comment

"The uncritical reports of missed GP appointments strikes me as odd" **DAVID OLIVER**
"The patient relationship I aim for is a meeting between equals" **HELEN SALISBURY**
PLUS Vaping is a response to poor cessation programmes; advocating for LGBT+ patients

CUT TO THE CHASE Gabriel Weston

Doctors' time is out of sync with patients

I accompanied a friend to dialysis this week. She's gone on alternate days for the past 20 years, while, in all my years as a doctor, I'd never been to one of these centres.

It ran like clockwork. My friend was allocated a bed and weighed. Numbers were punched into the machine directing four litres to be drawn off at a rate of 380 mL/min, a bag of dialysis fluid was popped in, and her neck line was hooked up. Within moments of her arriving, a pie chart on the monitor showed that the first fraction of her four hour session had elapsed. Swaddled in a jumper, scarf, and blanket, she didn't feel much like talking. So, after fidgeting a while, I resolved to stop checking the screen every few minutes and fell instead to thinking about time.

Aristotle and Newton said that time is universal, a dimension that exists outside of us, steadily present, whether we perceive it or not. Our western model of healthcare provision, with its emphasis on calendar and clock time, owes plenty to this position.

It's harder to see how Einstein makes himself felt in everyday clinical life, but he certainly revolutionised our understanding of time, proving with his theory of relativity that it isn't universal after all but differs between objects, depending on their frame of reference. Two identical synchronised clocks, one on top of Everest and one at sea level, will diverge by about 30 microseconds a year.

But phenomenology, in its clear distinction between objective and subjective time, is the school of philosophy that speaks to me most. Havi Carel, a brilliant thinker who also—relevantly—has chronic lung disease, explains it like this: "The world of the ill is different in many ways to the world of the healthy. Its space and time are different."

S Kay Toombs, another philosopher-patient, adds that the objective dimension of clock time is the one in which doctors operate but that its rhythm is often out of sync with the altogether more subjective time signature of a patient's illness. If only we could tackle the "incommensurability" between these two time zones, she argues, we would solve many problems of doctor-patient communication.

We doctors feel battered by our schedules, but, in health, we still enjoy a temporal freedom that has completely disappeared for many of our patients. In any week that my friend receives 12 hours of haemodialysis, my kidneys do their 168 hours of work silently. While I sit near the humming dialysis machine hatching plans, I see how her past and future have collapsed into a present that is defined by the demands of her disease.

I bide my time quietly until the four hours are up. But, after I drop my friend home, I hit the motorway hard, pressing the accelerator, as the sun reaches the height of its compass in the sky.

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We doctors enjoy a temporal freedom that has completely disappeared for many of our patients

PERSONAL VIEW Nicholas S Hopkinson

The rise of e-cigarettes is a symptom of decades of failing to tackle smoking

There is a danger that debate around vaping drowns out the work needed to implement the full range of tobacco control measures

The Public Health England SmokeFree Health Harms campaign, now in its seventh year, focuses on the toxins present in cigarette smoke and their harmful effects on the body. A novel feature this year is emphasis on the relative safety of e-cigarettes compared with smoking.

The levels of carcinogens found in people who vape are much lower than those seen in smokers show data which underpin estimates that vaping is no more than 5% as harmful as smoking, and that completely switching from smoking to vaping is associated with substantial health benefits.

There are now more than 3 million people in the UK who vape. Almost all have smoked and more than half are former smokers. Yet, a substantial proportion of the population believe, incorrectly, that e-cigarettes are as harmful as or more harmful than smoking. We also have convincing data that e-cigarettes are an effective stop smoking aid, and while long term users of e-cigarettes should be encouraged to quit vaping too, that should not at the expense of relapsing to smoking.

But why are e-cigarettes being proposed as part of the solution to smoking, and does it matter? The first thing to acknowledge is that the ongoing tobacco epidemic is the consequence of a profound, sustained, societal failure.

It is at least 60 years since unequivocal evidence of the catastrophic health harms of smoking became available. The solutions have also been obvious for decades—price increases, advertising bans, help for smokers to quit, health education campaigns, smoke free legislation, and excluding tobacco lobbyists from policy making. Yet generations have been born, taken up smoking, and died, or are dying, prematurely from smoking related diseases, because action to tackle uptake has been tardy and tentative, and undermined by the industry.

Dismal level of support

A second failure is the dismal level of cessation support. The majority of smokers want to quit, yet cessation treatment—a mix of psychological support and pharmacotherapy—has been and remains inadequate. Public health budgets continue to be slashed, leading to widespread cuts in cessation services. Although adult smoking rates are now around 15%, there is a danger of complacency. Smoking rates are much higher in poorer people and those with mental health problems. Smoking neglect in these groups is a major driver of health inequality.

Until we have maximised the offer of "conventional" cessation, it is unreasonable to object to vaping

Too often, clinicians consider smoking cessation to be someone else's problem, or neglect it at the expense of interventions that appear to be more technical or condition specific; witness the attention given to inhaler selection for chronic obstructive pulmonary disease, while only around 10% of COPD smokers receive quit smoking help.

There are positive signs. Active lobbying has helped to ensure that smoking cessation features prominently in the NHS's long term plan, including the provision of tobacco treatment programmes for all people admitted to hospital. Enthusiasm for this move is tempered by a target delivery date of 2023-24. Given everything that is known about the impact of smoking and the benefits of cessation, it is astonishing and embarrassing that we do not have this in place already.

BMJ OPINION Michael Farquhar

NHS staff are in a perfect position to be LGBT+ advocates

A sense of being judged is not unusual among people people in the LGBT+ community—a recent Stonewall UK study reported that one in seven LGBT+ people has avoided seeking NHS care, for fear of experiencing discrimination.

That fear isn't unfounded. Despite 25 years of major social and legal advances in the UK, LGBT+ people can still face significant challenges, particularly with respect to healthcare. Almost a quarter have witnessed NHS staff making negative remarks about LGBT+ people. One in eight reports experiencing unequal treatment.

LGBT+ people are far more likely to have mental health problems than the general population, with significantly higher rates of anxiety, depression, self harm, and attempted suicide. For some groups, particularly trans people or LGBT+ people who are black or from ethnic minorities, those figures rise further.

For younger LGBT+ people, still exploring their sense of self, dealing with these matters can be even more difficult. If they uncertain of the response they may get if they come out to an NHS staff member, they are less likely to do so—even the perception that discrimination may happen can cause harm.

Conversely, NHS staff are in a perfect position to be advocates and supporters of LGBT+ people when they most need it.

The rainbow NHS badge project, launched last year by the Evelina London Children's Hospital and funded by Guy's and St Thomas' Charity (working closely with the Royal College of Paediatrics and Child Health), is intended to be a small part of the solution to some of

The popularity of e-cigarettes is a symptom of decades of failure to make proper use of effective tools to reduce smoking, and in particular of the current failure to provide funded, comprehensive, evidence based smoking cessation services. Until we have maximised the offer of "conventional" smoking cessation, it is unreasonable to object to smokers adopting another strategy to help them quit and which lowers their health risk.

A real danger, which must be acknowledged and avoided, is that debate around e-cigarettes drowns out the work needed to implement the full range of tobacco control measures. This is particularly the case in poorer countries, where smoking faces few restrictions and where the tobacco industry is lobbying hard to promote the false idea that availability of e-cigarettes means that tobacco control is no longer necessary. This argument has also been used to decommission smoking cessation services in the UK.

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these challenges. The badge has a simple image: an NHS logo superimposed on the rainbow pride flag, worn on NHS staff lanyards or uniforms. It's intended to send a strong message: you can talk to me, without fear of judgment or discrimination, about sexuality or gender identity. The badges reinforce that our hospital is a place of inclusion, that LGBT+ children, young people, and families do not need to feel scared or alone here.

The response has been overwhelmingly positive, with a third of our staff now wearing a badge. The project rolls out across the rest of Guy's and St Thomas' this month; soon to be followed by other NHS organisations or trusts.

Michael Farquhar, consultant in sleep medicine, Evelina London Children's Hospital

ACUTE PERSPECTIVE David Oliver

The strange, dispiriting fuss over missed GP appointments

Last month, NHS Digital's analysis of data on patients missing GP appointments was eagerly reported by the mainstream media. "NHS England loses £216m a year to missed GP appointments," the *Guardian* said.

The data were on primary care sessions with GPs, nurses, or therapists in the 12 months to 31 October 2018. Some 90% of practices were included, and 40% of appointments reported were booked on a same day basis. NHS Digital found that around one in 20 of the 307 million available appointments was missed without enough notice to reallocate the slot. It estimated the average cost of each appointment as £30.

The BBC reported the story in similar terms to the *Guardian*, although it included some broader context and explained that the cost calculation required some big assumptions and sleight of hand. But most media outlets were happy simply to repeat NHS England's press release on the NHS Digital figures uncritically.

So—what was the story behind the story? In isolation, the £30 figure does little to further our understanding of what we might expect or why. For starters there's no clear, retrospective, like-for-like evidence that the rate of missed appointments has risen in recent years. And we have little idea whether one in 20 appointments missed is better or worse than what we'd see in other primary care systems worldwide. Maybe only one in 20 missed is a good result. And, by comparison, the "did not attend" rates in hospitals are more like one in 10.

Then there are the potential reasons for non-attendance. Patients may have life limiting, long term conditions. They may have chronic mental health problems or chaotic lifestyles. They may have responsibilities as carers or may themselves depend on carers, who may be unwell. Their access to transport may be limited. They may have become acutely ill or may have tried to contact the practice and not managed to do so in time to free up an appointment.

Furthermore, do we really believe those calculations of expense and opportunity cost? General practice is not funded on a fee-for-appointment basis. Salary costs and overheads don't change because some appointments are cancelled. Clinics are booked with the expectation that some appointments will be cancelled, and the gaps allow extra time for other patients. Seeing other patients in those slots would impose additional costs.

I'm disappointed that NHS England put out these lines—and the largely uncritical, analysis-free reporting strikes me as odd. Even more depressing was the public's reaction in so many rapid responses to articles, letters to newspapers, on social media, and in radio phone-ins. People often favoured draconian solutions for non-attenders, such as fines, suspension, or removal of access to general practices.

Where's the compassion or the desire to understand? Maybe more balanced and nuanced reporting would help. But initial press releases focused on individual responsibility and, by inference, individual blame.

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People favoured draconian solutions such as fines, suspension, or removal of access for non-attenders

The informed patient

Shame, guilt, and apology abound in the GP consultation room as people describe their failures to lose weight, give up smoking, or restrict their use of alcohol or other drugs. The language we use to talk about health status can compound these negative feelings.

"Good" and "bad" are used to describe levels of blood sugar, cholesterol, or blood pressure. It's very easy for those words to be interpreted beyond their intended scope, so that the patient whose diabetes is difficult to control feels judged and found wanting.

But the apology I find the most surprising is when patients "admit" to having informed themselves about their symptoms or illness. "I'm sorry doctor, I know I shouldn't . . ." they start, apologising for what's surely the most obvious response to an unfamiliar symptom—looking it up online. In earlier days, did patients feel similarly sheepish about consulting a copy of a *Family Medical Guide* before seeing their doctor?

Admittedly, there are risks: searches about the most innocuous of symptoms can lead down a terrifying rabbit hole to a terminal diagnosis within minutes (I just checked: hiccups can be a symptom of liver cancer). However, there are many reliable and balanced sources of information, and people increasingly seem to be able to find them.

The root of the apology seems to be a fear of being disrespectful, as if by consulting another source of information the patient is casting aspersions on my expertise. It speaks of an old fashioned relationship between patient and doctor—the supplicant and the dispenser of wisdom, where the former feels as though they are stepping out of role or even overstepping the mark by offering their own ideas or research findings. A few doctors may even perpetuate this, feeling their authority threatened by the informed patient and closing down any discussion of what's been learnt from "Dr Google."

By contrast, the relationship I'm aiming for is a meeting between equals, working together to solve a problem. If we can achieve this the potential for the internet to empower patients is huge. Often, patients will have arrived at a sensible conclusion that's based on their symptoms and family history, which makes our consultation that bit more efficient. Even if a patient has found something frightening but unlikely, as long as I discover this fear I can explain and reassure.

As doctors it's imperative that we find a way to ask, "What have you found out so far?" Given an opportunity to share, we can together reconcile conflicting explanations of the symptoms. Without that conversation, the patient may leave still fearful of the web based, worst case scenario.

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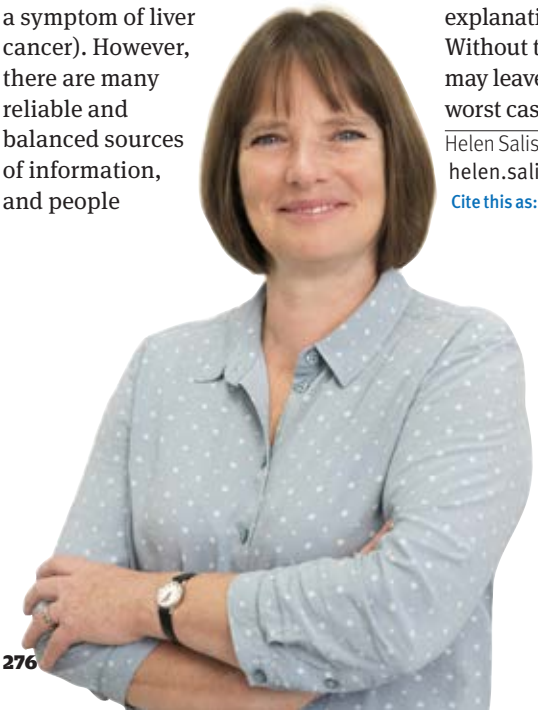
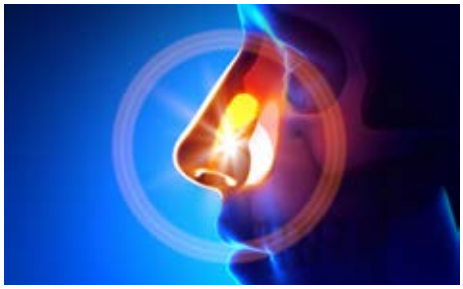


The most surprising apology is when patients "admit" to having informed themselves about their symptoms or illness

LATEST PODCAST



Chronic rhinosinusitis

Alam Hannan, an ENT consultant at the Royal Throat Nose and Ear Hospital in London, describes how to assess patients with chronic rhinosinusitis and help ease their congestion.

"With chronic rhinosinusitis, I've seen patients who've literally had the symptoms for years. I think partly that's because they realise that a blocked nose, a discharging nose, and a reduction in sense of smell are relatively innocuous symptoms in the grand scheme of things, and we certainly got that impression when we spoke to patients. One of their worries was that these symptoms may be seen as trivial, which is why they've ignored them for a while.

"But the symptoms, as time goes on, can become debilitating. They can affect one's sleep, exercise, and concentration, so they require us to take them seriously."

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LATEST VIDEO

Give us a break

To launch *The BMJ*'s campaign for adequate rest breaks for doctors, Abi Rimmer and Cat Chatfield spoke to Anthea Mowat, chair of the BMA representative body, and Michael Farquhar, consultant in sleep medicine, about why taking breaks is so important. As Farquhar explains:

"The basic truth of it is that we are not able to sustain function and performance for long periods of time without taking a rest or a break. People often think that breaks are an optional luxury—they're a nice thing that you get if a shift is going quietly—when actually we should be saying the exact opposite.

"If a shift is really busy, it's even more important that people are getting those breaks to make sure they carry on functioning."

Watch the video discussion on *The BMJ*'s Facebook page facebook.com/bmjdotcom

Curated by Kelly Brendel, assistant web editor, *The BMJ*

HRT AND VTE

Transgender studies show safety of estradiol

Vinogradova and colleagues show that treating postmenopausal female hypogonadism with an equine xenohormone, rather than physiological estradiol, is associated with a greater risk of venous thromboembolism (Research, 12 January).

Studies of transgender people have already shown that trans women who take conjugated equine oestrogens have an eightfold greater risk of venous thromboembolism compared with those taking oestrogen orally or transdermally. A stronger signal emerging from the transgender literature is the adverse cardiovascular and prothrombotic profile of ethinylestradiol, a synthetic oestrogen receptor modulator that is found in almost all combined oral contraceptives.

Despite this, many younger hypogonadal women continue to be prescribed combined oral contraceptives, rather than safer and more physiological estradiol plus progesterone hormone replacement.

Richard Quinton, consultant and senior lecturer in endocrinology, Newcastle upon Tyne; Du Soon Swee, consultant endocrinologist, Singapore

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What about progesterone?

Vinogradova et al provide further evidence that oral but not transdermal oestrogen is associated with increased risk of venous thromboembolism among postmenopausal women who use hormone therapy.

Surprisingly, the effect of progesterone on risk of venous thromboembolism is not discussed, despite strong evidence that progesterone has no effect on clotting factors and resistance to activated protein C. Furthermore, an updated meta-analysis has shown that among users of transdermal oestrogen, progesterone was associated with the lowest risk of venous thromboembolism compared with other progestogens.

Encouraging women to switch from oral to transdermal oestrogen is important, but the choice of progestogen is also critical, and the most recent clinical guidelines recommend transdermal oestrogen combined with progesterone, especially for those at high risk of venous thromboembolism.

Pierre-Yves Scarabin, emeritus research director, Inserm

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LETTER OF THE WEEK

Worrying health visitor numbers

Hiam and Dorling critique the government's new prevention plan (Editorial, 5 January). My colleagues are I are concerned about access to health visitors.

In 2012 there were 76 full time equivalent health visitors in Cornwall, which rose to a peak of 117 in 2015, then fell to 83 in 2018. The Institute of Health Visitors reports a 20% cut since 2015, when responsibility moved from the NHS to local authorities.

The institute recommends a ratio of one health visitor to 250 children, or to 100 children in deprived areas. Using 2011 census data, I estimate that at least 33 232 children in Cornwall are in the target group, meaning there should be a minimum of 133 full time equivalent health visitors. Without even considering deprived areas, this indicates a shortfall of 50 health visitors.

There is an overwhelming case for a prevention agenda, given that 80-90% of health is shaped by social determinants. But advocating for this approach while presiding over cuts to public health and crucial services like health visiting is misleading.

Expanding the health visitor programme would align perfectly with the government's objectives, improving opportunities for all, but especially those who are most disadvantaged.

Chris Tiley, GP, Truro

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COMPLAINTS

Complaints go with the job

Managers used to encourage doctors to treat complaints as jewels to be treasured, but Gerada presents us with the opposite side of the coin (Wounded Healer, 12 January). As someone attempting to help sick doctors, she finds that complaints often feature in the narratives of doctors who take their own lives.

But this association does not necessarily imply causation. If patients were to refrain from complaining for fear of damaging the mental health of medical professionals, I doubt the suicide rate would change very much.

It would, however, impede the identification of rogue practitioners, who in the worst cases have been arrogant or overconfident and lacked insight.

In my experience, complaints were accepted as part of the job; sometimes a useful and constructive solution could be found, but even vexatious ones formed valuable material for reflection at one's appraisal, rather than triggering depression.

John R King, retired psychiatrist, Redditch

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We need complaints

We need complaints—not just for learning but also to underline good practice. If a doctor never declares any complaints, it is reasonable to ask why: do they say "yes" when they should say "no" to patients? Are they using resources wisely?

In discussions with a colleague who had just received a complaint about her refusal to prescribe a benzodiazepine, I congratulated her on what sounded like good practice. Good medicine is not always the medicine that patients desire. Good doctors will get complaints and will be able to evidence their good practice by their response.

Deborah A White, locum GP, Stockton on Tees

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LUNG HEALTH

Sing a song of lung health—beyond the UK

It was a pleasure to read about the biopsychosocial benefits of group singing for people with chronic lung disease (Cut to the Chase, 19 January).

My colleagues and I have been exploring the use of music making as a component of holistic care for chronic lung disease outside the UK. In 2014, I started a dance group for people with multidrug resistant tuberculosis in rural South Africa, as well as their family members and staff. We have set up Singing for Breathing Uganda and have been exploring the use of music and dance for chronic lung disease in the Kyrgyz Republic.

The participants and staff report the same positive effects as in the article—improved physical functioning, symptom control, mood, and social relationships. Such activities deserve our attention.

Keir E J Philip, respiratory specialty registrar, London

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ANALYSIS

PREDIMED trial of Mediterranean diet: retracted, republished . . . still trusted?

Arnav Agarwal and **John PA Ioannidis** consider the lessons that should be learnt from the correction process of the influential nutrition study

The Prevención con Dieta Mediterránea (PREDIMED) trial[1] is one of the most influential randomised trials ever. It was cited 3364 times in Google Scholar in the five years after its publication. However, in June 2018 the trial was retracted and republished because serious protocol deviations were detected. Moreover, the repercussions of these deviations and of the correction process raise many questions. How do you correct one of the most influential trials and the universe of its secondary publications?

The original paper had already generated 267 secondary publications before its retraction and republication

Initial results and early raised concerns

PREDIMED was originally published in 2013.[1] Heralded as a pioneer effort in nutrition,[2] it randomised 7447 participants to a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with nuts, or a control diet. It showed a 30% relative risk reduction in a composite clinical endpoint of cardiovascular death, stroke, or myocardial infarction in the Mediterranean diet groups.[1]

PREDIMED was an important effort and one of the few long term trials with clinical outcomes in nutrition. However, some concerns were raised at the time of the publication.

The interventions tested were not a typical Mediterranean diet but single food supplementations. The control group experience was not necessarily non-Mediterranean. The primary outcome was a composite of three endpoints,[3 4] and significant differences were driven by a single endpoint (stroke) without differences in other cardiovascular disease or death. Effect sizes were probably inflated because the trial was stopped early after interim analyses showed benefit.

Several systematic reviews and guidelines have either omitted PREDIMED[5 6] or have rated it as having serious risk of bias and being difficult to interpret.[7] Moreover, secondary PREDIMED analyses reported results that were deemed implausible.[8 9]

Retraction and republication

Recent developments questioned PREDIMED at its core. An analysis of reported baseline characteristics in 5087 trials by Carlisle identified trials in which the compared randomised groups were too similar or too dissimilar, raising questions of potential fraud or non-random sampling.[10] PREDIMED stood out for implausible P value patterns when comparing the baseline characteristics of the three arms.

An audit of the trial found serious irregularities: enrolment of household members without randomisation; assignment of participants to study arms based on clinic site rather than true randomisation; and inconsistent use of randomisation tables. These deviations affected 1588 participants (21% of the total).[11]

The randomised trial was no longer a randomised trial. The original paper was retracted and replaced with a reanalysis that treated PREDIMED as a non-randomised study and excluded participants who were not truly randomised.[11] The reanalyses gave similar point estimates for the primary endpoint.

Is republication justified?

Whether republication is justified in such cases is controversial. In theory, it can be used when there is an error that significantly affects parts of the study but does not completely refute it.[12]

In PREDIMED, the detected irregularities may not entirely explain the peculiar baseline characteristics and they also raise questions about the quality of other aspects of the conduct of the trial, such as data collection, data arbitration, and adjudication. Participants, investigators, and assessors were not blinded, potentially compounding any bias—for example, if investigators and sponsors favour specific interventions. Here, it is unclear if the correction of the specific identified errors also corrected all the potential accompanying problems and consequences of these errors.

Additionally, the title of the republication does not make it clear that it is a reanalysis and republication, and many readers may be confused.[13]

KEY MESSAGES

- PREDIMED, a highly influential trial of nutrition, was recently retracted and republished after major protocol deviations were noted
- Republication may not solve multiple problems that remain, including the inappropriateness of stopping early given the revised results and the effects on more than 200 secondary publications
- Multiple contradictions between data reported across PREDIMED publications suggest a more generic problem with the trial's quality.
- PREDIMED may provide useful lessons on how to reassess and correct large volumes of published literature and on what methodological safeguards are needed for pivotal multicentre trials

Examples of inconsistent data on main endpoints across some PREDIMED publications

Publication	Median follow-up (years)	No of participants*	Primary composite endpoint	Mortality			
				All causes	Cancer related	Cardiovascular	Other
Martinez-Gonzalez 2015[23]	4.3	7216	277	328	—	81	—
Henriquez-Sanchez 2016[24]	4.3	7015	—	319	166	102	—
Martinez-Gonzalez 2014[25]	4.8	7216	—	323	130	76	117
Hernandez-Alonso 2016[26]	4.8	7216	277	323	130	81	112
Estruch 2013[1] (original publication)	4.8	7447	288	348	—	87	—

*Differences in sample size across studies are mainly because of different exclusion criteria and may be justifiable. However, even then inconsistencies are noted. For example, the first three publications in the table[23-25] all report that they exclude 231 participants but Martinez-Gonzalez 2015[23] states that they all had extreme values of total energy intake, whereas the other two state that some had extreme values of total energy intake (n=153[25], n=152[24]) and other had incomplete dietary data at baseline (n=78[25], n=79[24]). Also these papers give different median follow-up despite the similar exclusions.

Continuing follow-up

Had randomisation problems been detected while the study was ongoing, would it have been stopped early? The reanalysis does not satisfy the P value boundary required for early stopping for each intervention arm.

PREDIMED has in fact continued follow-up, and the investigators have published papers with 1.2 additional years of follow-up, during which the number of participants experiencing an event included in the composite primary endpoint increased by 19%. However, information is not provided on the comparison of the three arms for the primary endpoint with this extended follow-up. The full follow-up data should be disclosed and analysed for an intention-to-treat comparison to determine whether there is still benefit.

Full follow-up would also allow more complete assessment of mortality differences. Since mortality is linked to a national registry and thus cannot be biased, analysis of the full mortality data is essential to understand the robustness of the trial's conclusion.

We have asked the corresponding authors of PREDIMED papers and the head of the steering committee to provide the number of primary outcome events and deaths in each arm in the extended follow-up. PREDIMED investigators responded that "information you have asked for is the main topic of ongoing analyses on PREDIMED data."

What about secondary publications?

Importantly, the original PREDIMED paper had already generated 267 secondary publications before its retraction and republication.[14] Thirty two of them have already received more than 100 citations each in Google Scholar. Most of the publications come from the network of investigators who performed the original trial and their extended teams, with three investigators having each published more than 150 articles from PREDIMED.

Involvement of investigators with contrary views is pivotal for this reassessment to be fair and balanced

In July 2018 we identified 203 secondary papers with data (excluding reviews, editorials, and commentaries); 194 (95%) first authors, 201 last authors, and 223/225 (99%) corresponding authors (some papers have more than one corresponding author) belong to the original PREDIMED team in the 2013 paper or are affiliated with related Spanish institutions (see supplementary data on bmj.com).

The analyses presented in secondary papers use the data that led to retraction of the original. The PREDIMED authors have started correcting some of their work and have published several letters to this effect (at least five letters pertaining to eight secondary publications[16-20]).

Re-evaluation should be truly independent. Given the circumstances, it cannot be done only by the PREDIMED investigators and other investigators who hold similar views on the importance of specific foods to modulate disease risk and on the agreement between the results of non-randomised studies (what PREDIMED is perceived to be now) and randomised trials. Involvement of investigators with contrary views is pivotal for this reassessment to be fair and balanced.[21]

Instead of trying to correct one paper at a time, it may be more efficient for an independent team to make a centralised effort and report to all relevant journals. For a major multi-investigator effort like PREDIMED, the independent assessors should have international provenance.

Secondary publications that compare outcomes in the randomised arms are directly affected. However, even when secondary publications deal with the study dataset or subsets as an observational cohort, the clustering of recruited participants—household members co-randomised or a whole village recruited in one step—still affects results.[22] The clustering effect also needs to be incorporated in observational analyses and may lead to different estimates and conclusions.

Secondary publication Inconsistencies

Even without in-depth re-evaluation of the raw data underlying PREDIMED publications, there are some inconsistencies in the reported data in

these papers that suggest broader and more generalised problems that are not fixable by a single reanalysis.

To illustrate this point, we searched PubMed using the keyword "PREDIMED" and identified English language PREDIMED publications that included data on more than 7000 participants reporting either the primary composite endpoint or mortality (all causes and cause specific). The number of events varies widely even when publications have similar follow-up (see supplementary table on bmj.com).

Some discrepancies may reflect missing data and different eligibility criteria in different analyses. However, the table (p 279) shows a sample of contradictions in the reported data in paired papers that cannot be explained in this way and point to errors in one or both of the papers.

The original publication[1] reported 87 cardiovascular deaths for the full trial population and follow-up, while Henríquez-Sánchez and colleagues' secondary analysis of dietary antioxidants and mortality[24] reports 102 such deaths despite a more limited sample and follow-up. Two publications[23 24] have identical follow-up, but one[23] has a larger number of total deaths, while the other[24] has a higher number of cardiovascular deaths. Two other publications[25 26] have identical total number of deaths, but one has five more cardiovascular deaths (a component of the primary endpoint)[26] while the other has five more deaths from other causes (not a component of the primary endpoint).[25]

The original publication reported only cardiovascular deaths and total deaths.[1] However, if the 166 deaths from cancer reported by Henríquez-Sánchez and colleagues[24] are added to the 117 deaths from non-cancer, non-cardiovascular causes reported by Martínez-González and colleagues[25] and 87 deaths from cardiovascular causes in the original paper,[1] the total deaths are 370, exceeding the total deaths (n=348) reported in the original publication despite identical length of follow-up.[1]

Potentially useful actions for PREDIMED

- Disclose full long term outcomes with updated follow-up
- Issue notices of concern for secondary publications until they are reassessed
- Consider centralised effort to re-evaluate all PREDIMED publications together
- Include both sympathetic and contrarian researchers in the re-evaluation
- Correct obvious inconsistencies that already violate plain logic rules
- Audit raw data, not just the clean data
- Audit data collection and curation procedures
- Correct or retract secondary publications, as appropriate
- Make raw data widely available (not only those pertaining to recent reanalysis)

These discrepancies may point to poor reporting, erroneous or inconsistent statistical analyses, or deeper problems related to problematic data collection and curation. They are superimposed on a PREDIMED literature that shows all the hallmarks of data dredging, given the huge number of secondary publications. Most analyses are not prespecified or are specified imprecisely. For example, one secondary publication states that invasive breast cancer was a prespecified outcome,[27] but the published trial protocol states that all cancer—not just invasive breast cancer—was a secondary outcome.

Reanalysis needed

PREDIMED investigators have stated that the data that went into the recent republication can be requested by interested parties, but the concerns identified make a strong case for the complete PREDIMED dataset, not just the data that went into the recent republication, to become publicly available. A truly independent audit should examine the original data records, adjudication, and statistical analyses that underlie this voluminous published literature. Updated follow-up results should be independently assessed and reported, including all-cause mortality data (the most objective outcome).

The box (left) summarises some proposed actions. PREDIMED is a key example of using randomisation in the field (despite all the caveats discussed above) and it has major repercussions. An independent reanalysis may be more efficient and convincing than attempts by the authors to defend each secondary publication separately.

Future pivotal multicentre trials

PREDIMED may offer useful lessons about how to run future large multicentre trials that aim to revolutionise an entire field. The original publication[1] had 18 authors and 223 collaborators. Many secondary papers also feature impressive numbers of coauthors. However, studies with hundreds of investigators may still have blind spots where no one really is responsible or knowledgeable enough to avert major mistakes and protocol deviations.

PREDIMED investigators have a unique opportunity to disclose details on how the process failed, so that other trialists may avoid similar problems. Strong methodological expertise at all pivotal steps and function, both site specific and centralised, is essential. Also the inclusion of people who do not support the study hypothesis in the monitoring board is key to ensure balance and avoid bias.

PREDIMED's problems should not lead to a reduction in funding of diet related research to improve health. Conversely, the same or even higher funding should be diverted to well executed large trials in nutrition. This will require getting together people with different expertise and skill sets.

We also have an opportunity to investigate how large volumes of published literature can be reassessed and corrected, as appropriate, when serious problems are identified, and what is needed to run such important multicentre trials reliably in the future.

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Paola Domizio

Gifted pathology teacher and science communicator

Paola Domizio (b 1960; q UCL 1984; MRCP, FRCPath), died from breast cancer on 14 October 2018

Paola Domizio, pathologist and professor, may be the only person to have incorporated card tricks into her inaugural professorial lecture. It was typical of the flair she brought to teaching at Barts and the London School of Medicine and Dentistry at Queen Mary University of London and to her ambassadorial and leadership positions at the Royal College of Pathologists. Having served as assistant registrar and then registrar for nine years from 2001, Domizio used her communication skills and zest for the specialty as director of public engagement at the college from 2011.

Concerned that the public's view of pathology was shaped by television crime solving sleuths in pristine white coats, running between antiseptic laboratory and faintly exotic murder scenes, she wrote articles and took to TV and radio to redress the balance. This was in the 1990s, when Domizio was also among those to take on the discredited antivaccine activist Andrew Wakefield, writing two articles challenging his research and conclusions around links between the MMR vaccine and autism.

Communication skills

Domizio may also have been the first clinician to offer children who had undergone colectomies for bowel disease the chance to view and learn about the bowel resection tissue that had caused their symptoms. She saw this as an important part of their psychological recovery, and it became very popular. She also helped revitalise Barts Pathology Museum when she was appointed curator in 2010, giving regular talks to the public while helping to restore its specimens.

However, Domizio's communication skills were largely deployed teaching students at Barts Medical College from 1988, and then later at the merged Barts and London Medical School from 1995. She is credited with being a force for cooperation during the turbulent post-merger period. She was one of six academics to add the unpaid role of senior clinical tutor to her remit. This was in addition to her role as staff president of the students' union.

With her enthusiastic and friendly approach, Domizio was often voted best lecturer as she sought to instil a passion for a specialty she believed was at risk of being marginalised. The rise of computed tomography scanning and magnetic resonance imaging made fellow clinicians excessively confident in diagnosing disease, she thought. Having acquired an international reputation as a paediatric gastrointestinal pathologist, Domizio also feared the 1995 Alder Hey Children's Hospital body parts scandal further undermined pathology by exacerbating a decline in autopsy rates.

There may have been the zeal of the convert about her passion for pathology. At school she excelled in languages and science, but from an early age wanted to be a doctor. Similarly, she claimed to have accepted a SHO role in pathology at Barts in 1986 as an interim measure while she studied to pursue her intended career path as a surgeon. However, inspired by Gerry Slavin, professor of pathology at Barts, she became absorbed in the specialty, and by 1989 she was combining clinical work with teaching as lecturer and honorary senior registrar.

Career

A dearth of consultant histopathology posts in the early 1990s blocked Domizio's progress until, in 1994, Slavin, as she put it in an interview, wrote a job description that matched her skillset and created a new post of senior lecturer and honorary consultant. Nine years later she was appointed professor of pathology education and honorary consultant. But it was another four years before she delivered the card trick lecture.

With her enthusiastic and friendly approach, Domizio was often voted best lecturer

Early life

Domizio's career was the culmination of a long journey from poverty for one of three children born to parents who migrated from Italy in the 1950s. They lived above a butcher's shop in Islington, north London, then a largely impoverished area. Despite achieving A grades in all of her exams, Domizio was turned down by Cambridge University, but gained a place at University College London. She remained fluent in Italian—her first language on arrival at school—and the London Olympics in 2012 allowed her to combine two passions as a "gamesmaker" (volunteer) attached to the Italian team.

Four years earlier, a few weeks after adopting twin boys, she had been diagnosed with breast cancer. She returned to work at Barts and the London after treatment but was forced to resign in 2015 after being diagnosed with metastatic disease.

A prolific author of academic papers and textbook chapters, she wrote two chapters for the 2013 edition of *Morson and Dawson's Gastrointestinal Pathology* while she was unwell.

Paola Domizio leaves her husband, Michael; twin sons, Sasha and Aron; her mother, Luisa; a sister, Sandra; and brother, Ricardo.

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Ankie Borgstein van Wijk

Paediatrician Blantyre, Malawi (b 1925; q Utrecht, Netherlands, 1952; DCH), died from heart failure on 6 August 2018

Ankie Borgstein van Wijk met Jan, a fellow medical student, after the end of the war. They were married in 1951 and, with the help of the British Foreign Office, moved to what was then Nyasaland, where they stayed after it became Malawi, working at the 1000 bed Queen Elizabeth Central Hospital. Ankie sat the diploma in child health of the Royal College of Physicians in London in 1969. She singlehandedly set up the paediatric department at the QECH in Blantyre, and gradually built it up as one of the top departments in the hospital. She worked until the age of 87, completing 50 years of service for the Malawi health ministry in 2012. Jan had predeceased her by 39 years. Ankie leaves seven sons, 16 grandchildren, and five great grandchildren.

Johannes Borgstein

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Greta Rosenthal

Consultant psychiatrist Toronto, Canada (b 1943; q Royal College of Surgeons in Ireland, Dublin, 1969), died from lung cancer on 27 December 2018

Greta Rosenthal was born and brought up in Liverpool. After qualifying in Dublin, she returned to Liverpool and worked at Walton Hospital, Sefton General Hospital, and Chester City Hospital. In 1971, on a visit to Canada, she met her future husband. She took the Canadian medical exams and completed psychiatry training in Toronto. For the next 44 years she ran a successful psychiatric practice until she reluctantly retired owing to ill health aged 74, just months before she died. In later years Greta and her husband developed a passion for tango, becoming well known members of the Toronto tango community and travelling widely on tango holidays. Greta leaves her husband, Harvey Markowitz; a daughter; and two grandchildren. Her brother, Joe, and her sister, Diane, wrote this obituary.

Diane Rosenthal, Joe Rosenthal

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Michael Hudson

General practitioner (b 1938; q Trinity College Dublin 1963), died from complications of posterior cortical atrophy on 19 September 2018

After his hospital jobs, Michael Hudson took over as the village GP in Elstead, Surrey—a role in which he continued until he retired 37 years later. When he started, a GP was expected to manage all problems, from minor trauma to forceps deliveries, at any time of the day or night and on any day of the week. Patients had to be seen in the dining room of the family house until an extension was built a few years later. When the practice outgrew this, Michael built a new surgery in the centre of the village, which is still being used now. His kindness and deep knowledge of his patients and the village made him a popular doctor, who is remembered with affection. He leaves his wife and three children.

Patrick Hudson

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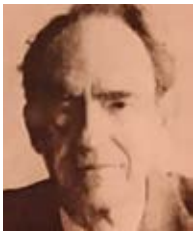
Patrick Plunkett Mulhall



Consultant chest physician Powys Area Health Authority, Wales (b 1920; q University College Dublin 1945), died after a stroke on 27 October 2018

Patrick Plunkett Mulhall ("Plunkett") moved from his native Ireland to the UK at the end of the second world war. He took part in the creation of the NHS and became a specialist in tuberculosis. Armed with needles designed to collapse tissues around primary foci, he was a physician of his time. He settled in south Wales and presided over many sanatoriums, notably Adelina Patti Hospital. He confronted the scourge of coal dust diseases, developed a deep respect for the men of the valleys, and was made an honorary member of the National Union of Miners. He also studied and published case reports on farmer's lung and hydatid disease. Predeceased by his wife, Meryl, in 2016, Plunkett leaves four children, seven grandchildren, and three great grandchildren.

B P Mulhall, R M Mulhall

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Pesi Bharucha

Surgeon (b 1920; q Grant Medical College, Mumbai, India, 1943; FRCS Eng, FRCS Ed, FRCS Glas, and FRCS I), died from extreme old age on 28 November 2018

Pesi Bharucha came to the UK shortly after Indian independence. He worked for several years at Walton General Hospital in Liverpool but returned to India in 1955 and became consultant surgeon at the Tata Main Hospital (TMH) in Jamshedpur, in the state of Bihar. He developed TMH into a multispecialty facility and with the World Health Organization arranged smallpox virus vaccination in remote areas. After retiring from TMH in 1980, Pesi became medical director for Breach Candy Hospital and research centre in Mumbai, where he worked from 1982 to 1996. After a stroke in 2008, his physical mobility declined, but he retained his cheerful demeanour and mental alacrity till the end. He leaves his wife, Gool; two children; and three grandchildren.

Azmy Birdi

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Gordon Edyvean Heard

Vascular surgeon Cardiff (b 1926; q 1949; FRCS Eng), died from pneumonia on 24 November 2018

In 1939 Gordon Edyvean Heard contracted osteomyelitis of the right tibia and became a patient in the Cardiff Royal Infirmary. In 1946 he was one of the first civilians to be successfully treated with penicillin. Between 1950 and 1952 he served as a captain in the Royal Army Medical Corps and was based at the Royal Victoria Military Hospital in Netley, Southampton. After a year at Michigan State University, Ann Arbor, US, he returned to Cardiff. In 1963 he was appointed consultant surgeon to the Cardiff United Hospitals. He also held office in professional societies and at the Royal College of Surgeons of England. He retired from surgery in September 1987 and had a long and happy retirement with his wife, Kate, whom he leaves, along with three children and three grandchildren.

Malcolm H Wheeler

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