

Dementia and marital status at midlife and late life

Risk is increased in people who are unmarried, especially if they are widowed



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Marital status late in life has been related to the risk of dementia or cognitive decline in the next 3-10 years. People who were classified as unmarried,¹ single,^{2,3} and single living alone⁴ are at increased risk of dementia or cognitive decline. This association was true even after adjustment for activities, social engagement, and living conditions and was independent of other risk factors for dementia.

Marital status seems to be only one risk factor among others, with a relatively small contribution to the development of dementia (relative risk 1.5-2.5). A change in marital status for cognitive reasons is probably rare in late life, but reverse causation cannot be excluded because of the long prodromal phase of dementia, particularly Alzheimer's disease.⁵

In the linked study, Håkansson and colleagues evaluated marital status more than 20 years before the onset of dementia or cognitive impairment and thus dealt with the problem of reverse causation.⁶ Moreover, causes of unmarried status were explored. They followed 1449 people in Finland aged 65-79 years for an average of 21 years and found a twofold increase in the risk of both cognitive impairment and dementia about 21 years later for unmarried people compared with those who were married. People who had been widowed were at particularly increased risk, with about a threefold increased risk. In addition, when considering the evolution of marital status over the 21 year period, people who cohabited in midlife but not late in life tended to be at increased risk, although results were only borderline significant. People who did not cohabit in both midlife and late life were at the highest risk, with risks especially high again for those who were widowed.

One explanation to the possible protective effect of cohabitation on cognitive impairment and dementia is the reinforcement of cognitive reserve.⁷ Indeed, increased stimulation throughout life among cohabitants could allow better recruitment of the neuronal network that protects against or delays the onset of dementia. This effect could be lifelong.

The theory of cognitive reserve could explain current and previous results that link both midlife and late life marital status with dementia. However, confounding factors like social activities and involvement in life, as well as risk behaviours, need to be considered. The only previous study that evaluated midlife marital status in men failed to find an association between a midlife social engagement index, that included marital status, and subsequent risk of

dementia; only the late life social engagement index was associated.⁸ Unfortunately, although Håkansson and colleagues had data on health factors and physical activities, they lacked data on social engagement in midlife.⁶

Håkansson and colleagues put forward an alternative explanation on the basis of a higher incidence of dementia and cognitive impairment in people who were widowed during midlife.⁶ Rather than marital status protecting against dementia, it could have its effect through the deleterious effects of stressful experiences such as widowhood, which could be linked with immunological dysfunction. However, the results for people who were widowed or divorced after midlife had only borderline significance, and previous studies failed to identify being widowed as a particular risk.

One possibility is that the age and conditions of widowhood are crucial factors. Being widowed late in life, as were most of the people in previous studies, is perhaps less stressful—especially as the person is widowed for a shorter duration—and might thus not be a risk factor. Nevertheless, the hypothesis of a deleterious biological effect of widowhood remains to be proved, as does the possibility of genetic vulnerability as a link between widowhood and dementia. This genetic hypothesis has been formulated on the basis of exploratory results showing a higher incidence of cognitive impairment for widowed or divorced apoE4 carriers than for non-carriers. However, caution is needed here. Indeed, in epidemiological studies, comparisons of risks between subgroups can rarely be interpreted directly, particularly when confidence intervals are large, and they should be validated by testing an interaction term.

Beyond dealing with reverse causation, the evaluation of marital status in midlife strengthens the hypothesis that the development of cognitive impairment and dementia is a long process that is affected by various factors throughout life. To understand the link between marital status and dementia, future research should focus on two points. Firstly, the accurate assessment of stress caused by a separation and the biological consequences of this stress; secondly, the quality of social engagement⁴—that is, satisfaction with relationships—which is probably at least as important as the quantity of social engagement but remains hard to evaluate in epidemiological studies.

A potential application of the findings involves collecting and using data about patients' marital status, which is easy to do in primary care. Unmarried, especially widowed, people could then be targeted for preventive strategies that encourage them to increase their social engagement by taking part in cultural, social, and sporting activities.

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Gene defects and allergy

Identifying specific genotypes of allergy is a major breakthrough in patient care



SIU/SPL

Allergic diseases—such as asthma, rhinitis, and eczema—have been increasing worldwide over several decades, and the increase has largely been attributed to a Western lifestyle (the hygiene hypothesis). However, the exact causes of the increase are unknown. Several trigger mechanisms are probably involved, but it is still not clear whether similar triggers are responsible for the increases seen in different allergic diseases.¹ In the linked systematic review, van den Oord and Sheikh assess the association between defects of the filaggrin gene (*FLG*) and the risk of developing allergic sensitisation and allergic disorders.²

Allergies form a heterogeneous group of diseases in which IgE mediated reactions are the key feature, and a wide variety of symptoms can occur. Diagnosis is largely based on the history, symptoms, and detection of IgE mediated hypersensitivity, usually through skin prick testing or specific IgE determination from blood. Symptoms of allergy are non-specific in most cases because they can all be present in the absence of allergy—for example, in viral induced asthma, vasomotor rhinitis, and constitutional eczema. Moreover, skin prick testing (still the first choice test for diagnosing allergy) and determination of specific IgE have limitations, such as false positivity and false negativity. Skin prick tests and specific IgE can also be positive in healthy people in the absence of allergic symptoms. The diagnosis of allergic disease is therefore still suboptimal (especially when based on questionnaires in large epidemiological surveys) because of the limitations of current diagnostic methods.

Different underlying mechanisms and pathways probably lead to the production of allergen specific IgE across the spectrum of allergic diseases. This suggests complex genetics and the contribution of multiple genes. For decades researchers have looked for genes that might contribute to allergic diseases. Most studies have suggested that many genes with small effects, rather than few genes with strong effects, contribute to the development of allergy. Until recently, no major associations had been described, and a real “allergy gene” was elusive. However, since 2006, several studies have consistently pointed to a strong influence of one particular gene—*FLG*.^{3,8}

The systemic review and meta-analysis by van den

Oord and Sheikh,² is a comprehensive summary of research into the effects of filaggrin. The review finds that *FLG* gene mutations significantly increase the risk of allergic sensitisation, atopic eczema, allergic rhinitis, and asthma in children with coexisting eczema.

However, *FLG* mutations do not account for all cases, and atopic eczema is not a monogenic disease. Instead, several genetic factors probably contribute to the complex pathophysiology of the disease.⁹ Different subtypes of atopic eczema—such as eczema with early onset, childhood eczema, adulthood eczema, and eczema without underlying allergy—might be based on distinct genetic constellations.

Nevertheless, it is now clear that *FLG* mutations are the strongest and most widely replicated genetic risk factor for eczema identified to date. The discovery that null (loss of function) mutations in the *FLG* gene are associated with atopic eczema and with allergic sensitisation is the most important breakthrough in understanding the genetic basis of this complex disorder. Furthermore, the defects have been linked to a specific type of allergic disease: a type of eczema with allergic sensitisation and an increased risk of rhinitis and asthma. This association has been replicated in several studies using various methods, and in populations around the globe. The next challenge is to identify all the common *FLG* genotypes in different ethnic groups to allow better disease stratification and optimisation of treatment.

Allergic diseases are complex, and genome-environment interactions play a key part. Distinguishing different genotypes of allergy will be a major step forward, and it could revolutionise the prevention, diagnosis, and treatment of allergy in children. Because different allergy genes and genotypes elicit the IgE mediated reaction via different underlying mechanism, with different clinical manifestations and prognoses, they are likely to need a different therapeutic approach. Pharmacogenetics could be used to tailor treatment to each patient. Large and well designed prognostic clinical studies, epidemiological studies, and interventional studies will need to be conducted to translate research about the mechanisms of disease into clinical practice.

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Immunosuppressants, mortality, and risk of cancer

New data raise concerns, but don't yet warrant a substantial change in practice

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The retrospective cohort study by Kempen and colleagues forces us to take a hard look at two of the most pressing questions in drug treatment today.¹ The first is what are the longer term risks of the increasingly powerful drugs we now prescribe routinely? The second relates to “pharmacoepistemology”—the question of “how we know what we know” about the risks and benefits of drugs.²

On the first topic, clinicians, patients, and policy-makers must live with the fact that drugs are generally approved on the basis of tests that may last just a few weeks or months, even if the drug is designed to be taken for years. Once short term efficacy is shown—even if it is in comparison with placebo, or by the achievement of a surrogate outcome, such as a laboratory test—subsequent drug effects cannot be systematically tracked. A report by the US Institute of Medicine argued strongly that failure to track longer term outcomes constitutes a major gap in the regulatory process.³

This can be a problem for conventional small molecule drugs—for example, the excess risk of myocardial infarction shown for rofecoxib (Vioxx) and rosiglitazone (Avandia), but it is even more of a problem for immunomodulatory drugs that interfere with basic mechanisms of cell function. Drugs used to treat chronic inflammatory conditions, especially tumour necrosis factor (TNF) inhibitors, are of particular concern. These biological agents are increasingly being used to manage chronic conditions as diverse as rheumatoid arthritis, Crohn's disease, and psoriasis. Concerns have been raised about these agents because of their potential to produce unwanted changes in the immune response, which could in theory result in the development of cancer.

Evidence to date has been mixed, as outlined by Kempen and colleagues. The findings have been complicated by the fact that these drugs are sometimes used in conditions that themselves raise the risk of malignancy or death. Kempen and colleagues sought to tackle this by studying the use of immunosuppressant drugs to treat ocular inflammation, a condition that is not normally associated with such increased risks. Their ambitious epi-

demiological analysis of the care of 7957 patients with this condition found no increase in risk for most of the drugs studied. The most important exception was the TNF inhibitors, for which the authors report a significant doubling of the risk of all cause mortality and a tripling of the risk of death from cancer compared with patients who did not receive these drugs. The authors are circumspect about the validity and implications of their findings, as they should be.

This raises the second major question highlighted by this paper—how can we know when we should take an apparent drug risk identified in a non-randomised study seriously? Epidemiological studies must evaluate the wide variety of actual therapeutic choices routinely made by doctors—including using no drugs at all. Some drugs (especially newer ones, such as TNF inhibitors) may be reserved for sicker patients, or those who had previously failed other treatments. A variety of designs and analytical methods can be used to adjust for such differences.^{4,5} Kempen and colleagues' findings are compatible with two conclusions (or a combination of both)—that TNF inhibitors increase the risk of death and cancer, or that they are preferentially used in the sickest patients with ocular inflammatory disease.

The authors studied all users of immunomodulatory drugs, both new users and ongoing users. This can cause bias because ongoing users are more likely to be people who have tolerated their treatment well, which makes them different from new users, who may also be patients who were recently switched because they were doing poorly with existing treatments.⁶ This approach can make older drugs look safer than they really are and newer drugs seem more dangerous. TNF inhibitors were marketed only in the later years of the cohort, so that many of these patients were using other immunomodulatory agents before the TNF drugs, as well as concurrently with them. Finally, the study inference is based on only 11 deaths in these patients, making analyses more sensitive to such bias.

The authors tried to control for confounding by the indication for treatment and other comorbidities. However, these attempts may not have been successful

because 74% of the patients treated with TNF inhibitors had systemic inflammatory disease, itself an important risk for severe adverse outcomes, compared with only 25% of the entire study sample. The excess risk associated with the TNF inhibitors disappears when these patients are excluded. Is this because of a reduction in sample size, or elimination of confounding? We cannot know.

Despite the availability of patients' entire medical records, the crucial issue of comorbidity was dealt with solely through the Charlson score.⁷ This score is a crude measure that was developed more than 20 years ago for other purposes, which has been supplanted in many pharmacoepidemiology studies by more accurate measures of coexisting illness.^{8,9} We must therefore worry how adequately patients' non-ocular conditions were controlled for in these analyses.

The deaths in patients taking TNF inhibitors were all attributed to different causes, which reduces the biological plausibility of a causal association. Finally, the highest risk of death and cancer was found for the TNF inhibitors despite these agents having the shortest duration of follow-up (median 2.8 v 7.1 years for the entire sample); in addition, the median duration of their use was only 1.2 years. Either these drugs kill people quickly or they are used mostly by the sicker patients in the population, in which case their apparent effects are probably the result of residual confounding.¹⁰

These methodological limitations do not, of course, rule out the possibility that TNF inhibitors may

increase the risk of cancer or all cause mortality. We simply cannot know from this analysis. Kempen and colleagues' study shows that this potentially important question needs further study, and it reminds us that the field of pharmacoepidemiology is evolving rapidly. Given the implausibility that a new randomised trial will provide answers in the near future (if ever), clinicians should neither reject nor uncritically embrace the use of this class of drugs until additional data from meticulously controlled observational studies can define their risk more completely.

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Distribution of insecticide treated nets in rural Africa

A range of delivery systems is needed to achieve equitable coverage

A concerted effort is currently under way across sub-Saharan Africa to increase the distribution of insecticide treated nets to achieve the Roll Back Malaria target of 80% coverage of children and pregnant women in endemic areas by 2010.¹ Views vary greatly on the best delivery strategy or mix of strategies for achieving such coverage, especially in poor rural populations at greatest risk of malaria.

Delivery strategies in Africa are categorised as public, private, or mixed.² Public strategies include community distribution campaigns, routine distribution through channels such as antenatal clinics, and a mixture of campaigns and routine channels. Publicly distributed insecticide treated nets are usually free or heavily subsidised. Private strategies are typically market based, with insecticide treated nets being sold to the public through private retailers, often at a subsidised price. Public-private strategies, such as the Tanzania National Voucher Scheme evaluated in the linked paper by Hanson and colleagues,³ consist of routine distribution through targeted subsidies from the public sector, with the treated nets being delivered through the private retail sector.

The aim of voucher schemes is to increase the coverage of treated nets by supporting a private sector net distribution system, which is hoped to be sustainable, efficient, and cost effective. To date, few formal evaluations of voucher schemes have been undertaken, and the results have been mixed.^{2,4}

Hanson and colleagues show that through a combination of distribution channels in 21 districts in Tanzania, household possession of insecticide treated nets in children under 5 years doubled over three years from 18% to 36%, and use the night before the survey increased from 12% to 26%.³ Increased household ownership was positively, but not significantly, associated with the time since the launch of the Tanzania Voucher Scheme programme. As has been seen elsewhere, however, the study found that incentive based distribution of insecticide treated nets through public-private channels is inefficient at reaching the poorest groups, especially when compared with free mass distribution.^{5,6} This concern is particularly relevant for malaria control because the poorest populations are usually at greatest risk of malaria and its economic consequences.⁷

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The authors should be commended for their attempt to evaluate the Tanzania National Voucher Scheme using the most rigorous methods possible given the nature of the full coverage programme. Their evaluation is a great improvement over previous attempts to assess incentive based distribution of insecticide treated nets through the private sector.⁸ It would have been helpful if they had stratified the results into urban and rural areas, however, because malaria mainly affects rural populations. Results from a 2007-8 national survey in Tanzania showed that children in rural areas were almost three times more likely to be infected with malarial parasites than those in urban areas (20% v 7%), whereas children in rural areas were less than half as likely to have slept under a treated net (21% v 49%).⁹ As the authors note, several factors may limit the validity of their evaluation in other settings—Tanzania has unusually well developed sectors for the manufacturing and retailing of treated nets, as well as high use of antenatal clinics, which provide the vouchers.

The authors correctly note that a variety of net distribution channels may be needed to achieve and sustain coverage targets.^{10 11} Evidence suggests that free wide-scale community distribution of insecticide treated nets rapidly achieves high and equitable coverage in rural populations.^{5 6} Hanson and colleagues' data could be interpreted to mean that the voucher scheme on its own cannot rapidly scale up equitable coverage in rural populations in Tanzania. Alternatively, the authors conclude that a voucher scheme is a good way to contribute to "keep-up" coverage through routine delivery of insecticide treated nets. Unfortunately, they did not test that assumption in their study, because high coverage had not yet been achieved, so keep-up strategies could not be tested. Although they might be correct, we look forward to studies that will assess various keep-up strategies in countries that have achieved high coverage.

We suspect that the Tanzania National Voucher Scheme is currently not leading to the purchase of a sufficient number of treated nets to meet the full keep-up need once high net coverage has been achieved, especially in poor rural areas. An effective and equitable keep-up strategy that reaches rural populations will undoubtedly need a combination of delivery systems. Evaluations of feasible widescale delivery systems to maintain high equitable coverage in households and



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Children holding insecticide treated bed nets

communities should be a high priority for countries once they achieve high bednet coverage.

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Libel law in the UK

Scientific disputes should take place in the pages of journals, not in court

OBSERVATIONS, pp 78, 79

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Clinicians know they face multiple jeopardy—patients may seek compensation for alleged negligent acts and employers may invoke disciplinary procedures, incidentally with many safeguards for doctors working in the UK NHS recently swept away.¹ They may be criticised by coroners, face criminal charges including manslaughter,² and be subject to sanctions by

regulatory bodies. Researchers uninvolved in direct patient care may have felt largely immune to such curbs on their activities, but they are increasingly being exposed to the risk of legal action by disgruntled manufacturers or interest groups.

The United Kingdom has the unenviable reputation of being a haven for those wishing to pursue

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claims for defamation.³ Peter Wilmshurst, a cardiologist in Shrewsbury, England, is having to defend such an action by NMT Medical, sponsor of the Migraine Intervention with STARflex Technology (MIST) I trial.^{4,5} Wilmshurst was an investigator in this study into the link between migraine and patent foramen ovale, which used a device to close the shunt. After a dispute about the proportion of subjects who had a postprocedural residual shunt, Dr Wilmshurst and another investigator withdrew from authorship of the study, which was subsequently published in *Circulation*.⁶ When a website in the United States publicised Wilmshurst's criticisms, NMT instituted libel proceedings against him. Twenty months into the pretrial process, he has had to commit to six figure costs. He says, "My salary now goes to the lawyers" (personal communication, 2009).

The case has echoes of that involving the science journalist and author Simon Singh, who is defending a libel action by the British Chiropractic Association (BCA) regarding an article he published in the *Guardian* in 2008 about the risks of chiropractic treatment and the evidence (or lack of it) behind claims that it is effective for certain non-musculoskeletal disorders in children, such as colic, sleeping problems, asthma, and frequent ear infections. In a preliminary hearing in May, Sir David Eady, the presiding judge, ruled that Singh's article represented "fact" not "comment," and that a certain phrase amounted to, "the plainest allegation of dishonesty and indeed it accuses [the BCA] of thoroughly disreputable conduct." Singh's submission was that his article was comment, and that the phrase meant nothing of the kind but was a description of his reasonable opinion about the lack of evidence for the disputed treatments. By a quirk of English libel law—where the words complained about are treated by the court as a factual statement—the burden of proof is reversed, so Singh must now prove their accuracy rather than his opponent showing that the statement was untrue. Because the judge ruled his words constituted an allegation of dishonesty by chiropractors and "thoroughly disreputable conduct" by the BCA, Singh faces the impossible task of justifying something he does not believe to be the case (because he does not agree with the judge's ruling on what his words meant).⁷ Correspondence between Richard Brown (vice president of the BCA) and Edzard Ernst (professor of complementary medicine) is published in this week's *BMJ* (2009;339:b2782; 2009; 339:b2766).

Journalists know that libel is an occupational hazard. Editors of medical journals are not spared. Frank Frizelle, a surgeon and editor of the *New Zealand Medical Journal*, received a letter before action alleging defamation, when he published two papers about chiropractors, which asserted, among other things, that many improperly used the honorific "doctor." The

lawyers' letter demanded an apology, a published retraction, a right of reply, and payment of all legal costs and any losses incurred by chiropractors as a result of the publications. Frizelle simply ignored the threats, published the letter in full in the journal, and re-emphasised his previous invitation to chiropractors to provide "your evidence not your legal muscle."⁸

The Royal College of Obstetricians, publishers of the *British Journal of Obstetrics and Gynaecology*, was recently embroiled in an action instituted by a US researcher, who contended that he was improperly removed from authorship of a paper. The counts against the college were dismissed on the grounds that it had no legal duty to the plaintiff, but the considerable costs could not be recovered.⁹

Given the constitutional right to freedom of speech, it is no surprise that other encouraging signs have come from the US. In a case with echoes of that involving Wilmshurst, a manufacturer brought suit against the authors of a paper that detailed the results of a study comparing the performance of five devices used in the preparation of sterile products.¹⁰ The publisher of the journal concerned (*American Journal of Health-system Pharmacy*) was joined in the suit, with disclosure demanded of the peer reviewers' identities and all correspondence with them. The editor supplied the anonymised reviews because he considered they were accurate and reasonable. In March 2009, two years after publication, the US Federal Court dismissed the action, holding that there was no actual malice, no knowledge of falsity, or reckless indifference to truth and therefore no basis for the suit.

Researchers, funders, editors, and publishers will have to be cautious. It is a pity that courts in other jurisdictions are not bound to follow the lead of the US judge in the above case, who stated: "Quite simply, this battle should take place in the pages of the ASHP [American Society of Health-System Pharmacists] journal and similar publications, not in a court."¹¹

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