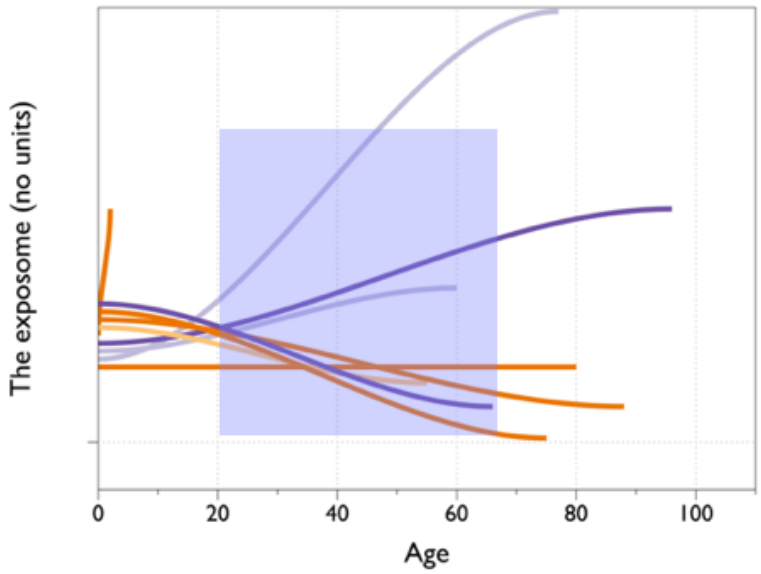
Design of an exposome study



Most exposome studies have chosen to start at the beginning. The study design can be conceptualised like this. The “exposome” is shown as some integrated dimensionless measure.

At birth our subjects are all drawn from relatively similar circumstances – they may all be from the same city or even from the same maternity hospital. They share some commonalities in their exposome. However, as time goes on they will diverge in their habits, and environment and their exposomes will correspondingly diverge. As a consequence this study design will be most informative about early life influences on health. And it will lack statistical power to investigate mid-life influences on exposure because the population will have a very diverse exposome

distribution by that stage of life.

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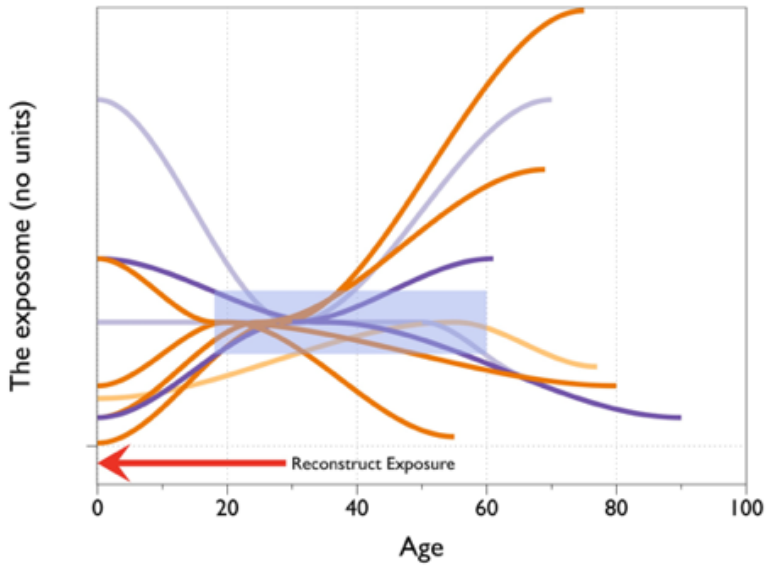
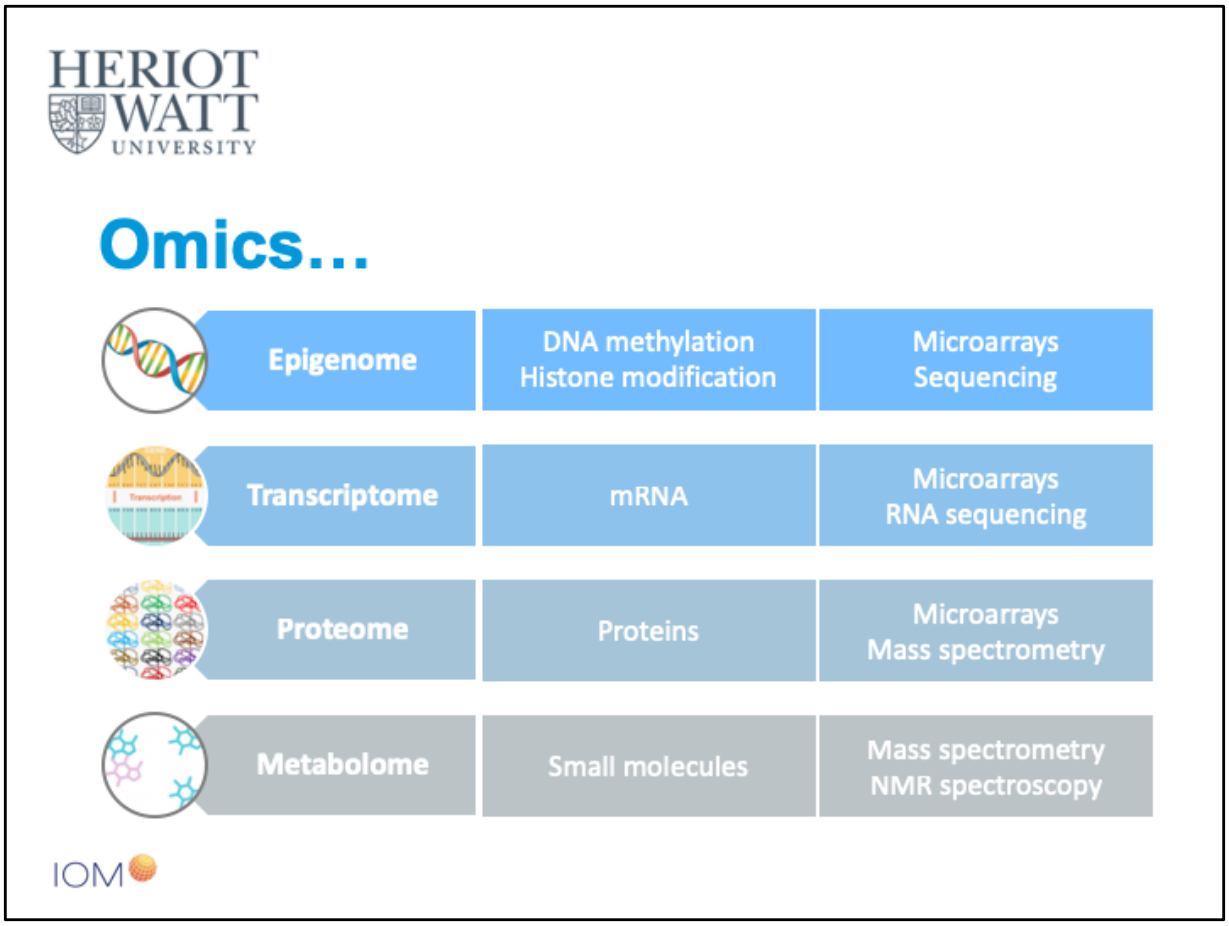
The exposome and work…



There are other strategies that can be used to develop exposome epidemiological studies and one approach that we advocate is as a way of getting greater insight into work-related risks within the exposome paradigm.

Of course these studies should consider all aspects of the exposome – work and non-work, but the advantage of recruitment being focussed in an industry or workplace is important



He main methods proposed for using biomonitoring within the exposome are the so called omics technologies. These rely on sophisticated instrumental methods of analysis, generally MS, NMR or sequencing technologies, to evaluate the epigenome, transcriptome, proteome or metabolome. The methods are applied in an untargeted way assessing hundreds or thousands of analytes simultaneously. Additionally, approaches to measure inflammatory markers, stress biomarkers and other endpoints have been suggested.

The untargeted nature of the analyses makes this an attractive approach to potentially identify causal exposures.

The main drawback, in my opinion, is the relatively short half-life of most of the biomarkers investigated, and the current relatively poor sensitivity of the untargeted analyses (this will improve).

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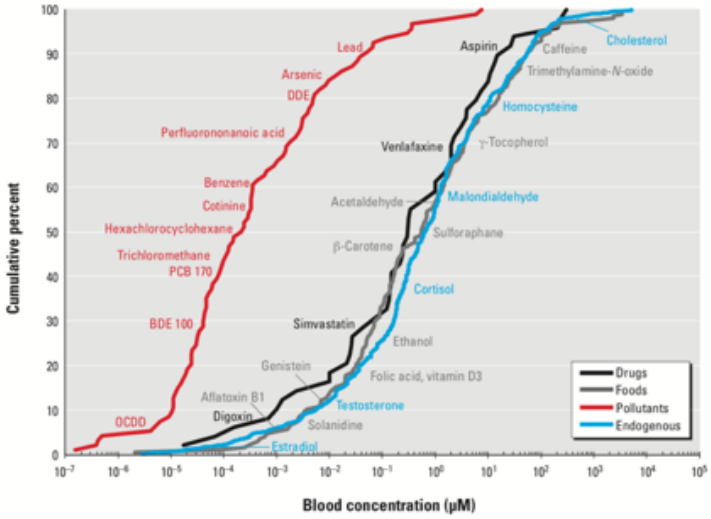
Exposome-Wide Association Studies (EWAS)…



IOM

Rappaport SM, Barupal DK, Wishart D, Vineis P, Scalbert A. 2014. The Blood Exposome and Its Role in Discovering Causes of Disease. *Environmental Health Perspectives*. 1–6.

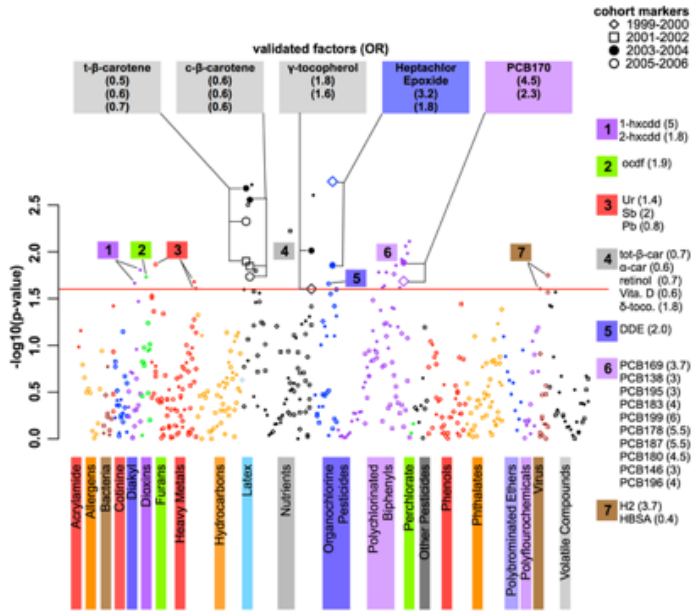
Rappaport and colleagues reviewed the published evidence for exposome biomarkers in blood. They estimated that there are more than 40,000 small molecules in the body. Of the data they were able to identify there was a very wide range of concentrations – spanning 11 orders of magnitude. The distribution of concentrations for endogenous chemicals, drug and food related molecules were indistinguishable, but the concentrations of pollutants were around 1000 times lower.

The authors noted that we only know the causes for around half of the diseases that occur and that these causes are linked to around 300 chemicals. They argue that finding the causes of disease using hypothesis driven research is unlikely to be successful and they propose that by

analogy with genetic studies – GWAS, we should conduct EWAS studies. Where we study the blood metabolome for cases of disease and controls to help generate hypotheses for further investigation.

EWAS

Patel CJ, Bhattacharya J, Butte AJ (2010) PLoS ONE 5(5): e10746.



There are few EWS studies carried out, but Patel and colleagues investigated associations between 266 environmental factors and T2D. They produced this Manhattan-like plot of –log10 (p-value) for the regression coefficients. They identifies a small number of candidate risk factors, including pesticides (heptachlor epoxide) and protective effect of b-carotenes.

However, as Rappaport noted one thing that hampers EWAS at the moment is because most environmental chemicals in the blood are at very low concentrations the untargeted analyses lack sensitivity to detect most.

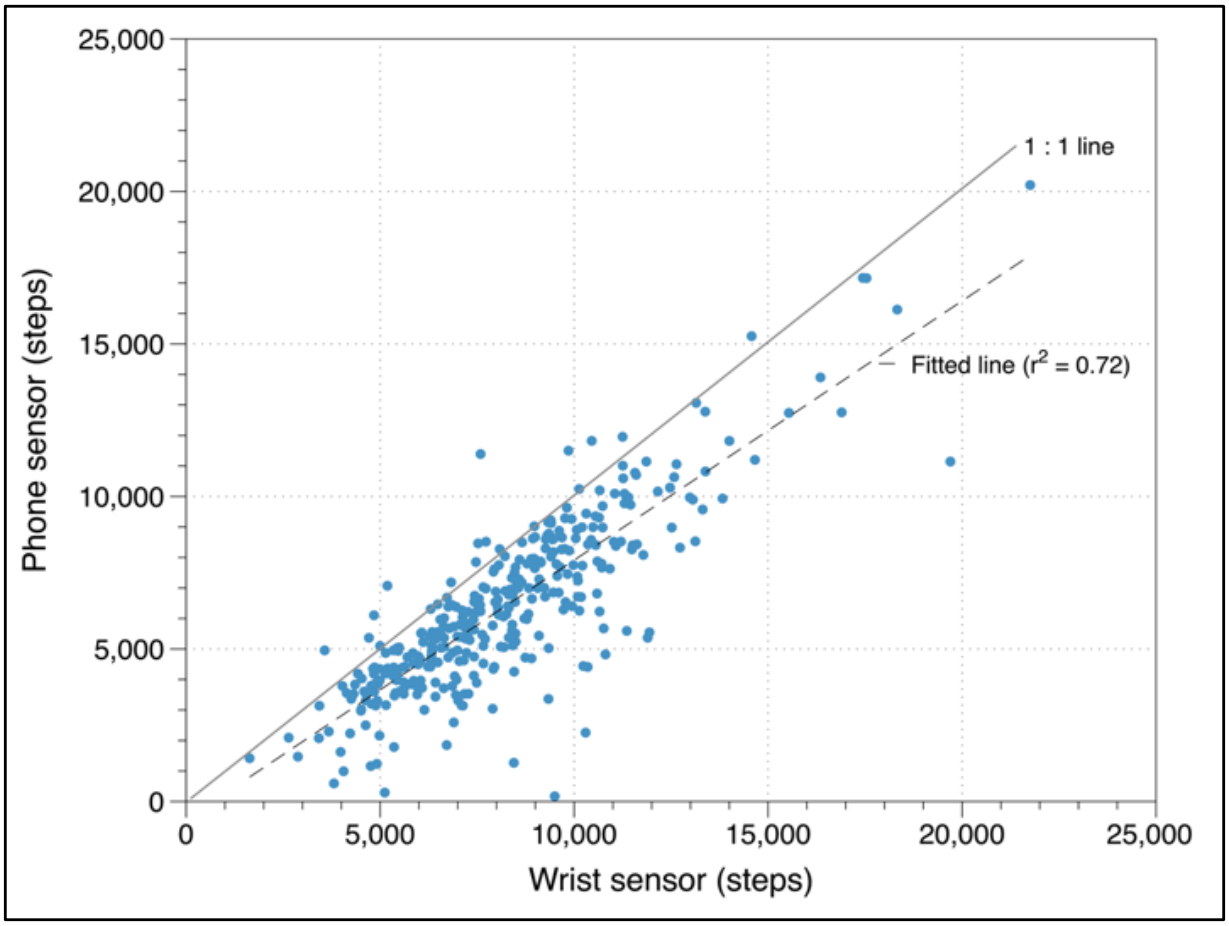
Monitoring the external exposome offers alternative strategies, although this is also not without challenges.

We argue that to be sustainable external exposome monitoring needs to be unobtrusive and require minimal involvement of the subject.

There are two core sets of data that can meet these requirements: tracking location and activity - these rely on smart phones and smart watches . Data is stored in the cloud.

These data can be used to model various aspects of the external exposome, e.g. exposure to air pollution, UV exposure, exposure to

“green space” etc.



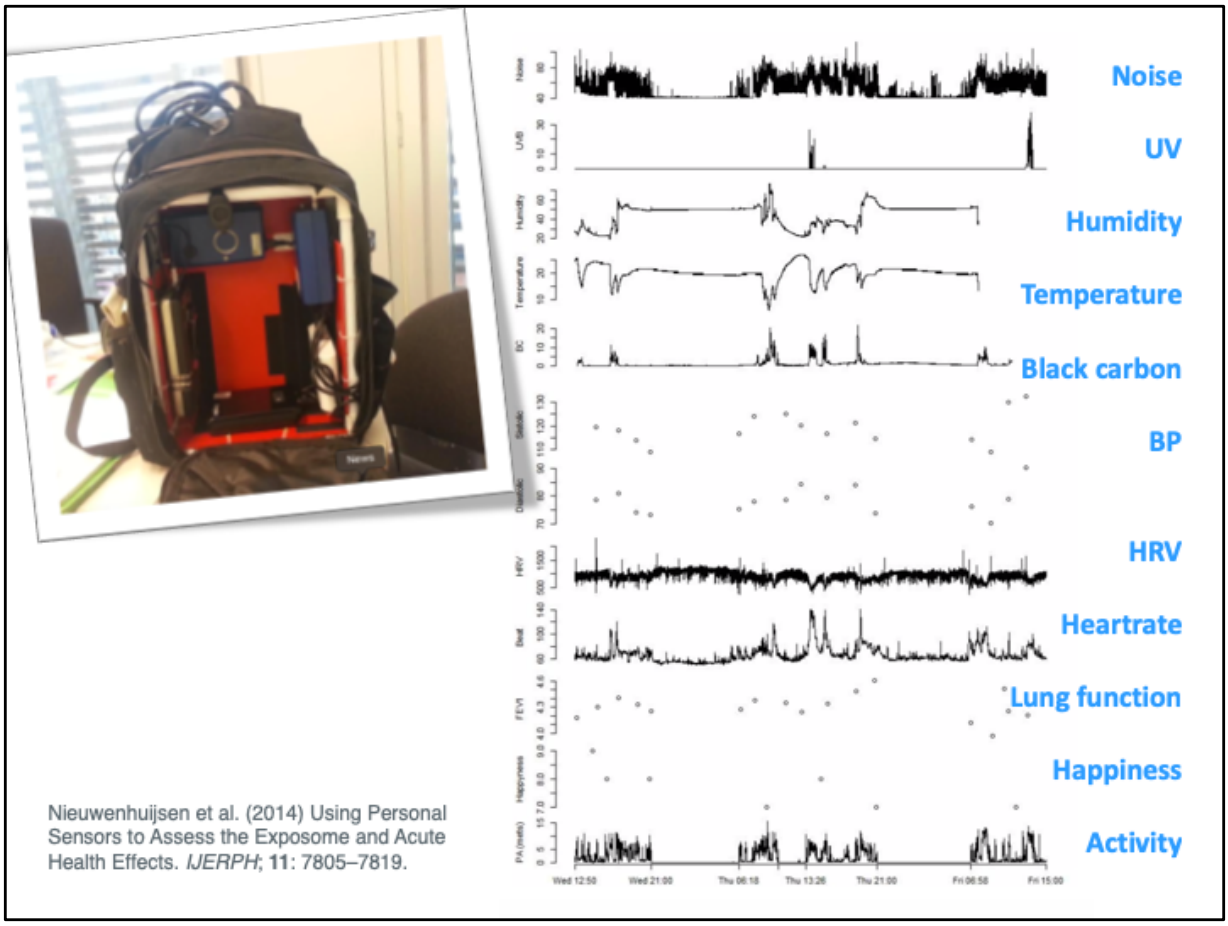
Although he phone cold provide all these data there is an advantage in a wrist sensor.

>> Explain

Also heart rate

There are a host of other sensors available but these are to a greater or lesser extent less practicable for subjects. Some are large and only practicable for fixed monitoring. Others like to temperature pill are swallowed and clearly require close supervision.

One problem is that these are emerging technological products and in some circumstances the products are not commercially successful and drop out of the market. The life-logging camera in the bottom right of the slide is no longer available.



Nieuwenhuijsen et al. (2014) Using Personal Sensors to Assess the Exposome and Acute Health Effects. *IJERPH*; **11**: 7805–7819.

It's possible to combine together several sensors, although this is intrusive – in this study the subject wore the equipment in a backpack.

This kind of measurement activity is time-consuming for the researcher and subject, and is only really practicable for a few days at a time.

To my knowledge nobody has attempted this type of study in workplaces.

Measure different exposures…

- Ambulatory EEG
- Audio content analysis of background sounds
- Body position, movement and physical loads
- Visual analysis people and landscape

We need to be more creative in what we measure - nobody has really tried to measure psychological or musculoskeletal exposures in an exposome study. Most studies concentrate on measuring pollutant chemicals and physical stressors like noise and UV. There has been some interest in using ecological momentary analysis – explain – to assess mood or other psychological states. However, it would be helpful if there were less obtrusive methods to measure EEG etc.

Life-logging cameras could provide a very useful way of characterizing many aspects of the external exposome, from dietary intake to social interactions.

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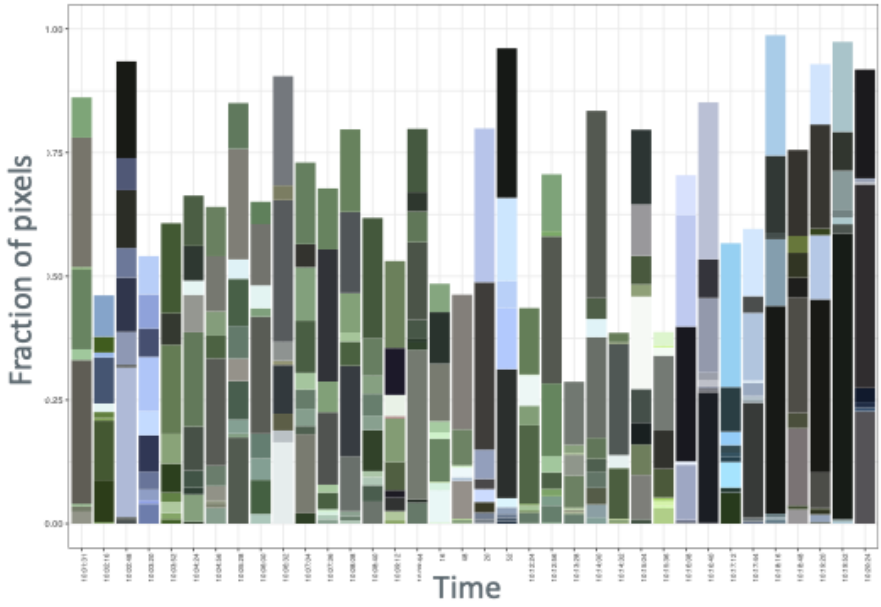
Green space…



Google Cloud

We have been using camera to assess exposure to greenspace. The plot shows data logged every 30 seconds through a task in a green environment. The colour analysis is carried out automatically using Googel Cloud Vision API (https://cloud.google.com/vision/).

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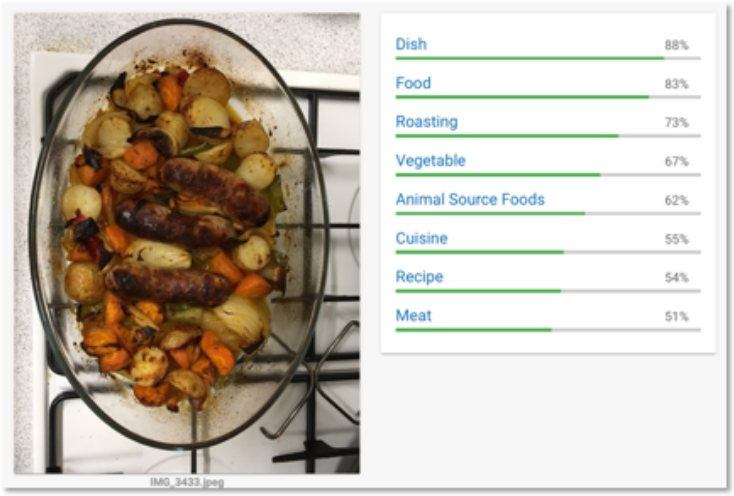
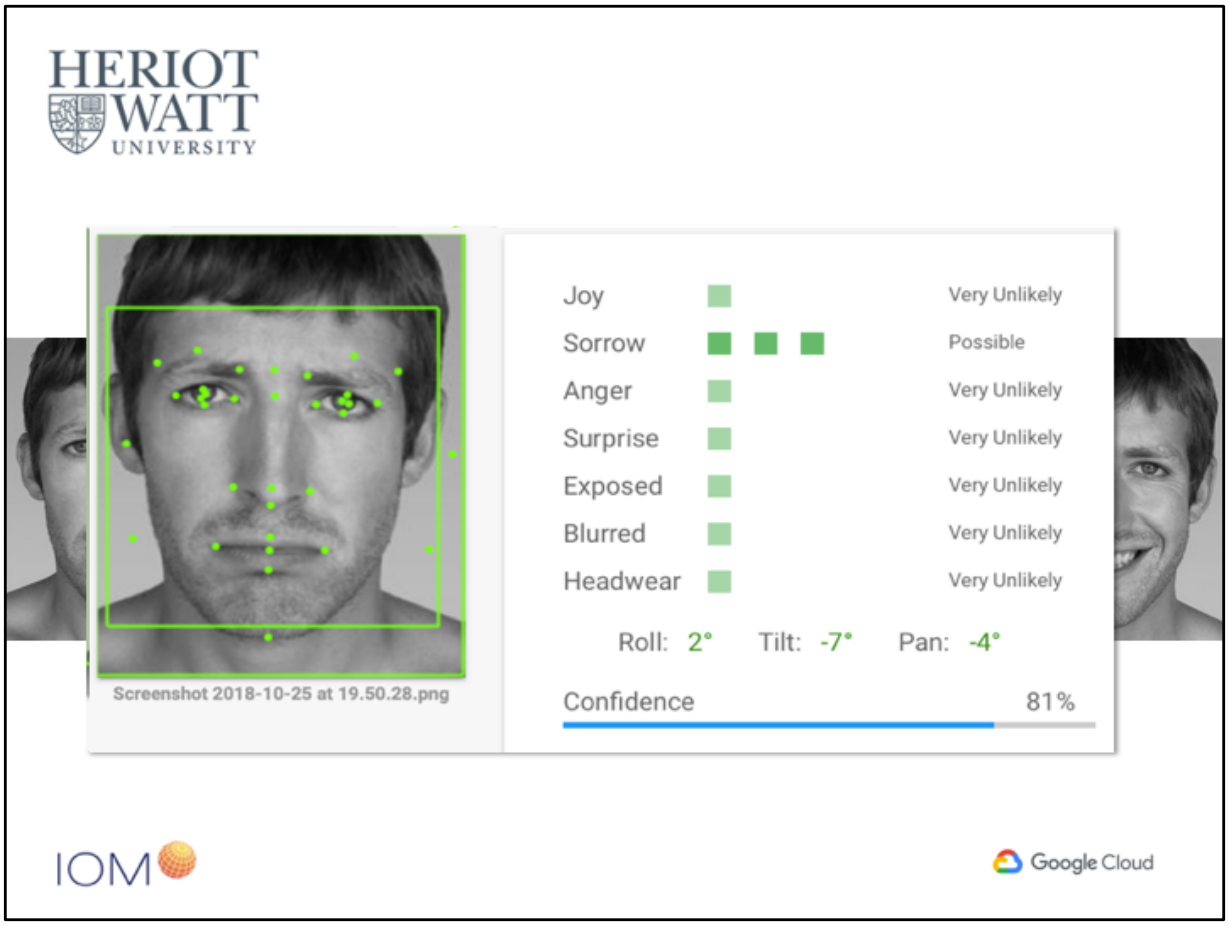
Food analysis…



IOM

Google Cloud

Again using Google Cloud API you can get an analysis of food items – the percentages show the confidence the algorithm has in the designation. More sophisticated automatic food analysis software systems are being developed.



Automatic facial analysis could also allow an assessment of the number of social contacts, the distance between individuals and the subject (based on face size in the image) and the emotional response of the person with whom the subject is interacting (in the photo the software assess that the persona made be showing sorrow). It is also possible to identify the individual concerned.

This kind of approach could be augmented with ecological momentary analysis (https://www.ncbi.nlm.nih.gov/pubmed/18509902).

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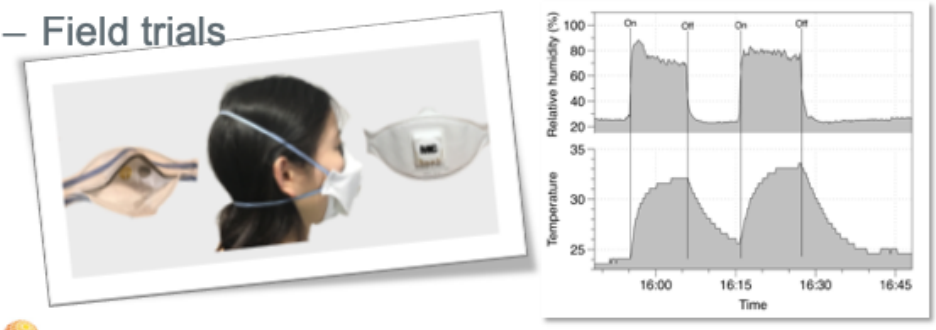
Sensor for mask wearing…

- Used data logging temperature and humidity sensor (iButton) inside mask
  - Laboratory assessment comparing with exhaled breath temperature (EBT) and time on/off
  - Field trials



IOM

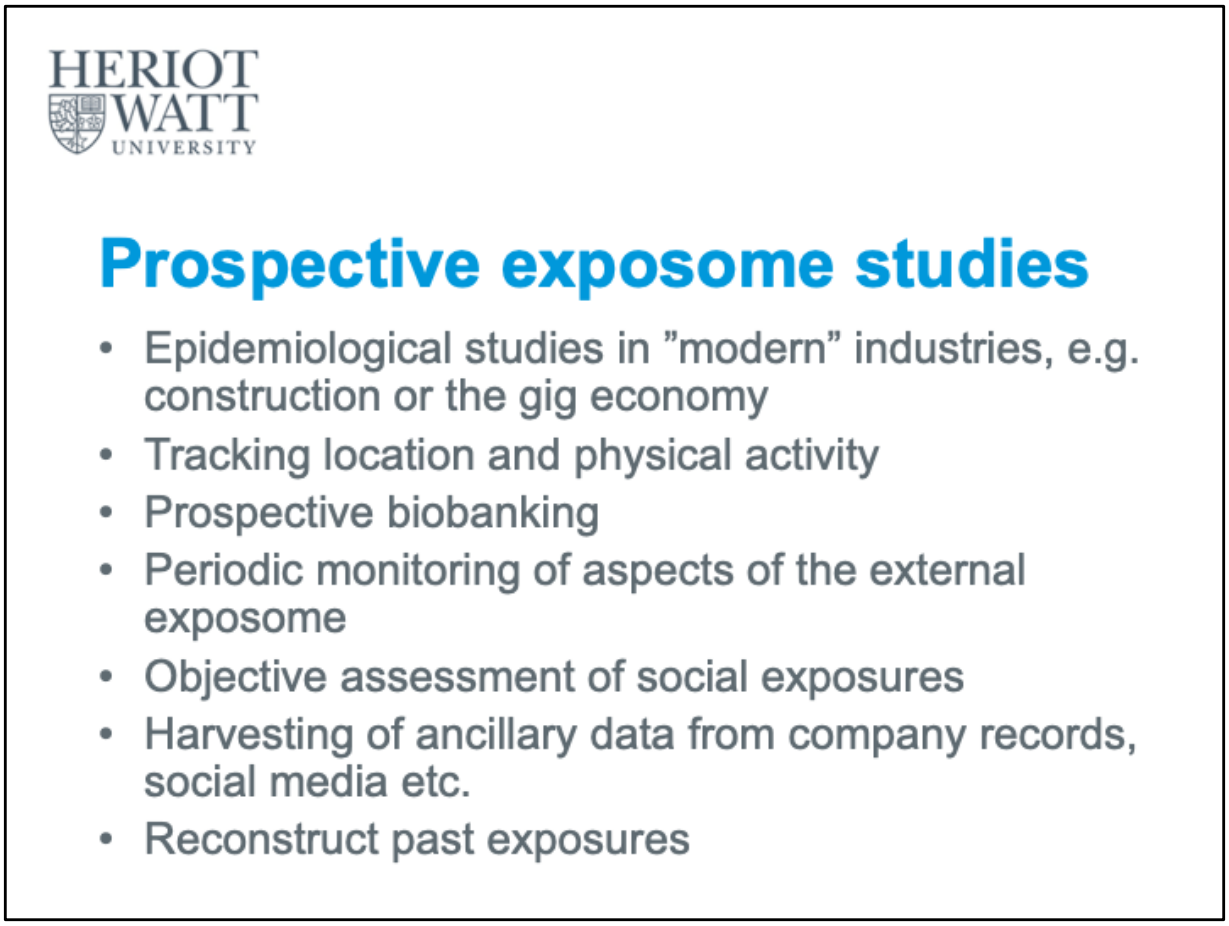
Cherrie et al (2018) In-mask temperature and humidity can validate wear-time and indicate lung health status. JESEE-18-2790.R1

We have been exploring the use of sensors inside respirators as a way of assessing when masks are worn. These log temperature and humidity and these data can be used to determine wearing times. The device also provides an assessment of the temperature in the exhaled air, which can be a biomarker of inflammation in the lung.

Finally…

Using big data collected on subjects. Examples are shown on the slide.

Challenges related to exposome research, for example, how to integrate all this data? How do we interpret them?



We advocate setting up new prospective occupational cohorts with an exposome paradigm. The items in the slide outline the characteristics of this type of study.

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Interventions to reduce risks…

- Knowledge of the external exposome facilitates interventions
- Worker-participation in data collection - citizen science
- Technological nudges using mobile phones
- Total Workers Health

IOM

Knowledge of the exposome and causal exposures facilitates interventions to reduce risks.

We have been using smartphones to send messages to construction workers to try to get them to take protective steps to reduce UV exposure during summer and increase vitamin Di intake during winter.

The exposome tools, especially sensors, could transform how workers understand their workplace exposures . What are the implications this may have for employers, employee empowerment, privacy.

In the US NIOSH have championed the concept of TWH – a way of introducing public health interventions through the workplace.

Work is changing and the way that we investigate risks using epidemiological investigations needs to change also. The causes of around half of the non-communicable disease burden are unknown. Using the exposome in new prospective studies could help identify these causes so that we can intervene to protect people more effectively.

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HEALS

Acknowledgement…

Miranda Loh, Martie van Tongeren, Anjoeka Pronk, Rob Stierum and many others

The HEALS project has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 603946.

IOM