

## Reifying Relevance in Mild Cognitive Impairment:

### An Appeal for Care and Caution

Janice E. Graham and Karen Ritchie

**Running Title:** Reifying Relevance in MCI

**Key Words:** Alzheimer's disease, construction, dementia, market forces, mild cognitive impairment

We thank the reviewers for their thoughtful comments that probe shadowy areas in our argument, and we welcome this opportunity to elucidate our position. First, we are not repudiating the natural and social facts of pathological brain degeneration and the physical and cognitive impairments that manifest in people affected by dementia disorders. We are, however, questioning the epistemology, politics and persistence by some to harden the construct of mild cognitive impairment prematurely as a “natural” precursor to dementia. We suggested insufficiencies in viewing mild cognitive impairment (MCI) as prodromal to Alzheimer's disease (AD) (Graham and Ritchie \*\*\*\*, \*\*)<sup>[JCH1]</sup>, and pointed to evidence for the prognostic irrelevance of some MCI subcategories (op. cit. \*\*)<sup>[JCH2]</sup>. The commentators have read our manuscript as suggesting that AD and MCI are different kinds, and that a diagnosis of AD is more “real” than that of MCI. But AD is also fraught with classification issues, as we describe in the section of our paper that deals with consensus committees, published practice

## Reifying Relevance in MCI

guidelines and the determination of treatment efficacy. Like MCI, AD is a heterogeneous condition, but unlike MCI, AD is a constructed practical kind that does some “work” beyond essentialist (neural degeneration, brain atrophy) claims. Its criteria identify people with well defined dementia symptoms and multiple cognitive and functional impairments who are in need, and benefit from support. Even with these criteria, however, there have been great attempts to achieve definitional accuracy in dementia diagnoses. Practical refinements to the differential diagnosis of dementia based upon solid research evidence have made way for more specific recognitions of vascular dementias, dementia of the Lewy body type and other sub-types beyond Alzheimer’s. So Alzheimer’s disease too has been subject to more careful, more cautious operationalization in recent years, with research supporting multiple factors and the comorbidity of several types (kinds) of dementia in any one individual.

Our paper takes up concerns that are not resolved for dementia and suggests that the nascent category of MCI is still so insufficiently defined as to be ambiguous, and as such, is in danger of identifying individuals with what will be, and has already been, linked to a debilitating and deeply stigmatizing and fatal disorder (AD). We are not contesting the reality that some people begin to display early signs of cognitive loss, and we are not suggesting that symptoms be ignored; as researchers, we stand behind the careful tracking of symptoms and signs in patients and research participants as an essential clinical and research practice. In an era where the public has been made wary of the potentially fatal effects of new treatments whose more careful scrutiny in specific

## Reifying Relevance in MCI

populations would have saved lives (e.g. Psaty and Furberg 2005, Fontanarosa et al. 2004), and made all the more popular by what Kramer coined “diagnostic bracket creep” (Kramer 1993, 15), we are questioning the drivers and value of a premature diagnostic classification whose definitional accuracy is neither sufficient nor effective for specific identification of individuals.

That matters of fact are constructed does not take away from their natural fact. Some people have subjective reports or show objective evidence of cognitive decline while having preserved activities of daily living – the construction of this evidence indicates they are not normal and they are not demented. Based on such evidence, where then does the balance of probability for MCI lie? A multidisciplinary international group of experts gathered in Stockholm in 2003 to discuss MCI concepts (Winblad et al. 2004). They acknowledged that the heterogeneous etiology of MCI contributes to “some confusion concerning the specific boundaries of the condition”, stating that this “not normal, not demented” condition is nonetheless “useful both clinically and as a research entity” (ibid. 241). Importantly, they concluded that MCI needs “better definition” (ibid. 246). It was at this stage that we first wrote our manuscript, and in the subsequent two years we have eagerly awaited new studies, and the recognition of flexible, practical subtypes to evolve.

We state “that MCI cannot be considered to be a separate clinical entity” (Graham and Ritchie \*\*\*\*, \*\*<sub>[JCH3]</sub>). That is separate and apart from recognition that MCI is an important clinical issue. But we do ask for useful criteria that are supported by sound

## Reifying Relevance in MCI

evidence and can be used to build (construct) a valid and reliable operational and clinically/socially meaningful definition. And we insist that evidence be carefully examined for conflict of interest that inevitably affects both methodological and interpretive rigour. Dr. Ticehurst tells us that we “should have more confidence that usefulness can be determined by science and that this will triumph in the end” (Ticehurst \*\*\*\*, \*\*). One need look no further than the history of thalidomide treatment to bracket this with healthy skepticism. Now effective for a range of indications including leprosy, HIV, multiple myeloma and prostate cancer, thalidomide damaged an estimated 15,000 fetuses in its early indication, raising a flag of caution for the use of emerging therapies on vulnerable populations. Thalidomide (and there are many more recent examples) was too quickly adopted without long-term study.

We are reminded by Dr. Petersen that, since our drafting of the original manuscript for a session on MCI at the 7th International Conference on Philosophy, Psychiatry and Psychology held in Heidelberg during 2004, “MCI is still evolving with regard to its refinement” (Petersen \*\*\*\*, \*\*[JCH4]), that it has become flexible, and that there is evidence for a neuropathological substrate for *amnestic* MCI consistent with early Alzheimer’s disease (Markesbery et al. 2006). But still more research needs to be done towards the construction of better evidence to understand, refine and operationalize early cognitive declines before MCI can be used to identify human kinds for intervention. Central to this is the critical difference between basic or population research and clinical trial research, which requires identifying patients for a therapeutic intervention. Clinical

## Reifying Relevance in MCI

trials must meet the principles of clinical equipoise. Physicians should only be offering patients enrolment into clinical trials when experts disagree about a preferred treatment. But first there should be strong evidence for the indication being treated. To be trialing treatments used for Alzheimer's patients on some broad category of MCI, then, is a breach of ethical standards. Markesbery et al's (2006) findings might well be used to support trials in the more refined amnesic MCI type. However, any trials performed prior to these findings, or afterwards, on a wider MCI population, are problematic.

Our concern here with MCI is not “is it or is it not constructed?” – adopting Hacking's “dynamic nominalism”, it could, for instance, be both socially created and real if evidence for “it” were convincing. Neither are we saying it can (or should) be deconstructed. Rather, we are trying to establish whether MCI as it was understood when we wrote our article, is a useful or “efficient” classification. We suggest that better “tools and resources would assure its upkeep and maybe even restore the built structure” (Latour 2003, 41). We take up Latour's lament: “How long will it be before the word [construction] is heard not as a war cry to take up arms or hammers, but as an appeal for the extension of *care and caution*, a request to raise again the question: ‘How can it be built *better?*’”(ibid. 42).

How might MCI be built better? We suggest that a hurry to recognize MCI as a clinical entity comes at a cost – hardened categories, like arteries, clog the free flow of ideas. The elderly are a vulnerable population; it is for all of us to ensure that they are not made more so when their everyday activities fall under the medical gaze. They and their

## Reifying Relevance in MCI

clinicians' hopes and fears are easily influenced (Mintzes et al. 2002). The desire to provide some (any) help to a patient and their family drives the sale of treatments for Alzheimer's disease; should it not also be a concern that MCI, which has the real potential to provoke one of our worst fears (losing one's mind), will target double the population with dementia? Studies have shown that dementia is not the inevitable outcome of most people followed with subclinical cognitive deficits (Ritchie 2004). Furthermore, if early treatment is the goal for early diagnosis of MCI, there are real dangers in treating a population who have a high probability of suffering the negative effects of anticholinergic drugs, with the current treatments for dementia (acetylcholinesterase inhibitors) (Ancelin 2006). There are real and constructed biological, social and ethical costs of treating a condition for which no expert group has yet to identify reliable and valid human kinds.

We have been asked whether professional or market values should take precedence in determining nosology, and told that "a professional market is still a market" (Ticehurst \*\*\*\*, \*\*<sub>[JCH5]</sub>). We agree, and perhaps this is a prolegomenon for a new direction in conflict of interest rules applied to clinical research and researchers. We support the design and funding of more studies addressing issues of "not normal, not demented" that provide sound scientific evidence, published in reputable journals that can be used to arrive at and effectively identify and help practical human kinds. Important advances have been made in the almost half century since benign senescent forgetfulness first appeared in the literature, in particular during this past decade with the concerted

## Reifying Relevance in MCI

effort of clinical researchers and epidemiologists working together to refine operational definitions to a point where valid “cases” can be identified. Not all has been driven by Pharma interests, and calling attention to this conflict should not take away from the good research being carried out. Data will continue to help researchers to tighten categories and to construct better arguments, but the processes and decisions that lead to the creation of these facts must be transparent and available for scrutiny. “The procedure of science”, Feyerabend tell us “is not to praise the good but to eliminate what is bad” (Feyerabend 1981, 194). Despite the best of intentions, physicians do fall short in monitoring their patients, and companies do forget to include negative findings in the reporting of their evidence. We hope that greater attention to more refined sub-types will contribute to efficacy, determined by specific targeting of treatments, and trump marketing. When researchers can construct their data in a context that respects the everyday lives of the folk who are their focus, without private sponsorship playing a major role in the provision of clinical trial evidence, then they will be able to concentrate on research in the public interest and the common good.

## References

- Ancelin, M. L., S. Artero, F. Portet, A. M. Dupuy, J. Touchon and K. Ritchie. 2006. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *British Medical Journal* 332:455-459.
- Feyerabend, P. K. 1981. *Problems of empiricism. Philosophical papers, volume 2.* Cambridge: Cambridge University Press.
- Fontanarosa, P. B., D. Rennie and C. D. DeAngelis. 2004. Postmarketing surveillance – lack of vigilance, lack of trust. *Journal of the American Medical Association* 292:2647-2650.
- Graham, J. E. and K. Ritchie. \*\*\*\*. Mild cognitive impairment: ethical considerations for nosological flexibility in human kinds. *Philosophy, Psychiatry, & Psychology* \*, no. \*:\*\*\*-\*\*. [JCH6]
- Kramer, P. 1993. *Listening to Prozac.* New York: Penguin.
- Latour, B. 2003. The promises of constructivism. In *Chasing Technoscience*, eds. D. Ihde and E. Selinger, 27-46. Bloomington: Indiana University Press.
- Markesbery, W. R., F. A. Schmitt, R. J. Kryscio, D. G. Davis, C. D. Smith and D. R. Wekstein. 2006. Neuropathologic substrate of mild cognitive impairment. *Archives of Neurology* 63:38-46.
- Mintzes, B., M. L. Barer, R. L. Kravitz, A. Kazanjian, K. Bassett, J. Lexchin, R. G. Evans, R. Pan and S. A. Marion. 2002. Influence of direct to consumer pharmaceutical

## Reifying Relevance in MCI

advertising and patients' requests on prescribing decisions: two site cross sectional survey. *British Medical Journal* 324:278-279.

Petersen, R. C. \*\*\*\*. MCI is relevant: a response to Graham and Ritchie. *Philosophy, Psychiatry, & Psychology* \*, no. \*\*:\*\*-\*\*.[JCH7]

Psaty, B. M and C. D. Furberg. 2005. COX-2 Inhibitors – lessons in drug safety. *New England Journal of Medicine* 352:1133-1135.

Ritchie, K. 2004. Mild cognitive impairment: an epidemiological perspective. *Dialogues in Clinical Neuroscience* 6:333-40.

Ticehurst, S. \*\*\*\*. Mild cognitive impairment: kinds, ethics and market forces.

*Philosophy, Psychiatry, & Psychology* \*, no. \*\*:\*\*-\*\*.[JCH8]

Winblad, B., K. Palmer, M. Kivipelto, V. Jelic, L. Fratiglioni, L-O. Wahlund, A.

Nordberg, L. Backman, M. Albert, O. Almkvist, H. Arai, H. Basun, K. Blennow, M. De

Leon, C. Decarli, T. Erkinjuntti, E. Giacobini, C. Graff, J. Hardy, C. Jack, A. Jorm, K.

Ritchie, C. Van Duijn, P. Visser R. Petersen. 2004. Mild cognitive impairment - beyond controversies, towards a consensus. Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, 256:240-246.