Mercury toxicity presenting as chronic fatigue, memory impairment and depression: Diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994–2006)

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Abstract
In a group of 465 patients diagnosed as having chronic mercury toxicity (CMT), 32.3% had severe fatigue, 88.8% had memory loss, and 27.5% had depression. A significant correlation was found between CMT and the Apo-lipoprotein E4 genotype (p=0.001). An investigation into an additional 864 consecutively seen general practice patients, resulted in 30.3% having evidence consistent with CMT, and once again a significant correlation was found with the APO-E4 genotype (p=0.001). Removal of amalgam mercury fillings when combined with appropriate treatment resulted in a significant symptom reduction (p<0.001) to levels reported by healthy subjects.

Conflict of Interest Statement
We declare that we have no conflict of interest from the publishing of this research paper.

INTRODUCTION
In the 1991 WHO Environmental Health Criteria No.118 (Inorganic Mercury) a list of 9 recommendations for further research was given and amongst them was the development of tests to identify individuals with special sensitivity to mercury [29]. In 1997, homozygous apolipoprotein (APO-E)-E4/4 was identified as a significant risk factor for early onset Alzheimer’s senile dementia (AD) with APO-E2 being identified as protective against AD [26]. Several subsequent papers failed to clarify the reason. APO-E has 299 amino acids with different ratios of cysteine and arginine at position 112 and 158. APO-E2 has 2 cysteines, apo-E3 one cysteine and one arginine, and APO-E4 two arginines [6]. As arginine, unlike cysteine, lacks the sulphhydryl (SH) groups to potentially bind bivalent metals such as mercury, lead, copper or zinc, it would be logical to suspect the possibility of increased metal accumulation in those chronically exposed individuals who had not inherited APO-E2.
In 2003, Godfrey and associates presented evidence that the APO-E4 allele was unable to bind to mercury and assist in its elimination [10]. Additional evidence has shown that mercury creates the unique brain lesions found in the AD brain [10, 13, 23]. The literature on the relative APO-E distribution since 1995 indicates that 1–2% of the population has homozygous APO-E4, approximately 20% heterozygous APO-E3/4, 50–60% APO-E3/3, and the remainder having small percentages of E2/2 or E2/3 and E2/4 [27]. In patients with evidence of chronic mercury toxicity (CMT) there was a statistically significant shift to the right with 3.6% having APO-E4/4 and 30% having APO-E3/4 [10]. The study presented here was designed to test the clinical validity of our earlier findings.

METHOD

GROUP ONE: CMT Patients (N = 465)
Over a 10 year period, of all patients attending a general medical practice (D.W.) in Northland, New Zealand, we found 465 patients with chronic physical and mental illness not previously diagnosed and without identifiable cause, or having poor response to standard treatment, who were considered for possible CMT. Many of these patients had already been extensively investigated and seen by at least two or more physicians in the preceding twelve months. They were asked to answer a detailed 124 symptom questionnaire with graded 0 to 3 responses based on the International Academy of Oral Medicine and Toxicology formulation (www.IAOMT.org.) to cover all the recognized symptoms and signs of CMT.

A careful search was made for possible sources of mercury exposure (Table 1). Occupational, dietary, social and environmental histories were obtained. A standard medical examination was carried out including a visual inspection of the oral cavity to obtain a dental amalgam status. Particular attention was given to detect the subtle signs of mercury toxicity (Table 2). All patients received a standard fasting blood test to exclude treatable diseases such as anemia, diabetes, or gross hypothyroidism. From 2000 on, an Apo-lipoprotein E genotype (APO-E) blood test was additionally requested after informed consent. If the patient could afford it, a 2-hour post Dimercapto-propane-sulphonate (Dimaval; DMPS-Heyl) provocation urine sample was collected for mercury analysis. DMPS (5 ml = 250 mg) was administered by slow intravenous (I/V) bolus injection via a secured 23g butterfly needle, with dose reduction to 3 mg/Kg body weight for elderly, low BMI, or particularly ill patients. Provided I/V access was assured, the patient was recumbent, and serum creatinine in the physiological range, there were no serious side effects reported. The test was considered positive if greater than 50 mcg mercury per Gram of creatinine was measured in the urine sample. A diagnosis of CMT was made in this group of 465 patients on the basis of identified mercury exposure (see Table 1), typical multi-system symptom profile, clinical signs, and where possible, a positive DMPS urine mercury test as above (N = 206).

From March 2003, three patient groups were selected to determine prevalence of CMT in a primary care setting, and to obtain control data.

GROUP TWO: Consecutive General Practice Patients (N = 864)
From 20 March 2003 to 11 May 2006, every consecutive new General Practice patient was requested to complete the same IAOMT health questionnaire as above and had their amalgam status recorded together with a detailed history and examination. Of the 864 patients, 28 failed to complete or return their questionnaire leaving 836 subjects. In 515 subjects where a blood test was requested after informed consent. If the patient could afford it, a 2-hour post Dimercapto-propane-sulpholate urine sample collection for mercury was requested. A blood test was considered positive if greater than 50 mcg mercury per Gram of creatinine was measured in the urine sample. A diagnosis of CMT was made in this group of 465 patients on the basis of identified mercury exposure (see Table 1), typical multi-system symptom profile, clinical signs, and where possible, a positive DMPS urine mercury test as above (N = 206)

From March 2003, three patient groups were selected to determine prevalence of CMT in a primary care setting, and to obtain control data.

GROUP 2B

TABLE 1: SOURCES OF MERCURY EXPOSURE

<table>
<thead>
<tr>
<th>Dental Amalgams</th>
<th>Fish especially tuna, marlin, and shark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides and Fungicides</td>
<td>Paint especially marine</td>
</tr>
<tr>
<td>Mercurial skin creams</td>
<td>Broken mercury thermometers with inadequate removal</td>
</tr>
<tr>
<td>Thimerosal (medical preservative)</td>
<td>Medical and scientific calibration instruments (manometers)</td>
</tr>
<tr>
<td>Industrial air pollution, especially from coal fired power stations</td>
<td>Crematoria and environs</td>
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</table>

TABLE 2: SIGNS OF MERCURY TOXICITY

Gross
- Ataxia
- Intention tremor
- Incoordination
- Dysarthria
- Psychomotor retardation

Subtle
- Fine tremor of tongue, lips or outstretched fingers
- Hypersalivation with pooling of saliva
- Cold but erythematous hands and feet
- Labile mood
- A personality characterized by irritability, anxiety, depression, and restlessness, with lapses in concentration, memory, and cognitive function.
GROUP THREE: Patients without dental amalgam fillings (N= 54)
Patients in Group Two who had never had amalgams were identified and their data were recorded.

GROUP FOUR: Police Recruits (N= 73)
Fit healthy police recruits were invited to complete an IAOMT health questionnaire at the conclusion of their final recruit medical examination by D.W. In addition an amalgam status was recorded.

TREATMENT
This followed standard toxicological, environmental, and functional medicine paradigms namely (i) to remove the source of mercury, (ii) detoxify the target tissues as much as possible, and (iii) support cellular metabolism and tissue regeneration with selected nutrients. Patients with CMT were advised to abstain from known mercury contaminated fish, replace their amalgams with non-mercury composite restorations using a safe proven protocol, and then complete a 3 month course of oral mercury chelation with Di-mercapto-succinic acid (DMSA) (Succimer in U.S. PDR), at a dose of 500 mg thrice weekly (Mon, Wed, Friday) on alternate weeks for a total of 9 Grams. Chlorella at a dose of 3 Grams/day, for the DMSA weeks, as well as nutrient and anti-oxidant support, were also given. Patients who wished to know about treatment progress or success had a follow-up DMPS provocation urine mercury test ( N= 33). This was performed not less than six months after completion of DMSA treatment, and more usually 12 months later. If the test was still high or patients felt their treatment was incomplete, a further shorter course of DMSA was administered. Patients who requested homeopathic only mercury detoxification were referred to one of two experienced practitioners in Northland, and their symptoms were recorded at a follow up visit with DW. All treatment for CMT was undertaken with full informed patient consent.

OUTCOME AND RESULTS
Treatment outcomes we considered were the Mercury Symptom scores, DMPS urine mercury test results, and scores of fatigue, loss of memory, and depression on a 0 to 3 scale. Predictors included continuous variables such as age, and amalgams, and categorical variables such as gender and APO-E genotyping. Analysis was done on Data Desk 6.0.1 using the Linear Models option with log transformed symptom scores and DMPS test results to normalize the data. Each result is expressed as the mean ± one standard deviation unless stated otherwise.

In GROUP ONE with 465 CMT patients (M:F = 153:312), mean age 45.1 ± 11.8 years, mean amalgams 10.2 ± 4.6 with 25.2 ± 13.4 surfaces, and a mean symptom score of 68.6 ± 33.5: 150 (32.3%) had Chronic Fatigue Syndrome according to current criteria; 413 (88.8%) had self reported memory loss of varying severity with a further 6 (1.3%) having physician diagnosed Alzheimer’s Dementia; 128 (27.5%) had depression (on anti-depressant medication for at least 6 months at presentation, or a past diagnosis of depression requiring medication for at least 12 months) and of these 12 had extreme depression (unwell for > 5 years, treated by more than 2 psychiatrists, needing several drugs and typically depressed for most of their adult lives); and 15 (3.2%) had psychiatrist diagnosed Bi-polar Mood Disorder, on presentation.

There was a significantly positive correlation between the APO-E4 genotype (E3/4 and E4/4) and (i) Chronic mercury toxicity (Chi square test, 1 df, p< 0.001, N= 836); (ii) Alzheimer’s Disease (Chi square test, 1 df, p= 0.028, N= 324) (iii) Bipolar Mood Disorder (Chi square test, 1 df, p= 0.014, N= 324) and (iv) Extreme depression (as above) (Chi square test, 1 df, p= 0.0006, N= 240)

Follow-up clinical evaluation and repeated IAOMT symptom scores were completed for the first 170 consecutive patients, which for the treated patients were deliberately delayed to avoid potential placebo effects. The mean time from first presentation to follow up was 41.6 ± 24.1 months, (Range 9 months to 10 years), identical for treated and untreated patients. In any case the shortest time from the end of DMSA treatment was six months.

Combined dental and medical treatment resulted in a significant improvement in overall symptom scores with an average reduction to 45% of baseline score (p<0.001). Analysis using the log of the ratio of before and after scores indicated dental amalgam removal caused the post treatment score to fall to 64% of baseline (p= 0.009), and medical treatment caused the score to fall to 70% of baseline (p= 0.005), both effects being cumulative. Combined dental and medical treatment gave evident improvement in depression and fatigue scores (p<0.02). Individually, no factor had a significant effect on loss of memory scores (p= 0.20), however in combination, dental and medical treatment had a significant positive effect (p= 0.01) (see Figures 1, and 2a-c) with a marked difference in outcome when subjects who remained untreated at follow up versus subjects who received combined dental and medical treatment are considered.

Homeopathic treatment also resulted in a significant improvement in overall symptom score with an average reduction to 47% of baseline score (p<0.001) (see Figure 1).
Untreated patients had no significant change in symptom scores (p=0.58).

Analysis of 26 subjects who had paired pre and post treatment DMPS challenge urine mercury tests showed a significant reduction from 422.3 ± 401.9 to 44.2 ± 27.9 mcg Hg/G creatinine, a reduction to 10% of pre-treatment values (p<0.001), in parallel with a significant symptom score improvement from 88.0 ± 36.1 to 39.0 ± 27.3, a reduction to 44% of pre-treatment scores (p<0.001) (see Figure 3).

In GROUP TWO with 864 general practice patients (M:F = 335:529), with a mean symptom score of 49.3 ± 28.2: 262 (30.3%) patients were considered to have CMT on clinical grounds (group 2A) and many had subsequent confirmatory testing. This is reflected in an elevated mean symptom score of 67.7 ± 29.2 compared to the 602 non-CMT patients (group 2B) with a mean symptom score of 41.0 ± 23.3 (see Figure 4). The age distribution with an evident CMT peak in the 4th to 6th decades, especially for women, is shown in Figure 5. There is a significant shift to the right towards the APO-E3/4 and 4/4 genotypes in the CMT symptomatic group (2A) (38.8%) versus the non-CMT asymptomatic group (2B) (18.7%). (Chi square test, 1 df, p<0.001) (see Figure 6). The amalgam status of the CMT group (2A) was 7.5 ± 4.6 amalgams with 16.3 ± 12.4 surfaces, while that of the non-CMT group (2B) was 5.6 ± 4.5 amalgams with 11.5 ± 11.2 surfaces.

In GROUP THREE with 54 patients (M:F = 24:30) who never had amalgams, the mean age was 22.1 ± 12.2 years, and the mean symptom score was 32.7 ± 25.2 (see Figure 4).

In GROUP FOUR with 73 healthy police recruits (M:F = 52:21), the mean age was 28.6 ± 6.3 years, mean amalgams were 3.8 ± 0.46(SEM) with 5.4 ± 0.87(SEM) surfaces, and the mean symptom score was 17.1 ± 11.9 (see Figure 4).

DISCUSSION
Doctors have a notional idea of mercury toxicity when it concerns a large predatory fish, much less when it involves a broken thermometer in their medical practice rooms and even less when it is in their own or their patients' teeth. Thus the diagnosis of CMT and any subsequent correct treatment depend on clinical awareness, as CMT symptoms are frequently non-specific as with other accumulative toxic metals such as lead, cadmium or arsenic. However, it is also a normal requirement that health practitioners consider manufacturers' health warnings when prescribing. Significantly, in 1997, the amalgam manufacturers Dentsply-Caulk and Ivoclar-Vivadent, altered their Manufacturer's Safety Data Sheets (MSDS) for Germany and California to include the following adverse health effects from chronic inhalation and/or ingestion: tremor, fatigue, headaches, irritability, excitability, depression, insomnia, loss of memory, hallucinations, psychiatric disorders, mental deterioration and resentment of criticism, bronchitis, kidney failure, chest pain and palpitations, colitis, dermatitis, blood disorders, infertility and birth defects. However, we have found no evidence that these are yet being given proper attention despite the release of the 1996 Health Canada's advisory on amalgam that included the above manufacturers' listed contra-indications i.e. No amalgam in: children under 7; with other metals; under crowns or in root-filled teeth; pregnant and breast-feeding women; people with reduced kidney function; people with hypersensitivity to amalgam [25].

We have also observed that a situation frequently arises when a patient with CMT symptoms appears to be in a state of toxic overload or potentially suffering from the Toxicant Induced Loss of Tolerance (TILT) syndrome as revealed by Claudia Miller at the Massey University at Palmerston North, NZ, meeting 10 years ago [15]. In this situation, identification and removal of the main toxicant appears to result in a restoration of...
energy and well-being that although subjective and not amenable to measurement unless complicated fatigue scales are used, is still much appreciated by the patient. Notably, a number of our patients independently interviewed some years after having been correctly diagnosed and helped, voiced considerable anger at the lack of awareness of mercury toxicity shown by their previous general practitioners and specialists during the years of prior investigations and attempts at treatment [12].

The CMT patients in this study included the mainly middle aged population as shown in Figure 5. Notably, according to a 1968 NZ Health Dept study, the then 21 yr old adults averaged 16 amalgam fillings with teenagers averaging 13 [3]. This amalgam loading significantly reduced following changes in dental practice instigated in 1976 that resulted in a 64% reduction within 5 years [8]. However, these now middle-aged persons would have been exposed to considerably more mercury than the next generation.

Of significance was the finding in this study that the high symptom score in patients with clinical CMT (group 2A) was not solely due to an increased mercury exposure as they only had an average of 1.9 amalgam fillings more than the non-CMT asymptomatic patients (group 2B), (average 7.5 versus 5.6), but rather due to a genetic inability to excrete mercury when the APO-E4 allele had been inherited.

In CMT patients who were treated with proper protocols that combined protected removal of amalgam with metal chelation (DMSA) or homeopathic detoxification by an experienced practitioner, and antioxidant supplementation, there was a significant sustained symptom score improvement (p<0.001) to levels better than the non-CMT (Group 2B) patients and commensurate with healthy controls in Groups 3 & 4, whereas those who did nothing remained symptomatic (See Figures 1 and 2a-c, cols 2 and 4).

Several papers have been published over the past years variously minimizing any adverse health effects from amalgam. These include a 20 year retrospective study into 20,000 New Zealand soldiers comparing their dental records with the incidence of diseases [2]. There was a potentially significant limitation in that at follow-up and the end of the study, 57% were still less than 35 years old, 83% were still under 45 and 93% under 55 years of age. In our experience and that of other investigators, most patients have reached middle-age before presenting with CMT and thus the majority would not have been detected by this study into young predominantly male soldiers. Another limitation by these
investigators was their focus on comparing dental status with hospital admissions for recognized diseases. However, mercury, like lead or arsenic, is a poison causing multi-system predominantly non-specific symptoms and thus many with CMT are likely to be missed when specific diseases are investigated. Nevertheless, they did identify a weak amalgam-multiple sclerosis association and a further follow-up of these soldiers in 10 or 20 years time could reveal conditions more commonly seen in the older cohorts.

Nerdrum et al. also concluded in 76 patients that removal of amalgam failed to reduce health complaints to normal levels and questioned the hypothesis that dental amalgam was an important source of health complaints [20]. Bjorkman et al. from the Dental Biomaterial Adverse Reaction Unit, University of Bergen, subsequently criticized Nerdrum's statistical analysis because they had deleted those worst affected. They indicated that their conclusions were at variance with the published data [5].

Another flaw in research papers purporting to show a lack of toxicity has been either a lack of true controls never exposed to mercury, or using controls with a lesser number of amalgam fillings. In the nun's study [28], Alzheimer's diseased subjects were compared to age-matched controls with apparently very similar amalgam exposures and no significant differences were found in mercury brain levels. However, they did find one significant difference which was not discussed. The mercury levels in the olfactory tissues of controls were double that of the Alzheimer's diseased subjects. The controls having no posterior teeth (molars) about 10 to 15% of the nuns had brain mercury levels in the micromolar range and much higher than the average level found in all other subjects. These high levels were found in both controls and Alzheimer's diseased subjects and raises the question as to how a normally functioning person could have such high mercury levels and not show some sign of neurotoxicity. However, this data clearly shows that among nuns living in the same environment and eating the same food there can be dramatically different retention levels of mercury in the brain tissue in a subset of their population. It is plausible that the APO-E4 versus E2 genotype could help explain this difference. An in-depth independent critique of these studies revealing their flawed methodologies or interpretations appeared in 2004 [16] and another paper by the same German university group further confirmed the pathogenicity of mercury and the clinical relevance of APO-E genotyping in AD [17].

Two recent papers in JAMA concluded that dental amalgam in children did not pose a significant health risk [4, 9]. Their conclusions can be questioned on several grounds. They did not include any reference to the amount of mercury emitted from an average sized amalgam outside of the mouth. However, in a study of long term dissolution of mercury from a supposedly
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non-mercury releasing amalgam it was determined that 43.5mcg /cm2/day Hg was released and this remained constant for 2 years [7]. They used urine and blood mercury levels even though mercury is mainly excreted in the feces [22] and unchallenged urine mercury levels are unreliable with regards to exposure as toxic accumulations in the target organs can occur without elevated levels in the blood or urine [1]. In addition, the authors did not state that their conclusions of amalgam safety should not include children with any prior neuro-developmental or systemic illness although these could logically be the most likely to be affected by mercury. They also disregarded the drop in mercury excretion in the urine after the second year even though the mercury exposure from amalgams remained the same or increased. However, the drop in excretion could be seen as an indication that the body was losing its ability to excrete mercury in reaction to continued exposure to this toxic metal.

The two JAMA articles excluded the data that they collected on urinary porphyrin profiles, one of the most sensitive tests for toxic mercury exposure. This is increasingly important with the latest finding that dentists and dental assistants show aberrant porphyrin profiles in 85% of the subjects studied and 15% of these show dramatic differences based on a polymorphism in the CPOX4 gene [31]. This again, shows that a non-disease causing polymorphism may make an individual much more susceptible to a toxic exposure than the general population. It is also important to reflect on the effects of mercury inhibition of the porphyrin pathway as the final major product is heme a cofactor bound to globin to make hemoglobin. Heme is also required by one of the complexes in the electron transport system (ETS) of the mitochondria, the major energy producing pathway of the body. Therefore, a lack of heme would have a major effect on energy levels by reducing oxygen transport and impeding the reductive energy flow from citric acid cycle derived NADH to the mitochondrial ETS and thus a role in chronic fatigue. Notably, Needleman's editorial in the same issue of JAMA also included considerable reservations as to their methodology and conclusions [19].

In our opinion based on APO-E genotyping, for controls with unrecognised homozygous APO-E4, any exposures to mercury could place them potentially at greater risk of adverse neuro-psychiatric effects than someone with amalgam but an inherited APO-E2. Further strength to this was given by Jin et al.[11] reporting on the adverse effects of thimerosal an ethyl-mercury preservative. They showed that thimerosal increased inflammatory pain receptor activity by oxidizing SH on cysteine residues but that this could be prevented by the co-application of a reducing agent, di-thiothreitol. It is therefore biologically plausible that those with less SH groups would be more prone to CMT than others. A 50% reduction in methionine synthetase has also recently been confirmed several days after exposures to ethylmercury as thimerosal [18]. Notably, methionine synthetase is a vital prerequisite for glutathione production. Biochemistry is thus beginning to explain the predominantly limbic dysregulation and autonomic nervous system malfunction that typifies these chronically ill patients with their numerous complaints of chronic fatigue, headaches, irritability, myalgias,
impaired thermo-regulation and short-term memory loss. Although these symptoms are all-too-often dismissed as neuroses they appear to be due to a heavy metal organic brain toxicity syndrome in many cases.

Others experienced in environmental and heavy metal toxicology, have observed the real clinical benefits of protected removal of amalgam when combined with appropriate detoxification [14]. Lindh et al. from Uppsala University, Sweden, included 796 patients in their retrospective study using a similar symptom questionnaire. In the Lindh study they categorized the subjects into 3 groups for comparison. The smallest group became worse within the three year period after amalgam removal, the next smallest group showed no change in relative health and the third group, the largest (70%), showed marked improvement. Reviewing the mercury levels in their blood showed the group with marked improvement had the highest pre-amalgam removal blood mercury levels and the lowest three years after removal. The group that continued to get worse had the lowest pre-amalgam removal blood mercury levels and the highest three years after removal. The intermediate group fell in between these levels. This data can be explained by implying the group with marked improvement was better at excreting mercury than the group that continued to deteriorate. Also, blood levels in low level mercury exposures seem to be a measure of ability to excrete more than a measure of level of exposure. Lindh et al. thus recognised that there was a previously unidentified factor, where some people were apparently better able to eliminate mercury from amalgam, whereas others were not and recommended further research into the development of laboratory tests to help identify these patients. Our study was therefore designed to see if patients in the primary health or general practice environment could be assisted by early identification of an underlying genetic factor. Correct diagnosis and appropriate treatment would then obviate the often costly and inappropriate investigations experienced by patients in their previous search for medical help that can span decades as also mentioned in the Lindh paper. The significant reduction in the properly treated CMT patients’ symptom score to that of the non-CMT patients bears this out.

According to the WHO, dental amalgam is the greatest source of mercury body burden in the non-occupationally exposed populations [30]. Furthermore, the 1996 Health Canada report on dental amalgam revealed that the maximum tolerable daily intake (TDI) of mercury vapour would be reached from 4 average sized amalgam fillings (or 8 tooth surfaces) for a 70 kg adult when based on industrial safety levels [25]. Even though we used post-DMPS urine Hg levels to indicate exposures and accumulation, stool mercury levels could apparently be even more relevant. In this regard, Osterblad et al. found that 92 subjects with amalgam had 13 times more fecal mercury than 43 never exposed to amalgam and 56 in whom amalgam had been removed [22]. Further recent mercury research involving PET scans and MRI showed severe reductions in metabolism in hippocampus, medial thalamus, mammillary bodies and posterior cingulate [21]. The conclusions of these authors that "The amnesia of very early AD reflects severe but localised limbic dysfunction" thus supports our memory loss findings in the field of primary health medicine.

CONCLUSION

This research supports a correlation between a genetic inability to eliminate mercury when the APO-E4 allele has been inherited and an increased incidence of common symptoms and signs of chronic mercury toxicity. APO-E genotyping is thus a clinically useful additional investigation to help identify these susceptible patients and dental amalgam needs to be considered as a potential underlying and treatable cause of chronic non-specific ill-health in the predominantly middle-aged population.

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