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 2; peer review: 1 approved with reservations, 1 not approved]

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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 adverse events. 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 (‘below threshold (BT)’: <130/70 mmHg vs. ‘above threshold (AT)’: ≥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 BT and frail by FRAIL treated BT had increased risk of hospitalisation, heart failure and falls/fracture by W2. The frail by FRAIL treated BT also had increased risk of mortality by W2. The frail by FI treated AT had increased risk of syncope and falls/fractures. The non-frail by FI or FRAIL did not have any increased risk 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. Future hypertension management guidelines should consider incorporating specific frailty identification tools to help guide clinicians in making personalised BP medication treatment decisions.

Keywords
Frailty, hypertension, frailty index, FRAIL scale

This article is included in the TILDA gateway.

This article is included in the Ageing Populations collection.

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Author roles: O'Donoghue P: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; O'Halloran A: Data Curation, Investigation, Writing – Review & Editing; Romero-Ortuno R: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: TILDA is funded by Atlantic Philanthropies, Irish Life and the Irish Department of Health. Roman Romero-Ortuno is funded by a grant from Science Foundation Ireland under grant number 18/FRL/6188. Of note, the funders had no role in the study design, data collection/analysis or in the preparation of this manuscript.

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How to cite this article: O'Donoghue P, O'Halloran A, Kenny RA and Romero-Ortuno R. 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 2; peer review: 1 approved with reservations, 1 not approved] HRB Open Research 2022, 5:45 https://doi.org/10.12688/hrbopenres.13522.2

First published: 09 Jun 2022, 5:45 https://doi.org/10.12688/hrbopenres.13522.1
Amendments from Version 1

Following on from the reviewers’ comments on Version 1, we have made a number of changes to the manuscript.

Firstly, the introduction has been shortened to become more concise and to help focus on the research question more. As part of this change, some of our reflection of the existing studies on hypertension management in frail older adults that were originally in the introduction section, have now been moved to the discussion section.

The nomenclature of the four blood pressure/frailty groups have also been changed. In Version 1 the groups were frail/non-frail with BP treated ‘low’ or ‘high’. Instead, in Version 2 we have changed these groups to frail/non-frail with BP treated ‘below threshold’ (BT) or ‘above threshold’ (AT). This change aims to reflect that our study assesses blood pressure in the context of the ESC/ESH guidelines that recommend the lowest end of the target BP range for older adults treated for hypertension is 130/70mmHg. Therefore our study divides participants into groups based on whether they are a) frail or non-frail and b) whether they are above or below this lower end of the treatment target threshold.

As a result of this change in nomenclature, these 4 frailty-BP groups in the manuscript, including in the Figures and Tables, are now described as either frail AT, frail BT, non-frail AT and non-frail BT.

Finally, in the flow diagram in Figure 1, the description of the participants 'treated for hypertension' has been changed to "Prescribed/taking anti-hypertensive medications" as our study didn't specify the indication for the anti-hypertensive medications as there may have been indicators other than hypertension for these medications being prescribed.

No changes have been made to the original the statistical analyses of Version 1.

Any further responses from the reviewers can be found at the end of the article.

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 if tolerated; and if not tolerated, a higher BP may have to be accepted. ESC/ESH recommend monitoring frail patients closely for side effects of BP lowering medication and in particular to monitor for postural hypotension. 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 impaired cerebral autoregulation and has also 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 may have unintended consequences such as orthostatic hypotension.

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 below ESC/ESH treatment thresholds (BT), had an increased risk of hospitalisation at 2 years. However, in the same study, the frail by Clinical Frailty Scale (CFS) with BP treated BT 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 below the current recommended BP treatment threshold, 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. The W1 assessments comprised of participants engaging in a self-completion questionnaire (SCQ), a computer assisted personal interview.

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(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/): 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\(^{12}\). FRAIL was previously operationalised in TILDA\(^{13}\). 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 reported 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\(^{14}\). FI-32 was previously operationalised in TILDA\(^{15}\). Participants were identified as frail with a FI-32 score of \(\geq 0.25\), which is in keeping with existing studies\(^{15}\). The individual components of this 32-item FI are available in the Extended data\(^{16}\).

- 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 (BP treated ‘above threshold’ (AT) or BP treated ‘below threshold’ (BT)) 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 frailty status by FI or FRAIL and if their BP was treated ‘below threshold’ or ‘above threshold’.

Wave 2 follow-up characteristics
In keeping with the methodology of our previous study\(^{4}\), 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 position. OH was measured in TILDA and described in detail elsewhere\(^{11}\).
   - Polypharmacy, which for this study was present if a participant was taking \(\geq 5\) 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.

The baseline characteristics of both FI/BP and FRAIL/BP groups are summarised in Table 1 and Table 2, respectively.

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, BT = Blood pressure treated below 130/80mmHG threshold, AT= Blood pressure treated above/equal to the 130/80mmHG threshold.
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 below threshold (BT) 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

### Table 1. Baseline Characteristics and Outcomes of BP-Frailty Groups – Frailty by Frailty Index, 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 Below Threshold n= 153</th>
<th>Frail Treated Above Threshold n= 276</th>
<th>Non-Frail Treated Below Threshold n= 277</th>
<th>Non-Frail Treated Above Threshold 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>
</tr>
<tr>
<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>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>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>
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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>
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<tbody>
<tr>
<td></td>
<td>60 (45.5)</td>
<td>6 (6.1)</td>
<td>48 (36.4)</td>
<td>5 (3.8)</td>
<td>5 (3.8)</td>
<td>3 (2.6)</td>
<td>12 (7.8)</td>
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<tr>
<td></td>
<td>93 (39.9)</td>
<td>15 (8.8)</td>
<td>72 (30.9)</td>
<td>13 (5.6)</td>
<td>0 (0)</td>
<td>3 (1.4)</td>
<td>19 (6.9)</td>
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<tr>
<td></td>
<td>49 (20.0)</td>
<td>6 (3.0)</td>
<td>50 (20.3)</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>2 (0.9)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td></td>
<td>137 (26.0)</td>
<td>17 (3.9)</td>
<td>104 (19.7)</td>
<td>17 (3.2)</td>
<td>7 (1.3)</td>
<td>4 (0.8)</td>
<td>15 (2.6)</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test; # Chi-Square test.
BP treated BT were also at increased risk mortality (P=0.019) in the fully adjusted models. The frail by FI treated above threshold (AT) had an increased risk of syncope (P=0.030) and falls/fractures (P=0.006). Frail by FRAIL scale treated AT had increased risk of hospitalisation (P=0.024). 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 BT 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).

**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. 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

<table>
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<tr>
<th>Wave 1 characteristics</th>
<th>Frail Treated Below Threshold n= 29</th>
<th>Frail Treated Above Threshold n= 41</th>
<th>Non-Frail Treated Below Threshold n= 401</th>
<th>Non-Frail Treated Above Threshold 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>
<td>0.207*</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>15 (51.7)</td>
<td>23 (56.1)</td>
<td>203 (50.6)</td>
<td>386 (48.0)</td>
<td>0.641#</td>
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<tr>
<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>
<td>0.070#</td>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<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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</tbody>
</table>

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.

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

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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.

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.
to a systolic BP of less than 120 mmHg. A secondary analysis of SPRINT also showed no increased risk of falls in those with intensive blood pressure management compared to standard treatment. 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. 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.

However, different operationalisations of frailty exist in the literature. Following on from our previous study, in this companion paper we re-analysed the same population cohort but applied 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 below current ESC/ESH recommended threshold (BT). 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. 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\textsuperscript{38}.

Within the frailty 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 with BP treated AT. Low blood pressure and over-treated hypertension are well-known risk factors for syncope\textsuperscript{39,30}, 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 AT. 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 BT. 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\textsuperscript{40}. 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 BT, 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\textsuperscript{42,43}. As outlined in our companion paper\textsuperscript{3}, frail by FP (which also includes fatigue) treated BT also captured increased heart failure risk. However, this consistency across the FP, FI and FRAIL with BP treated BT 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 scale treated BT 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 CFS\textsuperscript{44}. 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\textsuperscript{45}. 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\textsuperscript{46,37} and this may also explain why the FRAIL scale is 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\textsuperscript{38}. The frail treated BT for both FI and FRAIL had an increased risk of fall/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\textsuperscript{40}. On the other hand, the frail by FI with BP treated AT 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”\textsuperscript{41} and vision deficits which are all risk factors for falls\textsuperscript{40,41}. This may explain the mechanism by which the frail by FI with BP treated AT 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 BT compared to the FRAIL/FI.

Our study has a number of limitations. Firstly, there is potential for misclassification of participants blood pressure control status at Wave 1 as BP readings used were solely based on the average of 2 readings and may not take into account variables such as white coat hypertension, BP variability etc., Secondly, the number of participants at baseline in Wave 1 that did not have complete data (638 in total) likely resulted in reduced statistical power when analysing the sub-groups 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). Future studies should include sub-group analysis for those with co-morbidities requiring specifically lower or higher BP treatment targets e.g. patient with diabetes, chronic kidney disease etc.. In addition, our data does not account for the burden of anti-hypertensive medication or doses of these respective medications. This nuanced analysis is not possible in our observational epidemiological design. Unfortunately, the reduced statistical power of our study did not allow us to perform these subgroup
analyses’ of participant co-morbidities/medications and this is another limitation of our study. However, even though the number of frail participants according to FRAIL was the lowest (n=70), the FRAIL scale with BP treated BT 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, while studies using the FP and CHSA-CFS reported proportions of 68.8% and 75.6% respectively.

Therefore, our study did not capture outcomes in the most frail. In addition, TILDA is based on an observational epidemiological longitudinal study design. Therefore, any significant results in this study are associations (not causation) that could potentially serve as the basis for future studies with higher power such as RCTs. In order to compare observational studies to RCTs on this topic, potentially a target trial design would need to be employed as observational studies are prone to biases.

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.

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.

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, 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, the FRAIL and FI may be a superior frailty identification tool to utilise 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 be considered for 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. Frailty has not yet proven in the few existing RCTs to be the ideal construct (versus other geriatric dimension such as cognition) for differentiating who might not benefit from more strict blood pressure control. These future studies should evaluate what clinical dimension will be best used to help differentiate those who may benefit versus from tight BP control versus those who won’t benefit.

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 paper’s analysis is based on) are available from the Irish Social Science Data Archive (ISSDA) at www.ucd.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@ucd.ie).

Extended data


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).
Acknowledgements

This article is based on methodology first reported by Patrick O'Donoghue, Aisling M. O’Halloran, Rose Anne Kenny, Roman Romero-Ortuno, Do The Frail Experience More Adverse Events From Intensive Blood Pressure Control? A 2-Year Prospective Study In The Irish Longitudinal Study On Ageing (TILDA), Lancet e-Clinical Medicine, 2022, https://doi.org/10.1016/clinm.2022.101304. The current article reports results with Frailty Index and FRAIL scale, while the previously published paper reported results based on Frailty Phenotype and Clinical Frailty Scale.

References

6. Romero-Ortuno R, O’Connell MD, Finucane C, et al.: An alternative method for Frailty Index cut-off points to interpret results with Frailty Index and FRAIL scale, while the previously published paper reported results based on Frailty Phenotype and Clinical Frailty Scale. Publisher Full Text
32. Falk K, Swedberg K, Gjeston-Johansson F, et al.: Fatigue is a prevalent and


Jane A. H. Masoli
Epidemiology and Public Health Group, College of Medicine and Health, University of Exeter, Exeter, UK

Thank you for addressing the review points. The manuscript is significantly improved. In particular, it is easier to read with the changed nomenclature, the previous paper is more explicitly integrated and the introduction is clearer.

There is still some imprecise scientific wording - e.g., p.6 "seemed" older - this is statistically significant so they were older.

Suggest truncate the OR of the outlier with the wide CI in figure 3a to add clarity to the forest plot as it means that it is hard to see the detail.

The interpretation of figure 2 needs expanding and should include a comment on the key role of frailty. I think that this is more important that the role of the two frailty measures (as per comment previously on power). Frailty is highly associated with hospitalisation and falls and fractures, regardless of BP BT/AT. Similarly, that AT BPs i.e., higher BPs are associated with stroke/TIA is not surprising, but it is an important distinction that AT was associated with excess risk in frail and BT reduced risk in non frail.

See other key reference on BP in the context of frailty tagged below¹.

References

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Blood pressure and cardiovascular ageing.
I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 27 September 2022

https://doi.org/10.21956/hrbopenres.14877.r32747

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Nicholas M. Pajewski
Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA

I thank the authors for their revisions. I must have missed this the first time, but the presented analyses seem strange, in that it is not clear what is being compared to what? For example, in Figure 3a, how can there be 4 odds ratios with 4 groups? One of the groups needs to serve as the reference. Presumably, interest really only lies in two comparisons, within the frail, BT vs AT, and then same the comparison in the non-frail. Based on the looking at the appendix logistic regression results, I really can't follow how the modeling was done, as it appears to be separate models for each group somehow? The authors should clarify their approach, making sure to focus on comparisons by BP group within each frailty status.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics, Frailty, Hypertension

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 30 June 2022

https://doi.org/10.21956/hrbopenres.14755.r32285

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X
Below are some comments relating to the paper presented. This is overall an interesting and important area. However, this study, and indeed the write up, is very similar to the previous paper by this group. The statistical significance of the different frailty definitions for each outcome is limited. It may be preferable to take a combined approach to frailty phenotype to increase the power to test associations between BP and outcome.

It is also important to consider that the majority were not intentionally treated to <130 and subgroup analysis based on targets would be useful. E.g., diabetic/CKD would have a lower target, 80+ a higher target. Why are BPs <130? Likely partly due to changing physiology, frailty, co-morbidity. Heart failure may be driving both the prescription of antihypertensives and the lower achieved BPs.

The introduction is lengthy, before even introducing the research question. Suggest streamline to increase focus and readability, the pertinent points can be extended in discussion.

In Figure 1 it states treated for hypertension, but presume the codes are for hypertension diagnosis and then antihypertensive medication. Minor point, but important as the prescribing indication is not explicit.

The group names eg. "frail with BP treated low" make the text difficult to follow and find the clinical context. Suggest making these clearer.

Here you compare <130 vs >=130 but if sufficient nos need to compare 130-140 or 150 and >140/150 as normotensive may have different risks to hypertensive, which may be affecting your results. E.g., for TIA/stroke. "High" is somewhat misleading as it currently encompasses normotension and hypertension.

The multiple outcomes of interest do not have sufficient statistical power - leading to wide confidence intervals and unclear results. Could consider combined outcomes or indeed combined exposure - what was the overlap in frailty phenotype. You could define the frailty phenotype by either FI or FRAIL given that the results are similar but don't reach statistical significance for the FRAIL scale and increase the numbers for analysis. Separating the two doesn't add value to the narrative or the science.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Blood pressure and cardiovascular ageing.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 18 Aug 2022
Patrick O'Donoghue, Trinity College Dublin, Dublin, Ireland

Replies to reviewer Jane A. H. Masoli:

1. Below are some comments relating to the paper presented. This is overall an interesting and important area. However, this study, and indeed the write up, is very similar to the previous paper by this group.

Response: Thank you for your review and constructive comments/feedback. Regarding the similarity with the previously published paper, we have already declared/disclosed in the acknowledgements section that this is a companion paper that utilises the same methodology to evaluate two different frailty tools (Frailty index and FRAIL scale in the current, and frailty phenotype and Clinical Frailty Scale in the one previously published). Please note that these two papers have sequentially emerged as part of an M.D. thesis that the first author is undertaking in Trinity College Dublin. So in essence, we agree that the two papers together represent a single body of work. This is why the write up is similar as the methodology used is the same as that in the companion paper with the only change being the frailty tools assessed. We have added in a sentence in the introduction (as well as already being in the Acknowledgements section) stating that this is a companion paper to re-iterate this point (see Introduction section paragraph 3)

1. The statistical significance of the different frailty definitions for each outcome is limited. It may be preferable to take a combined approach to frailty phenotype to increase the power to test associations between BP and outcome.

Response: We agree that the statistical significance of the different frailty definitions for each outcome is limited and we have acknowledged the likelihood of reduced statistical power in the discussion (see Discussion section, paragraph 8, sentence 3). In addition, this paper does not assess/look at the frailty phenotype at all but rather the FRAIL scale and
Frailty Index only. The only mention of the frailty phenotype in this paper is in the introduction & acknowledgements section where we disclose that we previously studied this hypothesis using the frailty phenotype and clinical frailty scale in the same population - a companion paper published in E-Clinical Medicine The Lancet.

1. It is also important to consider that the majority were not intentionally treated to <130 and subgroup analysis based on targets would be useful. E.g., diabetic/CKD would have a lower target, 80+ a higher target.

Response: Regarding your suggestion of performing subgroup analyses, this is an important point. It would be very interesting to perform this subgroup analyses but unfortunately the statistical power cannot allow it in our design. We have added in the limitations in the manuscript that further studies should consider subgroup analysis based on different targets and/or main morbidities (see Discussion, paragraph 8, sentence 5&6). In the present paper, with the limited power available, our aim was only to investigate the specific BP threshold mentioned in the ESC/ESH guidelines.

1. Why are BPs <130? Likely partly due to changing physiology, frailty, co-morbidity. Heart failure may be driving both the prescription of antihypertensives and the lower achieved BPs.

Response: We agree that those with BP less than 130mmHg systolic is likely multifactorial including physiology, co-morbidity, heart failure and medication related. We acknowledge in the discussion that heart failure could be driving the lower blood pressure and not just the antihypertensive therapy. We discussed these factors contributing to low BP (heart failure, multi-morbidity and medication) in detail in the discussion (See Discussion, paragraph 5).

1. The introduction is lengthy, before even introducing the research question. Suggest streamline to increase focus and readability, the pertinent points can be extended in discussion.

Response: We have edited and cut down to introduction to make it more concise. In addition, we have updated the paper to overtly state in the introduction that this is a companion paper to make it clear to the reader/give context to the research question (this is in addition to the acknowledgements section). The pertinent points re existing evidence in RCTs re intensive blood pressure control and health outcomes has now moved to the discussion section as you suggested (See Discussion, Paragraph 1)

1. In Figure 1 it states treated for hypertension, but presume the codes are for hypertension diagnosis and then antihypertensive medication. Minor point, but important as the prescribing indication is not explicit.

Response: Thank you. This is an important differentiation which was an oversight on our behalf in this figure. We have removed from Figure 1 “treated for hypertension” and replaced it with “Treated/ Prescribed anti-hypertensive medication”.


The group names eg. "frail with BP treated low" make the text difficult to follow and find the clinical context. Suggest making these clearer. Here you compare <130 vs >130 but if sufficient nos need to compare 130-140 or 150 and >140/150 as normotensive may have different risks to hypertensive, which may be affecting your results. E.g., for TIA/stroke. "High" is somewhat misleading as it currently encompasses normotension and hypertension.

Response: Thank you. Yes, another reviewer has also commented/raised concerns regarding the use of “intensive blood pressure” and “low” versus “high”. In order to clarify this, we have changed the nomenclature throughout the manuscript to frail “treated above threshold (AT)” instead of “frail treated high” and frail “treated below threshold” (BT) instead of “frail treated low”. Therefore, in the paper the previously frail treated high is now replaced with frail treated AT and so forth for frail treated BT, non frail treated AT etc. This new nomenclature addresses your point (with which we agree) that "High" is somewhat misleading as it currently encompasses normotension and hypertension. The new nomenclature re-inforces that we are assessing BP in the context of the ESC/ESH treatment target threshold. Again this was highlighted by another reviewer and we hope the new nomenclature clarifies it a bit more.

The multiple outcomes of interest do not have sufficient statistical power - leading to wide confidence intervals and unclear results. Could consider combined outcomes or indeed combined exposure - what was the overlap in frailty phenotype. You could define the frailty phenotype by either FI or FRAIL given that the results are similar but don’t reach statistical significance for the FRAIL scale and increase the numbers for analysis. Separating the two doesn’t add value to the narrative or the science.

Response: Your suggestion to combine exposures and outcomes is interesting but regarding exposures (frailty classifications) a previous published study from the same TILDA cohort showed that Clinical Frailty Scale and FRAIL scale had modest overlap¹ (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8860790/). However, our departing aim was to isolate the signals from different validated frailty tools rather than combining them even if some tools are conceptually related. Regarding the combination of outcomes, it would have probably increased the significance of longitudinal associations but make it more difficult to interpret clinically. Whilst we agree that your suggestion could have led to more statistical significance, we preferred separate analyses knowing that underpower might be affecting some of them.

References:
I think my primary issue with this work is that the investigators are not comparing apples to apples in comparison to trials like STEP and SPRINT. Those trials specifically evaluated adding on additional antihypertensive medication to achieve a lower level of blood pressure control. Here, “intensive treatment” is a heterogeneous mix of patients that may or may not have had anything done to their hypertension regimen recently. It is very odd to think of a patient on monotherapy with a systolic blood pressure of 129 mm Hg as being “intensively treated”, but that’s what the definition used in this work does. I think the authors should acknowledge two significant limitations with this work. First, if there is a desire to evaluate a potentially causal link between blood pressure control and adverse outcomes, and to compare to the randomized trials, then one really needs to employ a target trial design (see Madenci et al., 2020 as an example). Otherwise, observational analyses such as this aren't even attempting to answer the same clinical question. Second, it should be mentioned that the analyses do not account for the actual burden of antihypertensive medication. I doubt the available data would permit a more nuanced analysis of medications, but it is a critical issue here in terms of identifying participants that are actually being intensively treated.

In terms of the question of which frailty identification tool to use, it is well known that the myriad of instruments available tend to identify different subsets of older adults as frail. Calling for the selection of a single optimal tool is an unrealistic expectation. This debate has been going on for years, and is unlikely to get anywhere. I think the view of many in the field is that clinicians should use whatever frailty assessment approach they have available. If you can do comprehensive geriatric assessment, great. If you have limited geriatric resources, but have a frailty index baked into the electronic health record, use that. Doing any sort of formalized frailty screening will be better than the clinician eye-ball test.

In addition, the authors might also want to acknowledge that frailty itself may not even be the best construct for differentiating who might not benefit from more intensive blood pressure control. In both SPRINT and HYVET, recognizing both trials solely relied upon deficit accumulation, there really wasn't any indication of treatment effect heterogeneity with respect to cardiovascular disease. There was certainly risk magnification where frailer adults benefited more in absolute
terms because they were at higher risk, but the relative benefit didn’t vary much moving from lower to higher frailty index scores. In contrast, at least based on analyses we’ve done in SPRINT in adults older than 80 years of age, there does seem to be heterogeneity with respect to cognitive function (Pajewski et al., 2020). Almost all of the cardiovascular benefit in SPRINT was in participants with higher performance on the MoCA at baseline (and this same result holds in the larger 75+ subgroup). It may be that cognitive screening could be a more powerful differentiator in this case as compared to frailty. Of course, cognitive screening is not something that is done well in primary care either, there are numerous instruments to consider, and so it is an equally complicated screening problem to solve.

Minor Comments

“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.”

It should be mentioned that the randomized trials have shown no indication of increased risk of falls.

“In addition, neither trial used a frailty identification tool at enrolment to stratify patients by frailty status.”

True, but what is the relevance of this? SPRINT has done analyses based on baseline FI, and one does not need to stratify randomization in order for baseline subgroup analyses to be valid.

Another limitation that should be mentioned is misclassification from relying upon a single blood pressure reading.

“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.”

At least in America, this is totally infeasible. For example, in my health system, we have over 15-20k older patients identified as frail based on an eFI. It works out to 30 frail patients for every single primary care provider we have, with <5% of those having specific geriatrics expertise. There is just no way to broadly do CGA.

References


Is the work clearly and accurately presented and does it cite the current literature?  
Yes
Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** I was an investigator involved in the Systolic Blood Pressure Intervention Trial (SPRINT).

**Reviewer Expertise:** Biostatistics, Frailty, Hypertension

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Author Response 18 Aug 2022**

Patrick O'Donoghue, Trinity College Dublin, Dublin, Ireland

Responses to reviewer Nicholas M. Pajewski:

**Reviewer:** I think my primary issue with this work is that the investigators are not comparing apples to apples in comparison to trials like STEP and SPRINT. Those trials specifically evaluated adding an additional antihypertensive medication to achieve a lower level of blood pressure control. Here, “intensive treatment” is a heterogeneous mix of patients that may or may not have had anything done to their hypertension regimen recently.

1. Response: Thank you for your detailed review and comments. In our study, we are not presenting data from a randomised controlled trial, but from an observational epidemiological longitudinal study on ageing, which has the limitations that you correctly outline in the paper you referenced by Medenci et al. We are happy to explicitly acknowledge that our desire is NOT to evaluate causal links, but to report associations that could serve the basis for future RCTs. We have edited the manuscript to include this point as a limitation in the discussion section (see Discussion section, paragraph number 8). In addition, to fully acknowledge this limitation, we have also included this reference of the paper by Madenci et al to re-iterate this important point (see Discussion section, paragraph 8, reference number 45).
Reviewer: It is very odd to think of a patient on monotherapy with a systolic blood pressure of 129 mm Hg as being “intensively treated”, but that’s what the definition used in this work does.

1. Response: Yes we agree that a systolic blood pressure of 129mmHg may not represent “intensively treated” per se. However, as per the 2018 European Society of Cardiology / European Society of Hypertension (ESC/ESH) guidelines for the management of arterial hypertension in adults, the lowest blood pressure treatment target range for older adults is 130-139mmHg systolic/70-79 mmHg diastolic if tolerated. Therefore, for systolic BP, 130mmHg was used as a cut-off for BP treated below versus above current recommendations ( hence the word ‘intensive’). Of note, another reviewer did have some reservations about the nomenclature such as ‘Frail treated low’ or ‘frail treated high’ etc., and as a result we have changed this in the manuscript to “frail hypertensive treated above threshold (AT) vs “frail hypertensive treated below threshold” (BT) and non-frail AT versus non-frail BT. AT/BT will be used in the paper instead of ‘high’ or ‘low’. We hope this change of using above BP threshold or below BP threshold will also address your concerns re using the word ‘intensive’ for the people with BP treated below current guidelines.

Reviewer: I think the authors should acknowledge two significant limitations with this work. First, if there is a desire to evaluate a potentially causal link between blood pressure control and adverse outcomes, and to compare to the randomized trials, then one really needs to employ a target trial design (see Madenci et al., 2020 as an example). Otherwise, observational analyses such as this aren't even attempting to answer the same clinical question. Second, it should be mentioned that the analyses do not account for the actual burden of antihypertensive medication. I doubt the available data would permit a more nuanced analysis of medications, but it is a critical issue here in terms of identifying participants that are actually being intensively treated.

1. Response: Thank you for highlighting these limitations. As per our response number 1 above to your first point, we have now updated the paper to acknowledge clearly that we are not seeking to identify causation in our study but rather to identify any associations in this longitudinal study. ( see Discussion, paragraph 8). To re-inforce this point, we have also referenced the paper on this by Madenci et al in our discussion.

In relation to the burden of anti-hypertensive medication, our data doesn't provide details on the anti-hypertensive burden of the participants. We also agree that we should explicitly add a limitation that our analyses do not account for the actual burden of antihypertensive medication and this nuanced analysis (including types and exact dosages) is not possible with our observational epidemiological design (see Discussion section, paragraph 8)

Reviewer: In terms of the question of which frailty identification tool to use, it is well known that
the myriad of instruments available tend to identify different subsets of older adults as frail. Calling for the selection of a single optimal tool is an unrealistic expectation. This debate has been going on for years, and is unlikely to get anywhere. I think the view of many in the field is that clinicians should use whatever frailty assessment approach they have available. If you can do comprehensive geriatric assessment, great. If you have limited geriatric resources, but have a frailty index baked into the electronic health record, use that. Doing any sort of formalized frailty screening will be better than the clinician eye-ball test.

1. Response: We also agree that calling for the selection of optimal tools is an unrealistic expectation given our study design. Therefore, we will remove the sentence in the conclusion that “we recommend that FRAIL and FI are regarded as the methods of choice to identify frailty when applying the ESC/ESH guideline” and instead we continue to emphasise that given the heterogeneity of the older, frail population each patient should be considered for comprehensive geriatric assessment once frailty has been identified (with any tool) to help guide their BP treatment (see Conclusion section, paragraph 2).

Reviewer: In addition, the authors might also want to acknowledge that frailty itself may not even be the best construct for differentiating who might not benefit from more intensive blood pressure control. In both SPRINT and HYVET, recognizing both trials solely relied upon deficit accumulation, there really wasn’t any indication of treatment effect heterogeneity with respect to cardiovascular disease. There was certainly risk magnification where frailer adults benefited more in absolute terms because they were at higher risk, but the relative benefit didn’t vary much moving from lower to higher frailty index scores. In contrast, at least based on analyses we’ve done in SPRINT in adults older than 80 years of age, there does seem to be heterogeneity with respect to cognitive function (Pajewski et al., 2020). Almost all of the cardiovascular benefit in SPRINT was in participants with higher performance on the MoCA at baseline (and this same result holds in the larger 75+ subgroup). It may be that cognitive screening could be a more powerful differentiator in this case as compared to frailty. Of course, cognitive screening is not something that is done well in primary care either, there are numerous instruments to consider, and so it is an equally complicated screening problem to solve.

1. Response: We agree that frailty has not yet proven in the few existing RCTs to be the ideal construct (vs other geriatric dimension such as cognition) for differentiating who might not benefit from more intensive blood pressure control. We agree that at present the frailty paradigm is not quite ready for wide population screening, but awareness is important. Our aim is to stimulate further research in this area, ideally in robustly designed RCTs. We have acknowledged this in our conclusion by overtly stating that further research ideally in the form of RCTs may help guide this clinical question as to what construct or clinical dimension will be best used to help differentiate those who may benefit versus those who won't benefit (see paragraph 2 in the Conclusion section).

Minor Comments
“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." It should be mentioned that the randomized trials have shown no indication of increased risk of falls.

1. Response: Thank you for pointing this out. We have acknowledged this in our introduction by removing “injurious falls” from this sentence and have inserted a sentence highlighting that the RCTs have not demonstrated any risk of injurious falls citing this paper in the discussion section. (see Discussion, paragraph 1, References – number 21).

Reviewer: “In addition, neither trial used a frailty identification tool at enrolment to stratify patients by frailty status.”
True, but what is the relevance of this? SPRINT has done analyses based on baseline FI, and one does not need to stratify randomization in order for baseline subgroup analyses to be valid.

1. Response: Yes, thank this sentence is not necessarily relevant and we have removed it from the introduction.

Reviewer: Another limitation that should be mentioned is misclassification from relying upon a single blood pressure reading.

1. Response: Again this is an important point and we have added it in as a sentence in our limitations. (see Discussion section Paragraph 8)

Reviewer: 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.”
At least in America, this is totally infeasible. For example, in my health system, we have over 15-20k older patients identified as frail based on an eFI. It works out to ~30 frail patients for every single primary care provider we have, with <5% of those having specific geriatrics expertise. There is just no way to broadly do CGA.

1. Response: Yes, you are absolutely correct. In an ideal world comprehensive geriatric assessment (CGA) would be more accessible for all older adults who are frail. To acknowledge this, we changed the wording to each patient should be considered for comprehensive geriatric assessment in the discussion/conclusion (see conclusion, paragraph 2)

Competing Interests: No competing interests to disclose