Building Bridges in Medical Science 2021 Conference Proceedings

The Building Bridges in Medical Science 2021 Conference was held virtually on March 6th, 2021. Abstracts were judged by panel consisting of representatives from both the BBMS Organising Committee and the Cambridge Medicine Journal. A selection of abstracts are included in this set of conference proceedings, published by the Cambridge Medicine Journal.

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Title:
A systematic review of inequalities in the uptake of, adherence to and effectiveness of behavioural weight management interventions

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JMB, RAJ, SJG and ALA are supported by the Medical Research Council (MRC) (Grant MC_UU_00006/6). The University of Cambridge has received salary support in respect of SJG from the National Health Service in the East of England through the Clinical Academic Reserve. ALA is principal investigator on two publicly funded (NIHR, MRC) trials where the intervention is provided by WW (formerly Weight Watchers) at no cost. MPK has undertaken consultancy for Slimming World, and led the clinical and public health guidelines development for NICE from 2005 until 2014.

Abstract:
Background: It has been suggested that interventions focusing on individual behaviour change, such as behavioural weight management interventions, may exacerbate health inequalities. These intervention-generated inequalities may occur at different stages, including intervention uptake, adherence and effectiveness. We conducted a systematic review to synthesise evidence on how different measures of inequality moderate the uptake of, adherence to and effectiveness of behavioural weight management interventions in adults.

Methods: We updated a previous systematic literature review from the US Preventive Services Taskforce to identify trials of behavioural weight management interventions in adults that could be conducted in or recruited from primary care. Medline, Cochrane database (CENTRAL) and PsycINFO were searched. Only randomised controlled trials and cluster-randomised controlled trials were included. Two investigators independently screened articles for eligibility and conducted risk of bias assessment. We curated publication families for eligible trials. The PROGRESS-Plus acronym (place of residence, race/ethnicity, occupation, gender, religion, education, socioeconomic status, social capital, plus other discriminating factors) was used to consider a comprehensive range of health inequalities. Data on trial uptake, intervention adherence, weight change, and PROGRESS-Plus related-data were extracted.

Results: Data extraction in currently underway. A total of 108 studies are included in the review. Data will be synthesised narratively and through the use of Harvest Plots. A Harvest plot for each PROGRESS-Plus criterion will be presented, showing whether each trial found a negative, positive or no health inequality gradient. We will also identify potential sources of unpublished original research data on these factors which can be synthesised through a future individual participant data meta-analysis.

Conclusions and implications: The review findings will contribute towards the consideration of intervention-generated inequalities by researchers, policy makers and healthcare and public health practitioners. Authors of trials included in the completed systematic review may be invited to collaborate on a future IPD meta-analysis.

PROSPERO registration number: CRD42020173242
A systematic review of inequalities in the uptake of, adherence to and effectiveness of behavioural weight management interventions

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Background

- Health inequalities occur by Place of residence, Race/ethnicity, Occupation, Gender/sex, Religion, Education, Socioeconomic status, Social capital plus factors such as age and sexual orientation (PROGRESS-Plus). \([1]\)
- Interventions requiring high personal agency, such as behavioural weight management interventions (BWMMs), are likely to be inequitable. \([2,3]\)
- Some evidence suggests that if interventions are targeted (e.g. for low-income groups), they may reduce health inequalities. \([4]\)
- Previous systematic reviews have focused on mean weight loss \([5]\) and have not considered whether uptake, adherence or effectiveness differs by PROGRESS-Plus criteria.
- This systematic review synthesises the literature on inequalities in trials of BWMMs. The full protocol is published in BMU Open \([6]\) and is accessible via the QR code.

Aim

- To identify and describe inequalities in the uptake of, adherence to and effectiveness of behavioural weight management interventions.

Eligibility criteria

- (Cluster) Randomised controlled trials.
- Adults aged 18 years and older with overweight or obesity (BMI ≥ 25 kg/m\(^2\)).
- Study conducted in/recruited from/could be implemented in primary care.
- Minimum 12-month follow up.
- Population not selected on basis of weight status.
- Population with a chronic disease where weight loss is part of disease management.

Search strategy & sources

- Two phase search strategy:
  - Phase 1
    - Articles included in United States Preventive Services Taskforce (USPSTF) report published in 2018. \([4]\), AND
    - Replication of USPSTF search completed on 10\(^{th}\) March 2020 in Medline, Cochrane CENTRAL and PsycInfo.
  - Articles were dual-screened using Covidence.
  - Phase 2
    - Parent publication from each study identified and ‘publication families’ curated.
    - Publications relating to the parent publication were identified through searching Medline, Cochrane CENTRAL and PsycInfo.
    - Databases were searched using first or last author name.
    - Each publication family is considered as one study.

Data extraction & synthesis

- Data extraction
  - Data extracted using a modified version of Cochrane Public Health Group’s extraction form.
  - Risk of bias assessed using Cochrane’s Risk of Bias (RoB 2.0) tool.
  - Data extraction and RoB performed by one investigator and checked by another.

Data synthesis

- We anticipate that there will be insufficient data to conduct meta-analyses.
- We will conduct narrative synthesis to identify and describe inequalities in the uptake of, adherence to, and effectiveness of BWMMs.
- Harvest plots will be produced to synthesise evidence of differential effectiveness by PROGRESS-Plus criteria in a visual display.

Results to date

- Eligible studies from USPSTF report (n=89)
- Records Identified through database screening (n=4643)
- Records for title/abstract screening (n=4637)
- Records for full text screening (n=163)
- Studies for inclusion (n=14)
- Total studies included in review (n=103)

Discussion

- This review will identify and describe where inequalities in BWMMs occur (i.e. by PROGRESS-Plus criteria) and at what stage (uptake, adherence and/or effectiveness).
- The protocol was reviewed by a PPI representative, and received positive feedback on the review aims and plans.
- Findings will contribute towards the consideration of intervention-generated inequalities by researchers, policy makers and healthcare and public health practitioners.
- We anticipate the review will be completed by September 2021, with PPI support informing research dissemination.
- Authors of the 17 UK-based studies in the review will be invited to collaborate on an individual participant data (IPD) meta-analysis.

Acknowledgements

- JMB, RAJ, SJG and ALA are supported by the Medical Research Council (MRC) [Grant MCUU_00006/6].
The Choroid Plexus Is Permissive for a Preactivated Antigen-Experienced Memory B Cell Subset in Multiple Sclerosis

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Abstract:
Background: The role of B cells in multiple sclerosis (MS) is increasingly recognized. B cells undergo compartmentalized redistribution in blood and cerebrospinal fluid (CSF) during active MS, whereby memory B cells accumulate in the CSF. While B-cell trafficking across the blood–brain barrier has been intensely investigated, cellular diapedesis through the blood–CSF barrier (BCSFB) is incompletely understood.

Objectives: To investigate how B cells interact with the choroid plexus to transmigrate into the CSF, we isolated circulating B cells from healthy donors (HC) and MS patients, utilized an inverted cell culture filter system of human choroid plexus papilloma (HIBCPP) cells to determine transmigration rates of B-cell subsets, immunofluorescence, and electron microscopy to analyze migration routes, and qRT-PCR to determine cytokines/chemokines mediating B-cell diapedesis. We also screened the transcriptome of intrathecal B cells from MS patients.

Results: We found that spontaneous transmigration of HC- and MS-derived B cells was scant yet increased significantly in response to B-cell specific chemokines CXCL-12/CXCL-13, was further boosted upon pre-activation and occurred via paracellular and transcellular pathways. Migrating cells exhibited upregulation of several genes involved in B-cell activation/migration and enhanced expression of chemokine receptors CXCR4/CXCR5 and were predominantly of isotype class switched memory phenotype. This antigen-experienced migratory subset displayed more pronounced chemotactic activities in MS than in HC and was retrieved in intrathecal B cells from patients with active MS. Trafficking of class-switched memory B cells was downscaled in a small cohort of natalizumab-exposed MS patients and the proportions of these phenotypes were reduced in peripheral blood yet were enriched intrathecally in patients who experienced recurrence of disease activity after withdrawal of natalizumab.

Conclusion: Our findings highlight the relevance of the BCSFB as an important gate for the entry of potentially harmful activated B cells into the CSF.
Objective: The role of B lymphocytes in MS immunopathogenesis is increasingly recognized. B cells undergo compartmentalized redistribution in blood and cerebrospinal fluid (CSF) during active MS, whereby antigen-experienced memory B cells accumulate in the CSF. While B cell trafficking across the blood-brain barrier has been intensively investigated, cellular diapedesis through the blood-CSF barrier (BCSFB) is incompletely understood. We therefore investigated the interaction of B cells with the choroid plexus to transmigrate into the CSF.

Methods: Samples: Peripheral blood and/or CSF from 60 healthy donors (HC) and 30 MS patients with the relapsing-remitting form of MS (RRMS); isolation of PBMCs by Ficoll-density gradient centrifugation; Immunomagnetic isolation of B cell subsets; Migration assay: Inverted transwell culture system of human choroid plexus epithelium (HIBCPP) cells to assess B cell transmigration (TM) across the BCSFB epithelium.

Flow cytometry: Staining of PBMCs, isolated B cells, and migrated B cells with mAbs specific for B cell surface markers (CD20, CD27, CD38, IgD) to identify B cell subsets.

PCR Array: Total RNA isolation from migration-migrated B cells; cDNA conversion with a RT1 First Strand kit (Qiagen), qPCR with a RT1 SYBR Green PCR Master Mix on a custom array (Qiagen) designed to profile 19 genes involved in the activation and migration process of human B lymphocytes.

Immunocytochemistry: TM. Immunofluorescence studies of HIBCPP cells isolated from the choroid plexus of human autopsy material. B cells were labeled with CMFDA and DAPI (cell nuclei, blue); ZO-1 transmigrating B cells: TEM analysis of HIBCPP clearly seen by Ultrastructure microscopy and images were acquired from the lower chamber.

Conclusion: Our findings elucidate in more detail how antigen-experienced B cell phenotypes and the BCSFB act together to facilitate aberrant B cell accumulation in the CSF of patients with multiple sclerosis.
Title: 
A Computational Model of Cancer Metabolism for Personalised Medicine

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Abstract: 
Cancer cells must rewrite their “internal code” to satisfy the demand for growth and proliferation. Such changes are driven by a combination of genetic (e.g., genes’ mutations) and non-genetic factors (e.g., tumour microenvironment) that result in an alteration of cellular metabolism. For this reason, understanding the metabolic and genomic changes of a cancer cell can provide useful insight on cancer progression and survival outcomes.

In our work, we present a computational framework that uses patient-specific data to investigate cancer metabolism and provide personalised survival predictions and cancer development outcomes. The proposed model integrates patient-specific multi-omics data (i.e., genomic, metabolomic and clinical data) into a metabolic model of cancer to produce a list of metabolic reactions affecting cancer progression. Quantitative and predictive analysis, through survival analysis and machine learning techniques, is then performed on the list of selected reactions.

Since our model performs an analysis of patient-specific data, the outcome of our pipeline provides a personalised prediction of survival outcome and cancer development based on a subset of identified multi-omics features (genomic, metabolomic and clinical data).

In particular, our work aims to develop a computational pipeline for clinicians that relates the omic profile of each patient to their survival probability, based on a combination of machine learning and metabolic modelling techniques. The model provides patient-specific predictions on cancer development and survival outcomes towards the development of personalised medicine.
Computational Modelling of Breast Cancer for Personalised Medicine

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Problem: Understanding Cancer Progression

Cancer cells must rewrite their “internal code” in order to satisfy the demand for growth and proliferation. Such changes result in an alteration of cellular metabolism and they are driven by a combination of genetic factors (e.g., genes’ mutations) and non-genetic factors (e.g., tumor microenvironment). For this reason, understanding the metabolic and genomic changes of a cancer cell can provide useful insight on cancer progression and survival outcomes.

Proposed Solution: Computational Model of Cancer

We present a computational framework that uses patient-specific data to investigate breast cancer metabolism and provide personalised survival predictions and cancer development outcomes. The pipeline of the proposed model consists of four main steps:

(a) **Multi-omic data** (i.e., genomic, metabolic and clinical data) are collected from publicly available cancer repositories, such as The Cancer Genome Atlas and eBioPortal (Figure 1(a));
(b) The collected data are integrated into a metabolic model of breast cancer to produce a list of metabolic reactions affecting cancer progression (Figure 1(b));
(c) Quantitative and predictive analysis, through survival analysis and machine learning techniques, is then performed on the list of selected reactions (Figure 1(c));
(d) Since our model performs an analysis of patient-specific data, the outcome of our pipeline provides a personalised prediction of survival outcome and cancer development based on a subset of identified multi-omics features (genomic, metabolic and clinical data (Figure 1(d)));

![Figure 1. Pipeline of the proposed methodology for turning a metabolic model of cancer cell into a patient-specific tool for survival prediction and cancer development probability.](image)

**Results: Predicting Survival Outcomes**

Patients are stratified in high/low-risk groups based on their prognostic index, a numeric value that is used to determine the status of the cancer. The predictive model of breast cancer can be used to produce two main outcomes:

- **Selection of cancer-related metabolic reactions.** Five reactions resulted higher in the high-risk patients than in the low-risk patients. All the five reactions are involved in the fatty acids synthesis, which is strictly related to cancer (Figure 2(a));
- **Survival Probability Prediction.** The correlation between the selected fluxes and survival outcomes is used to build the predictive model (Figure 2(b)).

![Figure 2. (a) Top-5 differentially active reactions in high-risk and low-risk patients. (b) Kaplan-Meier validation plot. We used the discovery Metabolic set to train our model and to obtain a threshold for stratifying the patients in high/low-risk groups based on their prognostic index. Such threshold was then used to predict the risk group of an independent dataset (validation Metabolic set), never “seen” in the training phase. Figure (b) shows the obtained KM curve.](image)

**Methodology**

1. A computational model of cancer metabolism is developed to investigate the reactions taking place in the cancer cell.
2. Flux Balance Analysis is then applied to identify the reactions affecting cancer progression.
3. Machine Learning and Statistical Techniques are run to uncover the relationship between the selected reactions and patients survival.
4. Survival Analysis is finally applied to classify the patients into high-risk and low-risk groups, based on their omic information.

**Conclusions**

- We present a patient-specific metabolic model model of breast cancer to predict survival outcomes.
- Machine Learning techniques are used to investigate and analyze the metabolic reactions affecting breast cancer development.
- Multi-omics data were used to develop the model, providing a better predictions on cancer development and survival outcomes towards the development of personalized medicine.

![Figure 3. Main outcome of the proposed model. Starting from patient-specific data, our model uses machine learning techniques to predict the probability of developing breast cancer and provides patient-specific survival outcomes.](image)

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Title:
The Presence of Chemical Cross-Linking Stabilises HIV-1 Envelope Glycoprotein Trimer Antigens in a Model of Intramuscular Immunisation

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Conflicts of interest and funding sources:
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Abstract:
Background: The HIV-1 envelope glycoprotein (Env) is the target of antigen design for antibody-based vaccination. In 2019, four trimeric Env vaccines entered an experimental trial: ConM, ConS, and their cross-linked counterparts. The trimers were formulated with MPLA adjuvant. Studies have demonstrated that adjuvants trigger neutrophil infiltration. Neutrophils activate and degranulate releasing proteases, namely elastase and cathepsinG.

Aims: To assess the stability and immunogenicity of these vaccines in the presence of adjuvant-recruited neutrophils and their proteolytic enzymes.

Methods: Trimers were incubated with commercially-sourced proteases. To analyse stability, samples were reduced, denatured and separated using gel electrophoresis. To assess antibody binding, a trimer-protease incubation was followed by an ELISA. To establish more physiologically relevant conditions, harvested neutrophils were exposed to various adjuvants. The supernatant, shown to contain elastase, was incubated alongside the vaccines. The reducing and denaturing gels, as well as the ELISA, was repeated.

Results: Gel analysis revealed that un-crosslinked trimers underwent significant digestion whereas cross-linking conferred enhanced stability. In the presence of neutrophil-sourced protease-containing-supernatant, trimers displayed resistance to digestion. The differential stability profile of Env trimers when exposed to commercially sourced compared to supernatant-derived proteases may be due to the inhibitory effect of human serum on elastase. Antibody epitopes were maintained in vitro.

Conclusion: The vaccine antigens are sensitive to enzymatic degradation. This is reduced by cross-linking and human serum.
The Presence of Chemical Cross-Linking Stabilises HIV-1 Envelope Glycoprotein Trimer Antigens in a Model of Intramuscular Immunisation

Luiza Farache Trajano, University of Oxford

Introduction

HIV-1 envelope glycoprotein (Env) is critical for infection. HIV-1 infection can be prevented by blocking viral entry into cells via the action of neutralising antibodies, targeting Env. My project looked at Env-targeting vaccine candidates: 
- ConM, ConM-edc and ConS-edc.
- edc= heterobifunctional chemical cross-linking
- These vaccines entered an experimental vaccine trial in 2019.
- In these trials, adjuvant was used.
- Studies have shown that adjuvants trigger neutrophil infiltration.

Hypothesis:

![Diagram of antigenicity and binding]

Aim: To compare the stability and antigenicity of vaccine trimers in the presence of neutrophel elastase and cathepsin G

Vaccine Antigenicity

Antibody epitopes are preserved following protease exposure

- Antibody-trimer binding maintained following commercially-sourced elastase
- The same was true following supernatant treatment

Future Directions

- Chemical cross-linking and HS stabilise Env trimer antigens in vitro.
- Further work is required to determine the effect of HS on elastase potency in vivo, as well as the effect of other components of the immune system on trimer stability.
- The potential for adjuvant-induced protease release should be taken into consideration when selecting adjuvants.

Methods

Firstly, Env trimers exposed to:
- Commercially sourced elastase/ cathepsin G
- Supernatant, containing elastase, sourced from adjuvant-activated neutrophils.

Then:
1) To assess vaccine stability
- Samples reduced, denatured and separated using gel electrophoresis.
- The band intensity of treated samples was expressed as a % of its negative control (sample containing trimer only).
- This gives a read out of proteolytic digestion of the trimer.

2) To assess vaccine immunogenicity
- It was thought that proteases may attack specific antibody epitopes within Env
- ELISA assay performed to assess antibody-binding.

Vaccine Stability

Chemical cross-linking protects against proteolytic digestion

- Following exposure to commercially sourced proteases, proteolytic digestion occurred
- Elastase digestion > Cathepsin G digestion
- 1D C trimer more resistant to digestion

Human Serum Preserves Env Vaccine Stability

Why is Env stability so different in the presence of commercially sourced proteases in supernatant, containing the same protease?

- The supernatant contained 0.33% of human serum (HS)
- HS has inhibitory effects on elastase.
- An ELISA assay revealed that HS inhibits elastase digestion of ConM in a dose-dependent manner.

References and Acknowledgements

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Title:
The drivers of overdiagnosis within modern healthcare systems - An interdisciplinary analysis

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Conflicts of interest and funding sources: 
AV undertakes paid part-time work on an ad hoc basis at Outcomes Based Healthcare (OBH) - a health data analytics organisation providing insights for population health management.

Abstract:
“Overdiagnosis” - when people are labelled with or treated for a disease that would never cause them harm - is increasingly highlighted as a significant issue within contemporary healthcare, yet one which to date, has received little attention outside of the medical context. As a society, our collective enthusiasm to diagnose and treat disease has paradoxically been shown to potentially do more harm than good, impacting individuals whilst simultaneously increasing financial costs to the health system. As health systems across the world continue to face unprecedented pressures, tackling this phenomenon represents an important step in reducing the proliferation of low-value care inherent within the practice of modern medicine, and contributing towards the development of sustainable health systems. This research represents the first interdisciplinary analysis of the factors contributing towards overdiagnosis within modern healthcare systems. The analysis finds that individual disciplines of a medical and non-medical origin elude to important insights in relation to the drivers of overdiagnosis which are not necessarily reflected across multiple disciplines. Drivers identified within literature which lies beyond the medical context likely represent new knowledge in relation to the causes of overdiagnosis, and collectively provide a starting point from which to consider the role of patients and clinicians in influencing overdiagnosis, the nature of the interaction between the drivers of overdiagnosis, and the role of the different models of health in providing a unique perspective of the wider phenomenon. These findings highlight the importance of interdisciplinarity within health research and contribute towards efforts to reduce the rise of low value care within modern healthcare, fostering the development of sustainable health systems.
THE DRIVERS OF OVERDIAGNOSIS IN MODERN HEALTHCARE SYSTEMS

An Interdisciplinary Analysis
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"Overdiagnosis is a challenge to the sustainability of human health and health systems" (Pathirana et al., 2017)

OBJECTIVES
Looking beyond the medical context to develop innovative solutions

THE DRIVERS OF OVERDIAGNOSIS IN MODERN HEALTHCARE SYSTEMS
An Interdisciplinary Analysis

CONCLUSIONS
1. Failing to appreciate the novel insights found within non-medical disciplines will significantly hinder progress in tackling overdiagnosis
2. Important to consider implications of technology and performance and quality metrics within health systems in relation to overdiagnosis
3. Health policy focus on health system alone is insufficient. Consideration of the wider societal influences is essential

Drivers of overdiagnosis largely originate in societal beliefs as well as perceptions of technology, science and disease
Drivers of overdiagnosis manifest at global, national, regional and local levels
Understanding the role of patients, clinicians, the health industry, government and the wider society in exacerbating the issue
New knowledge about impact of technological advancements and medicalisation of risk on diagnosis

DONABEDIAN’S POINT OF OPTIMALITY
Developing the value-based healthcare framework by identifying origins of waste inefficiency and poor health outcomes

THEORETICAL CONTRIBUTIONS
Advancing the case for interdisciplinarity in health research

EMPIRICAL CONTRIBUTIONS

METHODOLOGY
MODERN HEALTHCARE SYSTEMS ACROSS THE WORLD
META-NARRATIVE REVIEW
SEARCHING PROCESSES
KEYWORD-BASED ELECTRONIC SEARCH
NON-SYSTEMATIC RETROSPECTIVE SNOWBALL SAMPLING METHOD HAND SEARCH
INTERDISCIPLINARY ANALYSIS

Too much medicine?

OVERDIAGNOSIS

Articles after duplicates removal (n=86)
Full-text articles appraised (n=61)
Sources included in the final report (n=49)

"The pressing problems in health require the intrinsic power of an interdisciplinary approach" (Kessel, 2008)

"Overdiagnosis is a challenge to the sustainability of human health and health systems" (Pathirana et al., 2017)

The Role of Patients, Clinicians, the Health Industry, Government and the Wider Society in Exacerbating the Issue

Effect of Appreciating Novel Insights Found within Non-Medical Disciplines on Progress in Tackling Overdiagnosis

Interview with Alice Vodden, MPhil Public Health, Department of Public Health and Primary Care, University of Cambridge