RESEARCH ARTICLE

Older adults identified as frail by Frailty Index and FRAIL scale who were intensively treated for hypertension were at increased risk of 2-year adverse health outcomes in The Irish Longitudinal Study on Ageing (TILDA) [version 1; peer review: awaiting peer review]

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Abstract

Background: Frailty is associated with adverse health outcomes. In frail older adults, blood pressure (BP) treated intensively may result in side effects including orthostatic hypotension, falls or fractures. We hypothesised that frail older adults, with BP treated below the threshold of the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline (<130/70 mmHg), could be associated with adverse health outcomes.

Methods: Data was gathered from participants in Wave 1 (W1) of The Irish Longitudinal Study on Ageing (TILDA) who were aged ≥65 years and on treatment for hypertension. Frail classifications as per a 32-item Frailty Index (FI) and FRAIL (Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight) scale were compared in their ability to predict W2 (2-year) adverse outcomes associated with intensive BP control ('low': <130/70 mmHg vs. 'high': ≥130/70 mmHg). We created eight participant groups based on frailty-BP status. W2 outcomes were analysed using adjusted binary logistic regression models.

Results: In W1, 1,920 participants were included. Of these 1,274 had complete FI-BP and 1,276 FRAIL-BP data. The frail by FI treated low and frail by FRAIL treated low had increased risk of hospitalisation, heart failure and falls/fracture by W2. The frail by FRAIL treated low also had increased risk of mortality by W2. The frail by FI treated high had increased risk of syncope and falls/fractures. The non-frail by FI or FRAIL did not have increased risk of any of the adverse outcomes.
Conclusions: FI and FRAIL captured increased risk of adverse health outcomes when BP was treated below the current ESC/ESH threshold. FI and FRAIL could be more useful than other frailty identification tools to signal risks associated with tighter BP control in frail older adults. Hypertension management guidelines should specify which frailty identification tools clinicians should use to help them make personalised treatment decisions.

Keywords
Frailty, hypertension, frailty index, FRAIL scale

This article is included in the TILDA gateway.
**Introduction**

The management of arterial hypertension in adults has several internationally recognised guidelines for blood pressure (BP) treatment target range. For adults aged ≥65 years, the 2018 European Society of Cardiology / European Society of Hypertension (ESC/ESH) guidelines recommend an office systolic BP treatment range of 130–139 mmHg and a diastolic BP of 70–79 mmHg. However, the guidance for BP management in relation to older adults who are living with frailty are less clear. ESC/ESH recommend monitoring frail patients closely for side effects of BP lowering medication and in particular to monitor for postural hypotension. Ultimately, the guidance is to aim for a BP of 130–139/70–79 mmHg if tolerated; and if not tolerated, a higher BP may have to be accepted. Frailty is a complex state of impaired regulation of physiological systems, which combined with increased vulnerability to stressors can result in adverse health outcomes. Frailty can result in reduced physiological control of blood pressure and has been proven to be associated with increased risk of cardiovascular morbidity such as stroke and myocardial infarction, and also with cardiovascular mortality. Therefore, intuitively by controlling and managing cardiovascular risk factors such as hypertension in frail older adults, the risk of adverse cardiovascular health outcomes should be reduced. However, the available evidence would suggest that the interaction between frailty and hypertension management in older adults is more complex and nuanced, as treating hypertension in older adults more intensively may have unintended consequences such as orthostatic hypotension and injurious falls.

A sitting BP of <120 mmHg systolic or <80 mmHg diastolic with lower standing BP has been associated with increased risk of falls in studies of healthy community-dwelling older adults. The evidence regarding potential harm from anti-hypertensive medication is mixed. In the REGARDS prospective population-based cohort study, the authors identified that two or more frailty indicators at baseline were predictive of increased risk of serious fall-related injuries, but there was no increased risk or association with systolic blood pressure (SBP), diastolic blood pressure (DBP) or number of antihypertensive medications. Conversely, Tinetti et al. suggested that anti-hypertensive medications may be associated with increased risk of hypotension, falls and fall-related injuries. Frailty has been associated with impaired cerebral autoregulation, which could be further exacerbated by the BP-lowering effects of anti-hypertensive medications and thus increase the risk of orthostatic intolerance, syncope and injurious falls. Therefore, the potential cardiovascular benefits of controlling hypertension in the frail needs to be balanced with managing the risks of adverse side effects from BP lowering treatment. This is the crux of a still unanswered clinical conundrum that clinicians continue to face globally.

In recent years, randomised controlled trials (RCTs) have advocated for more intensive blood pressure control in both frail and non-frail older adults. The STEP trial identified that intensive BP treatment in older adults to a target of 110–130 mmHg resulted in a lower incidence of cardiovascular events compared to standard treatment, without associated risk of dizziness, syncope or fractures. Similarly, SPRINT investigators reported a lower all-cause mortality and lower rates of adverse cardiovascular events in older adults treated to a systolic BP of less than 120 mmHg. A criticism of both trials is the exclusion of frail older adults such as those with heart failure, advanced cognitive impairment, poorly controlled diabetes or even those who require institutional nursing home care. In addition, neither trial used a frailty identification tool at enrolment to stratify patients by frailty status. Therefore, whilst undoubtedly these RCTs demonstrate the cardiovascular benefits of strict blood pressure control in relatively healthy older adult populations, the generalisability of these results to frail, multi-morbid patients is yet unproven. Therefore, current guidelines state that caution and individualisation of antihypertensive treatment should be applied in the frail.

When assessing older adults with hypertension, a limitation of the current ESC/ESH guidelines is that no frailty identification tool is specifically advised that would alert clinicians towards possible heightened risk of adverse health outcomes from more intensive BP control. Many clinicians regard the identification of frailty as rather subjective and prone to bias. If there was a recommended frailty identification method, this would, in theory, inform the clinician as to which patients may require more lenient BP treatment versus those who might tolerate more intensive treatment. Our previous companion study demonstrated in a prospective, observational study design that frail older adults, identified as such by the frailty phenotype (FP) and whose BP was treated intensely, had an increased risk of hospitalisation at 2 years. However, in the same study, the frail by Clinical Frailty Scale (CFS) with BP treated intensively did not have an increased risk of any of the adverse health outcomes considered. Neither CFS nor FP captured increased risk of falls or fractures, syncope, transient ischaemic attack or stroke, heart attack, heart failure, or mortality at 2 years. However, FP and CFS are only two of the many frailty identification tools available. Following on from our previous study, in this companion study we aimed to re-analyse the same population cohort but apply two alternative frailty identification tools (Frailty Index and FRAIL scale) to see how they were associated to the same 2-year adverse health outcomes in those intensively treated for hypertension, as defined by the ESC/ESH guidelines.

**Methods**

**Ethical considerations**

For each wave of TILDA, ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin: Wave 1 The Irish Longitudinal Study on Ageing (granted on 2nd May 2008) and Wave 2 The Irish Longitudinal Study on Ageing (granted on October 19th 2011). All participants provided written informed consent to participate in TILDA and all experimental procedures complied with the Declaration of Helsinki. Participants had the option to decline to take part or leave the study at any time.

**Study sample**

We analysed data from Wave 1 (W1) and Wave 2 (W2) of The Irish Longitudinal Study on Ageing (TILDA). TILDA is a longitudinal cohort study of the health, economic and social...
conditions of 8,504 community-living adults aged 50 years or over in Ireland. W1 took place between October 2009 and February 2011 and W2 between February 2012 and March 2013. The design and methodology of TILDA and full cohort profile has been documented elsewhere\(^2\). The W1 assessments comprised of participants engaging in a self-completion questionnaire (SCQ), a computer assisted personal interview (CAPI) and a health assessment performed by trained research nurses. In W2, the participants underwent a repeat SCQ and CAPI. For the purposes of this study, we focused on W1 and W2 only.

**Baseline characteristics**

At Wave 1, we reviewed the following participant characteristics:

- Participant on pharmacological treatment for hypertension and taking any of the prescribed drugs from the following Anatomical Therapeutic Chemical (ATC) Classification System codes ([https://www.whocc.no/atc_ddd_index](https://www.whocc.no/atc_ddd_index)): 1. C02 (anti-hypertensives), 2. C03 (diuretics), 3. C07 (beta blocking agents), 4. C08 (calcium channel blockers) or 5. C09 (agents acting on the renin-angiotensin system).

- Frail by Morley’s five-item FRAIL scale questionnaire (Fatigue, Resistance, Ambulation, Illness & Loss of weight): frailty was defined by the presence of three or more of these criteria\(^9\). FRAIL was previously operationalised in TILDA\(^10\). Fatigue was scored as 1 point if the participant reported feeling tired “most of the time” or “all of the time” in the previous four weeks. The participants scored 1 point for Resistance if difficulty was reported with walking up 10 steps on stairs without resting and without aids. For Ambulation, the participants scored 1 point if they reported difficulty walking several hundred yards alone without aids. For Illness, the participant scored 1 point if they had five or more of 11 pre-selected illnesses (hypertension, diabetes, cancer other than minor skin cancer, chronic lung disease, heart attack, congestive cardiac failure, angina, asthma, arthritis, stroke and kidney disease). Finally, Loss of weight was scored as 1 point if the participant had a 5% or more weight decline in the preceding 12 months. Participants scoring two or less for these five criteria were identified as non-frail.

- Frail by a self-reported 32-item Frailty Index (FI-32). The FI methodology was previously proposed by Rockwood and colleagues\(^11\). FI-32 was previously operationalised in TILDA\(^10\). Participants were identified as frail with a FI-32 score of \(\geq 0.25\), which is in keeping with existing studies\(^12\). The individual components of this 32-item FI are available in the *Extended data*\(^13\).

- Blood pressure (BP) reading: two blood pressure measurements were recorded in the W1 health assessment for each participant. The methodology for measuring BP was standardised with the participant in the upright seated position and two BP measurements taken one minute apart. The OMRON\(^\text{TM}\) digital automatic blood pressure monitor (MODEL M10-IT) with arm cuff was used for BP measurement. The average of the two BP readings was calculated and this reading was then used as the reference blood pressure for each participant. Intensive or ‘low’ blood pressure was defined as SBP < 130 mmHg and/or DBP < 70 mmHg. ‘High’ BP was defined as SBP \(\geq 130\) mmHg and/or DBP \(\geq 70\) mmHg.

**Baseline groups**

All Wave 1 participants who were both 65 years or older and had a self-reported history of hypertension that was treated with anti-hypertensive medication were included in the study. Frailty was operationalised as a dichotomous variable for FI and FRAIL as outlined above. Similarly, BP for a participant was dichotomous (‘high’ or ‘low’) as per the criteria outlined above. From this BP and frailty data, eight individual baseline Wave 1 BP/frailty groups were then formulated based on a participant’s frailty status by FI or FRAIL and if their BP was ‘low’ or ‘high’.

**Wave 2 follow-up characteristics**

In keeping with the methodology of our previous study\(^14\), the same Wave 2 outcomes were analysed:

- The occurrence of any new falls or fractures (hip, spine, wrist or other) since their first interview at Wave 1.
- The occurrence of a syncopal event, defined as having a faint or blackout, since the first interview.
- Any admission to hospital since Wave 1.
- Any new stroke/TIA, heart failure and heart attack that has been diagnosed or occurred since their first health assessment in Wave 1.
- Death that occurred since the initial Wave 1 assessment.

**Statistical analyses**

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 26.0, Armonk, NY: IBM Corp.). Descriptive statistics were provided as mean with standard deviation (SD), median with interquartile range (IQR) or number (N) with percentage (%). For the assessment of differences between the eight baseline BP/frailty groups formulated in Wave 1, the Chi-squared test was used for binary variables and the Kruskal-Wallis test for continuous variables.

Binary logistic regression models were used to assess the independent association between baseline Wave 1 BP/frailty groups and the Wave 2 longitudinal outcomes. The two differently adjusted models were utilised each time as follows:

1. Basic logistic regression model – adjusted for age and sex only.
2. Full logistic regression model – adjusted for age, sex, and all the following Wave 1 characteristics:
   - Orthostatic hypotension (OH), which for the purposes of this study we defined as a drop of \(\geq 20\) mmHg in SBP and/or \(\geq 10\) mmHg DBP on standing upright from a seated
Polypharmacy, which for this study was present if a participant was taking ≥ 5 regular prescribed medications.

Lower educational attainment (up to primary school level).

Cognition as determined by the Montreal Cognitive Assessment (MOCA) score.

Microsoft Excel version 2203 (Build 15028.20228) was used to generate forest plots in order to display the adjusted odds ratio (OR) for each of the BP/frailty groups and the longitudinal outcomes assessed at Wave 2. The 95% confidence interval (CI) for each OR and P value were also included in the forest plots. Statistical significance was set at P<0.05 throughout.

Results

Participants' baseline characteristics at Wave 1

In Wave 1 of TILDA, there was a total of 1,920 participants aged ≥65 years who were on medication to treat hypertension. Of these, 1,274 participants had complete FI/BP data and 1,276 complete FRAIL/BP data. Approximately one in three participants were frail by FI (n=429, 33.7%), while only 5.5% (n=70) were frail by FRAIL scale. Figure 1 summarises how the final frailty/BP groups were arrived at.

Figure 1. Flow diagram of selection of participants for analysis. FI = Frailty Index, FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses and Resistance), SBP = systolic blood pressure, DBP = diastolic blood pressure.
The baseline characteristics of both FI/BP and FRAIL/BP groups are summarised in Table 1 and Table 2, respectively. The frail by FI with BP treated low or high at Wave 1 seemed older (p<0.001), more likely to be of female sex (p<0.001), have a higher proportion of lower education (p=0.008), be more comorbid and disabled (both p<0.001), have lower MOCA scores (p<0.001), and have more frequent polypharmacy (p<0.001) (Table 1). For the frail versus non-frail by FRAIL scale at baseline, there was no significant difference in age or sex, but the frail also seemed more comorbid and disabled (both p<0.001), have lower MOCA scores (p<0.001), and have more frequent polypharmacy (p<0.001).

**Longitudinal health outcomes at wave 2**
The Wave 2 outcomes of both FI/BP and FRAIL/BP groups are summarised in Table 1 and Table 2, respectively. The results of the basic and full binary logistic regression models for the risk of longitudinal health outcomes at Wave 2 for the eight BP/frailty sub-groups are summarised in Figure 2. The results in Figure 2 are colour coded to highlight groups with a statistically significant increased risk (red), reduced risk (green) or no statistical significance/risk (yellow) for all the individual health outcomes analysed at Wave 2. The full detailed results of the binary logistic regression models are available in the Extended data.

In the fully adjusted models, the frail with BP treated low for both FI and FRAIL were at increased risk of hospitalisation, heart failure and falls/fractures in Wave 2 (FI: hospitalisation P=0.015, heart failure P=0.031, falls/fracture P=0.002; FRAIL: hospitalisation P=0.002, heart failure P=0.012, falls/ fracture P=0.007). The frail by FRAIL with BP treated low were also at increased risk mortality (P=0.019) in the fully adjusted models. The frail by FI treated high had an increased risk of syncope (P=0.030) and falls/fractures (P=0.006). Frail by FRAIL scale treated high had increased risk of hospitalisation.

### Table 1. Baseline Characteristics and Outcomes of BP-Frailty Groups – Frailty by Frailty Index, BP threshold SBP < 130 and/or DBP < 70 mmHg.


<table>
<thead>
<tr>
<th>Wave 1 characteristics</th>
<th>Frail Treated Low n= 153</th>
<th>Frail Treated High n= 276</th>
<th>Non-Frail Treated Low n= 277</th>
<th>Non-Frail Treated High n=568</th>
<th>P Value (overall difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>75.1 (6.3)</td>
<td>75.8 (6.8)</td>
<td>73.0 (5.9)</td>
<td>72.9 (6.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>95 (62.1)</td>
<td>161 (58.3)</td>
<td>123 (44.4)</td>
<td>246 (43.3)</td>
<td>&lt;0.001#</td>
</tr>
<tr>
<td>Education level: up to primary only (%)</td>
<td>74 (48.4)</td>
<td>138 (50)</td>
<td>114 (41.2)</td>
<td>220 (38.7)</td>
<td>0.008#</td>
</tr>
<tr>
<td>Median number of chronic diseases (IQR)</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median number of physical limitations (IQR)</td>
<td>6 (3)</td>
<td>6 (3)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median MOCA score (IQR)</td>
<td>22 (7)</td>
<td>22.12 (6)</td>
<td>24 (5)</td>
<td>25 (3.92)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Polypharmacy (%)</td>
<td>125 (81.7)</td>
<td>210 (76.1)</td>
<td>135 (48.7)</td>
<td>201 (35.4)</td>
<td>&lt;0.001#</td>
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<td>Mean seated SBP mmHg (SD)</td>
<td>119.5 (12.6)</td>
<td>152.9 (18.3)</td>
<td>122.4 (11.1)</td>
<td>151.4 (16.3)</td>
<td>&amp;0.001*</td>
</tr>
<tr>
<td>Mean seated DBP mmHg (SD)</td>
<td>70.9 (12.4)</td>
<td>90.7 (20.2)</td>
<td>71.0 (8.8)</td>
<td>86.0 (11.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Orthostatic hypotension (%)</td>
<td>13 (8.5)</td>
<td>51 (18.8)</td>
<td>18 (6.5)</td>
<td>72 (12.7)</td>
<td>&lt;0.001#</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Wave 2 outcomes</th>
<th>Any fall or fracture (%)</th>
<th>New syncope (%)</th>
<th>New hospitalisation (%)</th>
<th>New stroke or TIA (%)</th>
<th>New heart failure (%)</th>
<th>New heart attack (%)</th>
<th>Mortality (%)</th>
</tr>
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<tr>
<td>60 (45.5)</td>
<td>6 (6.1)</td>
<td>48 (36.4)</td>
<td>5 (3.8)</td>
<td>3 (2.6)</td>
<td>12 (7.8)</td>
<td>19 (6.9)</td>
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<td>93 (39.9)</td>
<td>15 (8.8)</td>
<td>72 (30.9)</td>
<td>13 (5.6)</td>
<td>3 (1.4)</td>
<td>19 (6.9)</td>
<td>10 (3.6)</td>
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<tr>
<td>49 (20.0)</td>
<td>6 (3.0)</td>
<td>50 (20.3)</td>
<td>3 (1.2)</td>
<td>2 (0.9)</td>
<td>10 (3.6)</td>
<td>15 (2.6)</td>
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<tr>
<td>137 (26.0)</td>
<td>17 (3.9)</td>
<td>104 (19.7)</td>
<td>17 (3.2)</td>
<td>4 (0.8)</td>
<td>15 (2.6)</td>
<td>0.005#</td>
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* Kruskal-Wallis test; # Chi-Square test.
Table 2. Baseline characteristics and outcomes of BP-Frailty Groups – Frailty by FRAIL scale, BP threshold SBP < 130 and/or DBP < 70 mmHg. Legend – SD – standard deviation, IQR – interquartile range, SBP – systolic blood pressure, DBP – diastolic blood pressure, MOCA – Montreal Cognitive Assessment score.

<table>
<thead>
<tr>
<th>Wave 1 characteristics</th>
<th>Frail Treated Low n= 29</th>
<th>Frail Treated High n= 41</th>
<th>Non-Frail Treated Low n= 401</th>
<th>Non-Frail Treated High N= 805</th>
<th>P Value (overall difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>74.9 (5.7)</td>
<td>75.6 (7.4)</td>
<td>73.6 (6.1)</td>
<td>73.8 (6.)</td>
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<td>Female Sex (%)</td>
<td>15 (51.7)</td>
<td>23 (56.1)</td>
<td>203 (50.6)</td>
<td>386 (48.0)</td>
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<td>Education level: up to primary only (%)</td>
<td>15 (51.7)</td>
<td>25 (61.0)</td>
<td>173 (43.1)</td>
<td>333 (41.5)</td>
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<tr>
<td>Median number of chronic diseases (IQR)</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median number of physical limitations (IQR)</td>
<td>7 (3)</td>
<td>7 (3)</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median MOCA score (IQR)</td>
<td>20 (6)</td>
<td>21 (7)</td>
<td>23 (6)</td>
<td>24 (6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Polypharmacy (%)</td>
<td>26 (89.7)</td>
<td>34 (82.9)</td>
<td>234 (58.4)</td>
<td>377 (46.8)</td>
<td>&lt;0.001#</td>
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<td>Mean seated SBP mmHg (SD)</td>
<td>118.9 (13.4)</td>
<td>150.8 (17.6)</td>
<td>121.6 (11.6)</td>
<td>151.9 (16.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean seated DBP mmHg (SD)</td>
<td>68.4 (7.1)</td>
<td>90.3 (20.2)</td>
<td>71.1 (10.4)</td>
<td>87.4 (14.8)</td>
<td>&lt;0.001*</td>
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<tr>
<td>Orthostatic hypotension (%)</td>
<td>1 (3.4)</td>
<td>5 (13.5)</td>
<td>30 (7.5)</td>
<td>118 (14.7)</td>
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Wave 2 outcomes

<table>
<thead>
<tr>
<th>Wave 2 outcomes</th>
<th>Frail Treated Low n= 29</th>
<th>Frail Treated High n= 41</th>
<th>Non-Frail Treated Low n= 401</th>
<th>Non-Frail Treated High N= 805</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fall or fracture (%)</td>
<td>13 (59.1)</td>
<td>14 (43.8)</td>
<td>96 (27.0)</td>
<td>216 (29.6)</td>
</tr>
<tr>
<td>New syncope (%)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>11 (3.8)</td>
<td>32 (5.4)</td>
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<tr>
<td>New hospitalisation (%)</td>
<td>13 (59.1)</td>
<td>14 (43.8)</td>
<td>85 (23.9)</td>
<td>162 (22.2)</td>
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<tr>
<td>New stroke or TIA (%)</td>
<td>1 (4.5)</td>
<td>1 (3.1)</td>
<td>7 (2.0)</td>
<td>29 (4.0)</td>
</tr>
<tr>
<td>New heart failure (%)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>4 (1.1)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>New heart attack (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (1.6)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>5 (17.2)</td>
<td>5 (12.2)</td>
<td>17 (4.2)</td>
<td>29 (3.6)</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test; # Chi-Square test.

Figure 2. Summary of outcomes at Wave 2 after basic and full binary logistic regression analysis. BP = Blood Pressure, FRAIL Scale = Fatigue Resistance Ambulation Illness Loss of weight Scale, TIA or Stroke = Transient Ischaemic Attack or Stroke.
The non-frail by FI or FRAIL did not have increased risk of any of the adverse outcomes studied. The non-frail by FI treated low had a significantly reduced risk of falls/fractures by Wave 2 (P=0.001) in the fully adjusted model.

The forest plots of the fully adjusted ORs for each of the frailty/BP sub-groups and longitudinal outcomes assessed, with 95% confidence intervals for the ORs and associated P values included, are available in Figure 3(a) and Figure 3(b).

Figure 3a. Forest Plot of Odds Ratio (OR) for Longitudinal outcomes at Wave 2 for frail by FRAIL scale. FRAIL Scale = Fatigue Resistance Ambulation Illness Loss of weight Scale, TIA or Stroke = Transient Ischaemic Attack or Stroke, O.R. = Odds Ratio, C.I. = Confidence Interval.

Figure 3b. Forest Plot of Odds Ratio (OR) for Longitudinal outcomes at Wave 2 for frail by Frailty Index/BP group TIA or Stroke = Transient Ischaemic Attack or Stroke, O.R. = Odds Ratio, C.I. = Confidence Interval.
Discussion

The latest 2018 guidelines from the European Society of Cardiology/European Society of Hypertension (ESC/ESH) for the management of hypertension in adults aged ≥65 years advise a blood pressure (BP) treatment target of 130–139/70–79 mmHg if tolerated by the patient. On the contrary, recent high profile randomised controlled trials have been promoting lower BP targets. However, this may lead to adverse outcomes, particularly in the frail. Yet, different operationalisations of frailty exist in the literature. Following on from our previous study, in this companion paper we aimed to re-analyse the same population cohort but apply two alternative frailty identification tools (Frailty Index and FRAIL scale) to see how they were associated to the same 2-year adverse health outcomes in those intensively treated for hypertension. Again, we showed that the increased risk of adverse outcomes did not occur in non-frail, but only frail groups. Here, we showed that most adverse health outcomes at 2 years occurred in the frail with BP treated more intensely. In this study utilising the FI and the FRAIL scale, we found more adverse outcome associations compared to our previous study with the Frailty Phenotype and the Clinical Frailty Scale. Taken together, combined results further establish that the way frailty is identified is crucial for the application of the ESC/ESH guideline, because different frailty identification tools behave differently in how they capture longitudinal risks.

The fact that again, frailty was seen in association with adverse outcomes reflects existing knowledge and previous studies that identified frailty as a risk factor for falls, fractures, mortality, heart failure and hospitalisation. However, within the frail groups of this study, there were some differences in how the FI and FRAIL scale predicted the outcomes assessed.

Firstly, for the outcome of syncope by Wave 2, the only group that had increased risk was the frail by FI treated high. Low blood pressure and over-treated hypertension are well-known risk factors for syncope, so a possibility (that we cannot verify with our design) is that some participants in this group may have been previously identified by their medical practitioners as having increased cardiovascular risk and had their anti-hypertensive medications reduced or de-prescribed. The FI incorporates more cardiovascular co-morbidities than the FRAIL scale and this may explain why this finding was not captured in the frail by FRAIL scale treated high. On the other hand, the prevalence of frail by FI was greater than that of FRAIL scale, which confers greater statistical power for the FI analyses.

Both FI and FRAIL identified an increased risk of a new diagnosis of heart failure by Wave 2 for the frail treated low. The FI incorporates multiple risk factors for cardiovascular disease and heart failure including hypertension, angina, heart attack, diabetes and high cholesterol. In this light, a higher risk of new heart failure would be in keeping with the cumulative deficits model of frailty. In addition, while heart failure is not a specific item of the FI, one of the deficits included in the 32-item FI was “other cardiovascular disease”, which could include heart failure. For the frail by FRAIL treated low, a different mechanism of how heart failure is captured is possible. The FRAIL scale incorporates fatigue as one of its criteria and fatigue is also a well-recognised clinical symptom in patients with chronic heart failure. As outlined in our companion paper, frail by FP (which also includes fatigue) treated low also captured increased heart failure risk. However, this consistency across the FP, FI and FRAIL with BP treated low in association with new heart failure could also be explained by reduced ejection fraction (“pump failure”) causing low BP that may still require long term cardiovascular medications to reduce morbidity and mortality.

The frail by FRAIL treated low had an increased risk of mortality by Wave 2. This is in keeping with an existing study on the TILDA cohort where the FRAIL scale was identified as the most specific frailty identification tool for the prediction of 8-year mortality in comparison with FP, FI and CPS. In the same study, the FI had the lowest specificity for predicting mortality and this is in keeping with our study where the FI did not capture any increased risk of short-term mortality for the frail treated low or high. The systolic BP decline in the final 2 years of life, in patients both treated and not treated with antihypertensive therapy, has been shown to be associated with increasing frailty as described by Ravindrarajah et al in a population-based cohort study. In addition, the FRAIL scale incorporates a number of co-morbidities that the FI does not account for including chronic lung disease and asthma, but also chronic kidney disease. In particular, both chronic lung disease and chronic kidney disease are associated with increased mortality and this may also be in relation with FRAIL being more specific for the prediction of mortality.

Physiological dysregulation of the cardiovascular system in combination with frailty has been demonstrated to be independently associated with mortality in other longitudinal studies. The frail treated low for both FI and FRAIL had an increased risk of falls/fractures by Wave 2. As discussed earlier in relation to heart failure, both FI and FRAIL incorporate multiple cardiovascular co-morbidities, which combined with the physiological dysregulation of organ systems that occurs in frailty, can result in an increased risk of impaired BP regulation – in particular OH when the BP is already being treated to a low/intense level. OH at 40 seconds after standing and sustained OH in TILDA have been shown to be independently associated with recurrent, injurious, and unexplained falls. On the other hand, the frail by FI with BP treated high also had an increased risk of falls/fractures. This possibly reflects the fact that OH and low BP related events are not the sole mechanism of falls/fractures in frail older adults. The FI incorporates mobility assessment in its self-reported deficit questionnaire similar to the FRAIL scale. However, unlike the FRAIL scale, the FI also assesses transfers such as difficulty rising from a chair or difficulty “stooping, kneeling or crouching” and vision deficits which are all risk factors for falls. This may explain the mechanism by which the frail by FI with BP treated high were also at increased risk of falls/fractures. It should be noted that in our previous study, CFS and FP did not specifically incorporate cardiovascular co-morbidities, which may explain why they did not capture falls/fracture risk in the frail treated low compared to the FRAIL/FI.

Our study has a number of limitations. Firstly, a number of participants at baseline in Wave 1 did not have complete data
(638 in total) and this likely resulted in reduced statistical power when analysing the subgroups we formulated. This reflects in some of the wide confidence intervals in some subgroup outcomes in the forest plots in Figure 3(a) and Figure 3(b). However, even though the number of frail participants according to FRAIL was the lowest (n=70), the FRAIL scale with BP treated low had more statistically significant outcomes than any of the other frail/BP groups in this study. A further limitation is that TILDA is a study of community-dwelling adults and thus excludes those living in residential or nursing care. Frailty is highly prevalent in nursing home residents with rates varying depending on the frailty identification tools used: one study using the FI reported a prevalence of 81.6% for new male nursing home admissions\(^4\), while studies using the FP and CHSA-CFS reported proportions of 68.8% and 75.6% respectively\(^45,46\). Therefore, our study did not capture outcomes in the most frail.

The current ESC/ESH guidelines do not specify what frailty tool to clinicians should utilise when assessing patients with potential frailty who have hypertension, and this is a significant limitation of these guidelines. A recent consensus statement published by Richter et al. on the topic of frailty in cardiology is a welcome development where the authors acknowledged the importance of explicit frailty screening in cardiology\(^47\). It is important to note that no specific frailty identification tool was recommended in their consensus document. Similarly, the ESC has recently acknowledged in The Cardiovascular Round Table forum the complexity of managing cardiovascular diseases in heterogeneous groups such as older adults. In particular, Lettino et al. have noted for frail older adults and those with functional dependence that anti-hypertensive treatment should be reassessed, and de-prescribing considered to avoid further deterioration in functional status and medication side effects\(^48\). Again, no specific frailty tool was recommended. Nevertheless, there is certainly an important conversation developing in the cardiology community and an acknowledgement that a patient-centred approach is needed for frail patients with cardiovascular diseases is welcome.

**Conclusion**

In this and our companion paper\(^45\), we compared four frailty classifications in their ability to predict 2-year incident adverse outcomes associated with below-target BP control (<130/70 mmHg) in The Irish Longitudinal Study on Ageing (TILDA). For the frail treated below target, hospitalisation by W2 was significantly more likely in those who were frail by FP, FI and FRAIL but not by CFS. The frail by FRAIL and BP treated below target were the only group with increased risk of mortality by W2. The frail by FI and FRAIL with BP treated below target had increased risk of hospitalisation, new heart failure and falls/fractures by W2.

Frailty was independently associated with adverse outcomes in hypertensive older adults treated below the ESC/ESH target. However, different frailty classifications had different prognostic implications. For those below the BP target, frailty by FRAIL was associated with the highest number of risks (falls/fractures, heart failure, hospitalisation and mortality), followed by the frail by FI (falls/fractures, heart failure and hospitalisation). Based on our results and frailty measures considered, we recommend that FRAIL and FI are regarded as the methods of choice to identify frailty when applying the ESC/ESH guideline. Models of frailty that do not explicitly measure comorbidities (such as FP and CFS) may be less useful to capture risk of adverse events from lower blood pressure control.

Given the heterogeneity of the older, frail population we conclude that patients should undergo comprehensive geriatric assessment once frailty has been identified (with any tool) to help guide their BP treatment. There needs to be larger, higher powered studies in clinical populations to definitively guide clinicians in this complex clinical scenario.

**Data availability**

**Underlying data**

The database from which the results were calculated and obtained cannot be shared due to data protection and ethical issues. Any requests to access the database can be made directly to TILDA (tilda@tcd.ie) and are considered on a case by case basis. The first two waves of TILDA data (upon which this papers analysis is based on) are available from the Irish Social Science Data Archive (ISSDA) at www.ucl.ie/issda/data//tilda/. To access the TILDA survey data, please complete an ISSDA Data Request Form for Research Purposes, sign it and send to ISSDA by email (issda@ucl.ie).

**Extended data**

Figshare: Appendix - logistic regression analysis basic and full model for FRAIL and FI BP groups.docx. https://doi.org/10.6084/m9.figshare.1964307v3.

This project contains the following extended data:

- Appendix - logistic regression analysis basic and full model for FRAIL and FI BP groups.docx (This file contains the results tables of the basic and full binary logistic regression statistical analysis calculated for each Wave 1 frailty/blood pressure group (for Frailty index and FRAIL scale) and their respective risk for the seven Wave 2 health outcomes studied. These results are summarised in the main manuscript of the paper in Figure 2, Figure 3(a) and Figure 3(b))

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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