Food Institutional Research Measure

Final Report

‘The Irish Longitudinal Ageing Study (TILDA) Nutritional Biomarker Database Enhancement Initiative (BIO-TILDA)’

DAFM Project Reference No: 13 F 492

Start date: 01/01/2014

End Date: 30/06/2016

Principal Coordinator and Institution: Dr Anne Molloy, Trinity College Dublin
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Collaborating Research Institutions and Researchers:
1. St James Hospital, Dublin: Dr Martin Healy
2. Trinity College Dublin (TILDA): Professor Rose Anne Kenny

Please place one “x” below in the appropriate area on the research continuum where you feel this project fits

<table>
<thead>
<tr>
<th>Basic/Fundamental</th>
<th>Applied</th>
<th>Pre Commercial</th>
</tr>
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<tbody>
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Please specify priority area(s) of research this project relates to from the National Prioritisation Research Exercise* (NRPE) report:

| Priority Area(s) | Food for Health | Connected Health & Independent Living |

Key words: (max 4): ageing, vitamin D, folate, vitamin B12
1. **Rationale for Undertaking the Research**

The proportion of older adults among populations is increasing dramatically. In 2011, older adults represented 11% (536,000) of the Irish population and this was estimated to double in 20 years. Such a profound shift in population demographics is likely to be accompanied by a rise in the prevalence of age-onset chronic diseases such as osteoporosis, cardiovascular disease, cognitive decline, diabetes, chronic kidney disease, age-related macular degeneration and other inflammatory conditions, all of which already constitute a major health and socio-economic burden in Ireland. Confronting and reducing modifiable age-related risk factors is therefore a crucial research goal and was the principal rationale for undertaking the research in this project.

Evidence suggests that good nutritional status is one of the factors that can delay the onset of age-related conditions. Within this concept, several micronutrients have received special attention for the following reasons. Vitamin D has a central role in bone health, muscle function and immune regulation and is a research priority in the EU in relation to healthy ageing. The B vitamins, folate and vitamin B12, have been linked to chronic conditions of ageing, particularly cardiovascular disease and cognitive decline. By investigating and improving status of these micronutrients within our older population, there is therefore a potential to avoid/delay the onset of chronic disease. Our objective was to estimate the status of three micronutrients (vitamins D, B12 and folate) within the older Irish population in order to (a) identify the potential relationships of deficiencies in these micronutrients with chronic disease development and (b) support Irish industry in responding to diet-related disease in the elderly and (c) provide strong Irish evidence to contribute to EU policy on ageing. A further goal was to quantitate the concentrations of C-reactive protein (CRP) a potent pro-inflammatory marker and creatinine, a key marker of renal function, in order to identify the relationships of inflammation and physiological factors with micronutrients status, disease development and healthy ageing.

The most effective way to achieve these goals was through the biobank of The Irish Longitudinal Ageing Study (TILDA). This is a representative cohort of over 8,000 people resident in Ireland aged 50+, charting their health, social and economic circumstances over a 10-year period. TILDA is unique amongst longitudinal studies internationally in the breadth of physical, cardiovascular, mental health and cognitive measures collected, including stored blood samples from over 5,500 individuals. An important primary objective of the project was therefore to enhance the existing TILDA database, which is a valuable national asset on ageing. In addressing these objectives within older Irish adults, our project was therefore strongly aligned with the EU Joint Programming Initiative “A healthy diet for a healthy life”. 
2. Research Approach

Specify the research methodologies employed, emphasising novel techniques and also outline any modifications from the original approved project proposal

In the first wave of recruitment into The Irish Longitudinal Study on Ageing (TILDA), bloods were collected and stored from approximately 5,650 people aged 50+. No funding was provided for blood biomarker analysis and so samples were stored at -80°C for future analysis of metabolites that are important determinants of healthy ageing. Our research approach was to:

1. Access and measure the blood concentrations of vitamin D, vitamin B12, folate, CRP and creatinine on these 5,650 stored blood samples.
2. Upload and merge the data with the full TILDA dataset then use a variety of statistical analysis techniques to investigate the relationships between these nutritional biomarkers, inflammation, chronic disease and healthy ageing
3. Disseminate the results to the relevant stakeholders and the wider scientific community

Vitamin B12 and folate concentrations were measured at the Vitamin Research Laboratory in the Institute of Molecular Medicine in Trinity College Dublin (IMM). This laboratory is an internationally-recognised centre for excellence in B vitamin research and has particular expertise in high-throughput analysis methodologies for these vitamins. The laboratory uses the current gold-standard microbiological assay for folate and has been used as an expert analysis laboratory for the US NHANES programme and to monitor the vitamin status of the Irish population for the FSAI and for the three sub-cohorts of the DAFM funded National Nutrition Phenotype Database (NNPD) JINGO project.

Vitamin D, CRP and creatinine concentrations were measured at the Department of Biochemistry & Clinical Pathology, St. James Hospital, Dublin. This is one of the largest hospital laboratories in Ireland and has high-throughput methodologies with particular expertise in vitamin D analysis. The method uses LC-MS/MS, the gold standard for vitamin D analysis, and has been used in the Trinity Ulster Department of Agriculture (TUDA) cohort (a sub-cohort of the JINGO project consisting of elderly persons with mild to moderate diseases of ageing, such as cognitive dysfunction, bone disease or hypertension.) Thus all of the data generated in this project were carried out using methodologies employed in other current Irish nutritional surveys. This ensured that the BIOTILDA project would provide comparability with current NNPD data on older persons.

The data were then uploaded onto the TILDA database for use to determine the prevalence of inadequate and/or imbalanced status of these micronutrients and their relationship with development of chronic diseases. Since these new biomarker data will be an integral part of the larger TILDA database, they will be available for future exploration by industrial and societal stakeholders in compliance with the appropriate Data Transfer Agreements and Data Use Contracts already in place for use of TILDA data. These contracts protect TILDA and TCD IP and meet the requirements stipulated in the Memorandum of Understanding between TILDA and the TILDA funders, which includes the Government.
3. Research Achievements/Results

The BIOTILDA project has achieved the primary objective of enriching the existing phase 1 TILDA database by providing blood data for 5,650 samples on micronutrients and related biomarkers that are known to have important links to age-related chronic disease. These micronutrients are the vitamins folate, vitamin B12 and vitamin D. The additional biomarkers are C-reactive protein (CRP) and creatinine.

Initial data analysis shows that the prevalence of deficient or inadequate vitamin B12 status is approximately 11% in the older Irish population. This is quite high but comparable to other Western populations. The median vitamin B12 concentration was somewhat higher in females and significantly decreased with increasing age decade (50-59, 60-69, 70-79, >80yrs) (P<0.05).

Approximately 15% of the cohort were vitamin D deficient (<30 nmol/L) while 32% had insufficient status (30-50 nmol/L). Median vitamin D concentration was significantly higher in females (52.7 nmol/L) compared with males (46.3 nmol/L) but only for the winter period (P<0.05). Concentrations of vitamin D also decreased significantly with increasing age (both in summer and winter) (P<0.05). By contrast, the median plasma folate concentration was well into the normal range, with less than 5% of the population having inadequate status (<7 nmol/L) and 10% having high status (>45 nmol/L). This probably reflects the widespread voluntary fortification of food with folic acid and use of folic acid supplements. In an analysis of the association of measured biomarkers with specific health outcomes, participants categorized as frail had significantly higher frequency of vitamin D deficiency (27%; P<0.001) compared to the pre-frail or non-frail. Furthermore, after adjusting for other relevant co-factors, each unit decrease in vitamin D concentration was significantly associated with incident pre-frailty/frailty measures (IRR=1.13; P<0.01) at the two year follow-up collection wave of TILDA participants.

The prevalence of mild inflammation (as denoted by a CRP >5 mg/L) in the cohort was 10.2% while the presence of severe inflammation (as denoted by a CRP >10 mg/L) in the cohort was 4.7%. It was also observed that frailty was associated with a significant increased risk of inflammatory stress (>40 mg/L) Relative Risk (RR) CRP = 1.3; P<0.001 after adjustment for covariates.

The first results from this project were disseminated at the Nutrition Society Summer conference at UCD in July 2016 and at the Irish Gerontological Society conference in Killarney in September 2016. Further exploration of the associations between micronutrient inadequacies and health outcomes will continue beyond the time period of this project.
4. **Impact of the Research**

One immediate impact of enhancing the TILDA baseline database with these micronutrient blood concentrations is the **new knowledge** gained on the general status in older Irish population of these vitamins that are highly relevant to the ageing phenotype. As further analysis of the enhanced TILDA data base proceeds, the impact will be felt in multiple spheres over medium to longer terms.

- For example, the data will have an impact for the **Irish Scientific Community** by adding to their research capacity and their capability in exploring the theme of healthy ageing. They can use the data to help understand the molecular mechanisms that drive chronic diseases of ageing. The new information will also aid researchers in the identification of early nutritional indicators that may predict disease onset and will provide additional power to attract funding under important initiatives such as the EU Joint Programming Initiative "A healthy diet for a healthy life".

- The improvement to the dataset will also have **economic impact** by facilitating the development of commercial functional food activities and will help underpin any future health claims that may develop from it.

- There will be a clear benefit to **Irish society** in several ways. For example, the new data from this project will help to address economic healthcare challenges by identifying simple nutritional strategies to promote wellness in our ageing population. The results will also inform both younger and older adults regarding the benefits of healthy diets and optimal nutritional status for prevention of chronic disease in later life.

- This research will provide important benefits to the **wider scientific community** by providing micronutrient data links between TILDA and other Irish nutritional cohorts, thereby enhancing and connecting all of these Irish cohorts. TILDA belongs to an international family of studies on ageing centred on the Health and Retirement Study (HRS) in the United States, with notable sister studies in England (ELSA) and more recently in Northern Ireland (NICOLA). TILDA also collects data in common with the Survey of Health Ageing and Retirement in Europe (SHARE).

  Due to the wealth of harmonised measures of physical, mental and cognitive health collected in the TILDA cohort, both national and international scientists will be interested in exploring the results of BIOTILDA project to aid the direction of future nutritional research in ageing populations. Furthermore, following the recruitment of the next ‘wave’ from the TILDA study, more biobanked samples will be available and other sub-analyses of all the data could follow, such as exploring a predisposition to inflammation/chronic disease in individuals according to status of these micronutrients.

- The enhanced biobank will be a more powerful tool in **contributing to evidence-based policy** in relation to national and European programmes for research and innovation and will help to address economic healthcare challenges by identifying future key strategic research areas for maximum health benefit and cost-effectiveness for future systemic and resource allocation decisions.
4(a) Summary of Research Outcomes

(i) Collaborative links developed during this research

Several researchers within TCD have submitted Applications of Interest to TILDA for use of the data and we have had preliminary communication with them regarding future grant proposals. For example, one researcher has expressed interest in collaborating on future grant proposals to explore the associations of vitamin D with measures of inflammation in older adults and with cognition. Another researcher has expressed an interest in exploring the data in relation to the epidemiological trends and determinants of vitamin D status in far-latitude countries. This work is based on the effects of sun exposure on vitamin D status in different sectors of the population. Among the wider group of TILDA researchers, the additional data are already being added to other factors explored in multinominal regression analyses of adverse conditions of ageing (as we have summarized in relation to frailty and this report).

(ii) Outcomes where new products, technologies and processes were developed and/or adopted

Since this was an exploratory project to determine and define the blood status of micronutrients in the Irish ageing population, no new products were developed.

(iii) Outcomes with economic potential

Dissemination of the new data, which has already begun, will provide the first step in informing the food industry of the nutritional needs for the older population in relation to these micronutrients. It is hoped that this new knowledge will lead to the development of new nutraceuticals and functional foods targeted towards improving the long-term health of older persons. The data generated in this study will also help underpin future health claims that may be developed in relation to micronutrient status and healthy ageing.

(iv) Outcomes with national/policy/social/environmental potential

The micronutrient data that we have added to the TILDA database will provide new information to aid the direction of future research into health and nutrition of older adults within Ireland. We expect that these data will add to current evidence on the beneficial effects of eating well and will help to identify simple nutritional strategies to promote wellness in our ageing population. The results will also inform both younger and older adults regarding the benefits of healthy diets and optimal nutritional status for prevention of chronic disease in later life. Furthermore, the data will contribute to making the TILDA biobank a powerful resource in relation to national and European programmes for research and innovation.
(i) Peer-reviewed publications, International Journal/Book chapters.


Popular non-scientific publications and abstracts including those presented at conferences


5. Canney M, Sexton DJ, O’Leary NO, Kenny RA, Little MA, O’Séaghdha CM. Distribution of Cystatin C and Creatinine with Advancing Age. (In press) - Accepted for the American Society of Nephrology (ASN) Kidney Week annual scientific meeting in Chicago November 17th-20th 2016 and will be published in the Journal of the American Society of Nephrology (supplement).


1. O’Halloran, A.M. 'Circulating Blood Biomarkers In Older Adults With Frailty: The Irish Longitudinal Study on Ageing (TILDA)’ Research Day: Department of Medical Gerontology, Trinity College Dublin. 19/10/2016

2. O’Halloran, A.M. 'Prevalence of Common and Chronic Conditions In Frail Older Adults: The Irish Longitudinal Study on Ageing (TILDA)’ Research Day: Faculty of Health Sciences, Trinity College Dublin. 19/10/2016


(v) Intellectual Property applications/licences/patents
None

(vi) Other
None

5. Scientists trained by Project

Total Number of PhD theses: 0

Total Number of Masters theses: 0

6. Permanent Researchers

<table>
<thead>
<tr>
<th>Institution Name</th>
<th>Number of Permanent staff contributing to project</th>
<th>Total Time contribution (person years)</th>
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<tbody>
<tr>
<td>Trinity College Dublin</td>
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<tr>
<td>St James Hospital Dublin</td>
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<tr>
<td><strong>Total</strong></td>
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7. Researchers Funded by DAFM

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<td>Post Doctorates/Contract Researchers</td>
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<tr>
<td>PhD students</td>
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<tr>
<td>Masters students</td>
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<tr>
<td>Temporary researchers</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>3.150</strong></td>
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8. Involvement in Agri Food Graduate Development Programme

<table>
<thead>
<tr>
<th>Name of Postgraduate / contract researcher</th>
<th>Names and Dates of modules attended</th>
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9. Project Expenditure

Total expenditure of the project: €197,046.23

Total Award by DAFM: €198,780.40

Other sources of funding including benefit in kind and/or cash contribution (specify): €0.00

Breakdown of Total Expenditure

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<td>Temporary staff</td>
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<td>Post doctorates</td>
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<td>Post graduates</td>
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<td>Sub total</td>
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<td>Durable equipment</td>
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<td>Other</td>
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<td><strong>Total</strong></td>
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10. Leveraging

Two additional post-doctoral fellows were closely involved with this project but were funded by outside research sources. These senior researchers contributed a total of 0.55 person years to this project.
11. Future Strategies

The data produced in this project have only recently been uploaded onto the main TILDA database and the primary outputs, dissemination of the new knowledge gained from the micronutrient analysis, are in hand. The first wave of dissemination will likely be the most important because it will inform a wide group of interested researchers of the enhanced infrastructure of the TILDA and will also provide the first evidence of the status of these micronutrients in the older Irish population. The next steps will be to build on these data and explore the enhanced TILDA dataset for associations between status of the micronutrient and risk of adverse health conditions such as bone disease, frailty, cognitive dysfunction etc. While the results will be submitted to international high impact scientific journals, an important follow-up will be public reports of the results through the TILDA website [http://tilda.tcd.ie/publications/reports/](http://tilda.tcd.ie/publications/reports/) via their Annual Reviews and Newsletters and in the National Press.

We are aware of several researchers in TCD and elsewhere who are interested in using our data as soon as it is made available for sharing on the TILDA database. Several researchers within TCD have submitted Applications of Interest to TILDA for use of the data and we have had preliminary communication with them regarding future grant proposals. Among the wider group of TILDA researchers, the additional data are already being added to other factors explored in relation to adverse conditions of ageing (as we have summarized in relation to frailty and this report). We have been informed at TILDA Biomarker meeting groups that a number of European and worldwide partners/collaborators of the TILDA project who are collecting similar longitudinal datasets in similar population groups may wish to examine the data and collaborate on future grant proposals. Following up and encouraging international collaborations of this kind is one aspect of our future strategy.

An important future strategy will be to use the biomarker data generated in the BIOTILDA project to leverage future funding. Target agencies will include the Health Research Board under the Investigator Led Projects programme, and also the SFI. In the case of the latter, a collaboration between TILDA and the sister ageing studies in Northern Ireland (NICOLA) and England (ELSA) has submitted a joint proposal under the SFI-BBSRC responsive ODE call. This proposal, if successful, will add metabolome data to the TILDA dataset. This will enhance the existing biomarker data within the TILDA study, which can also be harmonized to both the NICOLA and ELSA studies. Finally, an important end product of this research will be the commercial application of the knowledge that will be gained from these efforts. For this, we envisage applications to Enterprise Ireland. We will also approach Irish Food Companies to attract their interest in developing food products and nutraceuticals that would address nutritional deficiencies in older persons and also target younger population groups to encourage a habit of healthy eating in order to avoid preventable nutrient inadequacies as they approach old age.