


# Effects of age on blood pressure and heart rate responses to whey protein in younger and older men

Caroline Giezenaar PhD<sup>1,2</sup>  | Avneet Oberoi MSc<sup>2</sup> | Karen L. Jones PhD<sup>2,3</sup> |  
Michael Horowitz MBBS, PhD, FRACP<sup>2,3</sup> | Ian Chapman MBBS, PhD, FRACP<sup>2,3</sup> |  
Stijn Soenen PhD<sup>2,4</sup>

<sup>1</sup>Riddet Institute, Massey University,  
Palmerston North, New Zealand

<sup>2</sup>NHMRC Centre of Research Excellence  
in Translating Nutritional Science to Good  
Health, Adelaide Medical School, The  
University of Adelaide, Adelaide, South  
Australia, Australia

<sup>3</sup>Endocrine and Metabolic Unit, Royal  
Adelaide Hospital, Adelaide, South  
Australia, Australia

<sup>4</sup>Faculty of Health Sciences & Medicine,  
Bond University, Gold Coast, Queensland,  
Australia

## Correspondence

Stijn Soenen, PhD, Centre of Research  
Excellence in Translating Nutritional  
Science to Good Health, Adelaide Medical  
School, The University of Adelaide, Level  
5 Adelaide Health and Medical Sciences  
Building, Cnr North Tce and George St,  
Adelaide, SA 5000, Australia.  
Email: stijn.soenen@adelaide.edu.au

## Abstract

**Background:** Postprandial falls in blood pressure (BP) are more common in older compared to younger individuals. The effects of protein compared to carbohydrates and fat on postprandial BP, and the relation to gastric emptying rates, are poorly studied.

**Objectives:** To determine the effects of a whey protein compared to a control drink on systolic BP (SBP) and diastolic BP (DBP), and heart rate (HR) in healthy younger and older men, and to relate these effects to gastric emptying.

**Design:** A pooled analyses of two randomized, double-blind, cross-over studies.

**Setting:** Two acute clinical intervention studies with identical study design.

**Participants:** Nineteen older (age:  $74 \pm 1$  years, body mass index:  $26 \pm 1$  kg/m<sup>2</sup>) and 13 younger ( $23 \pm 1$  years,  $24 \pm 1$  kg/m<sup>2</sup>) healthy men.

**Intervention:** A 70 g/280 kcal whey-protein or control (water with diet cordial, ~2 kcal) drink (450 ml).

**Measurements:** BP and HR were assessed with an automated device immediately before and at 3-min intervals after drink ingestion (0–180 min). Gastric emptying of the drinks was measured using 3D ultrasonography (0–180 min).

**Results:** Older versus younger men exhibited a greater fall in SBP ( $-23 \pm 2$  vs  $-15 \pm 2$  mmHg,  $p = 0.001$ ) after whey-protein versus control, as BP did not change after the two drinks in younger men ( $p > 0.05$ ). The nadir in SBP occurred later in the older than younger men ( $114 \pm 11$  vs  $62 \pm 14$  min;  $p < 0.001$ ), with SBP still apparently declining 180 min after whey-protein ingestion in the older men. The magnitude of the rise in HR was greater ( $p < 0.05$ ) in the younger than older men.

**Conclusion:** Following ingestion of 70 g whey protein, healthy older men exhibited a sustained fall in BP, despite an increase in HR, whereas in younger men there was no change in BP. BP may need to be monitored after high protein meals in older people at risk of postprandial hypotension.

## KEYWORDS

aging, blood pressure, gastric emptying, heart rate, whey protein

## INTRODUCTION

Falls and syncope are common in older people.<sup>1</sup> Dizziness, syncope, and falls may reflect a substantial reduction in blood pressure (BP) induced by energy intake, so-called postprandial hypotension (PPH).<sup>2,3</sup> PPH occurs often in older people and represents a major cause of morbidity and mortality.<sup>4</sup> The prevalence of PPH ranges from ~13% in healthy older people<sup>5,6</sup> to ~24–36% in nursing home residents<sup>4,7,8</sup> and ~43% in hospitalized geriatric patients.<sup>9</sup>

We have reported that glucose, when infused directly into the duodenum, at rates within the normal range for gastric emptying (1–4 kcal/min), decreased postprandial systolic BP (SBP) and diastolic BP (DBP) in healthy older, but not younger, men, particularly during the first 60 min.<sup>10</sup> Similarly, after an oral glucose load, which is used often in the diagnosis of PPH,<sup>1</sup> the magnitude of the fall in SBP is greater when the rate of gastric emptying is relatively more rapid.<sup>11</sup> Other groups have similarly reported a greater reduction in SBP and DBP after mixed macronutrient meals in healthy older compared to younger adults.<sup>12</sup> The release of gut hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP),<sup>13–15</sup> and an impaired sympathetic nervous system response to compensate for the meal-induced splanchnic pooling are likely to be integral to the fall in SBP in older adults.<sup>16,17</sup>

There is increasing emphasis on the importance of protein, especially whey protein, consumption in older people, to prevent and manage malnutrition.<sup>18</sup> Information relating to the effects of protein on postprandial BP is limited, with some studies reporting a reduction in BP after protein,<sup>16,19</sup> whereas in other studies no effect was evident.<sup>20,21</sup>

PPH, defined as a sustained drop in SBP of  $\geq 20$  mmHg for  $\geq 30$  min,<sup>4</sup> is commonly diagnosed through measurement of BP for 2 h in response to a 75 g glucose load.<sup>1</sup> This timeframe, however, may not be sufficient to diagnose PPH following protein ingestion given its slower digestion time compared to glucose.<sup>22</sup> For example, administration of protein, carbohydrate, and fat (at a rate of 3 kcal/min) resulted in comparable reductions in SBP and a rise in superior mesenteric artery (SMA) blood flow (changes in SMA flow typically occur after nutrient ingestion) in healthy older men, but these responses were relatively delayed for protein and fat compared to glucose.<sup>16,23</sup>

The current study represents an analysis of secondary outcomes of previously published studies,<sup>24,25</sup> to determine the effect of orally ingested whey protein on SBP, DBP, heart rate (HR), and gastric emptying in healthy older and younger men. We hypothesized that older, when compared to younger, men will exhibit greater falls in SBP and DBP, and a smaller increase in HR, following whey protein ingestion compared to control.

### Key Points

- Following 70 g of whey protein ingestion, healthy older men exhibited a sustained fall in blood pressure, despite an increase in heart rate.
- In younger men, there was no fall in blood pressure in response to the protein.
- BP may need to be monitored after high protein meals in older people at risk of postprandial hypotension.

### Why Does this Paper Matter?

Postprandial blood pressure after protein supplements or high-protein meals may need to be monitored for at least 180 minutes in older people, particularly those at particular risk of postprandial hypotension.

## METHODS

### Subjects

Nineteen healthy older (age: mean  $\pm$  standard error of the mean [SEM]:  $74 \pm 1$  years; body weight:  $79 \pm 2$  kg; body mass index [BMI]:  $26 \pm 1$  kg/m<sup>2</sup>, 13 subjects from the study described in Giezenaar et al.<sup>24</sup> and six subjects from the study described in Giezenaar et al.<sup>25</sup>) and 13 younger men ( $23 \pm 1$  years;  $78 \pm 2$  kg;  $24 \pm 1$  kg/m<sup>2</sup> from Giezenaar et al.<sup>24</sup>) were included. Two older participants participated in both studies; only data from the most recent study<sup>24</sup> were included for these two participants. The exclusion criteria were smoking, alcohol abuse, use of illicit substances, (at risk of) diabetes mellitus ( $\text{HBA}_{1\text{C}} > 6.0$  mmol/L), major disease (i.e., cancer, Parkinson's, multiple sclerosis, etc.), gallbladder, or pancreatic disease, gastrointestinal surgery (apart from an uncomplicated appendectomy), significant gastrointestinal symptoms (abdominal pain, gastro-esophageal reflux, diarrhea, or constipation), use of medications known to potentially affect gastrointestinal motor function, known lactose intolerance, low plasma ferritin levels, or blood donation in the 12 weeks before the study, and cognitive impairment.

Four older men took anti-hypertensive medication (angiotensin-converting enzyme inhibitor,  $n = 1$ ; anti-arrhythmic,  $n = 1$ ; beta blockers,  $n = 1$ ; and angiotensin

receptor blockers,  $n = 1$ ). Participants were instructed not to take their medication on the morning of their study visit.

The study protocols were approved by the Royal Adelaide Hospital Research Ethics Committee (120503a and 140407, clinical trial registration: ACTRN12612000941864 and ACTRN12614000846628, [www.anzctr.org.au](http://www.anzctr.org.au)), and the studies were conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

## Protocol

Both studies included in this pooled data analysis had an identical protocol and a randomized double-blind cross-over design (using the method of randomly permuted blocks; [www.randomization.com](http://www.randomization.com)) including 3<sup>25</sup> or 4<sup>24</sup> study days, separated by 3–14 days. The sub-analysis related to two of these conditions, which were included in both studies (control and 70 g whey protein).

On study days, subjects fasted for ~14 h overnight, after consuming a standardized evening meal (beef lasagne [McCain Foods Pty Ltd, Australia], ~591 kcal), attended the laboratory at ~08:30 h, and ingested test drinks containing 70 g (280 kcal) whey protein or a control drink (~2 kcal).<sup>24,25</sup> The drinks were prepared by a research assistant who was not involved in the analysis of the study results, flavored with diet lime cordial (Bickford's Australia Pty Ltd, South Australia) to match for taste, and served at room temperature. Drinks were presented in a covered cup to achieve blinding. Upon arrival, participants were seated in a chair, and a cannula was inserted for blood sampling (results not presented in this manuscript). An automated BP monitor (DINAMAP ProCare 100; GE Medical Systems, Milwaukee, WI) was used to measure SBP, DBP, and HR. Subjects were studied for 180 min after drink ingestion, and were seated for the duration of the study.

## Measurements

### Blood pressure and heart rate

Measurements were taken three times immediately after the other at baseline (before drink ingestion), and every 3 min in the 3 h following the drink (0–180 min). Baseline BP and HR were calculated as an average of the three baseline measurements.  $T = 0$  min refers to the point immediately after drink consumption.

### Perceptions of light-headedness and drowsiness

At baseline,  $T = 0$  min, and every 15 min after the drink, perceptions of light-headedness and drowsiness were assessed using a visual analog scale which consisted of a 100-mm horizontal line for each outcome. Participants were asked to place a mark indicating the strength of the sensation at the specified times.

### Gastric emptying

At baseline,  $T = 0$  min and every 15 min after drink ingestion, gastric volume was determined using 3-dimensional ultrasonography (Logiq 9, GE Healthcare Technologies, Australia), a method that has been validated against the “gold standard” scintigraphy for measurement of gastric emptying.<sup>26</sup> Intragastric retention was calculated as total gastric volume minus baseline “empty” gastric volume at each time point, expressed as a percentage of the maximal gastric volume (100%), that is, ~450 ml volume of the ingested drink. The time at which 50% of the drink was emptied from the stomach (50% gastric emptying time; T50; min) was calculated.

### Statistical analysis

Statistical analyses were performed using SPSS software (version 25; IBM, Armonk, NY). Interaction effects of age and treatment were determined using a two-way repeated-measures analysis of variance (ANOVA), with age as the between-subject factor, and treatment as the within-subject factor. Effects of age, time, and their interaction were determined within treatment groups. For SBP, DBP, and HR, areas under the curve (AUC) were calculated from baseline to 180 min, using the trapezoidal rule. Cumulative changes from baseline were calculated for SBP, DBP, and HR (0–60 min, 60–120 min, and 120–180 min) by subtracting baseline values from the value at each time point, such that larger negative values indicate larger excursions below baseline, and larger positive values correspond to excursions above baseline. Nadir and time to nadir of SBP and DBP, and peak and time to peak of HR, light-headedness, and drowsiness were determined between 0 and 180 min. Assumptions of normality were verified for all outcomes before statistical analysis. Statistical significance was accepted at  $p < 0.05$ . Data in the text and tables are presented as mean values  $\pm$  SEM.

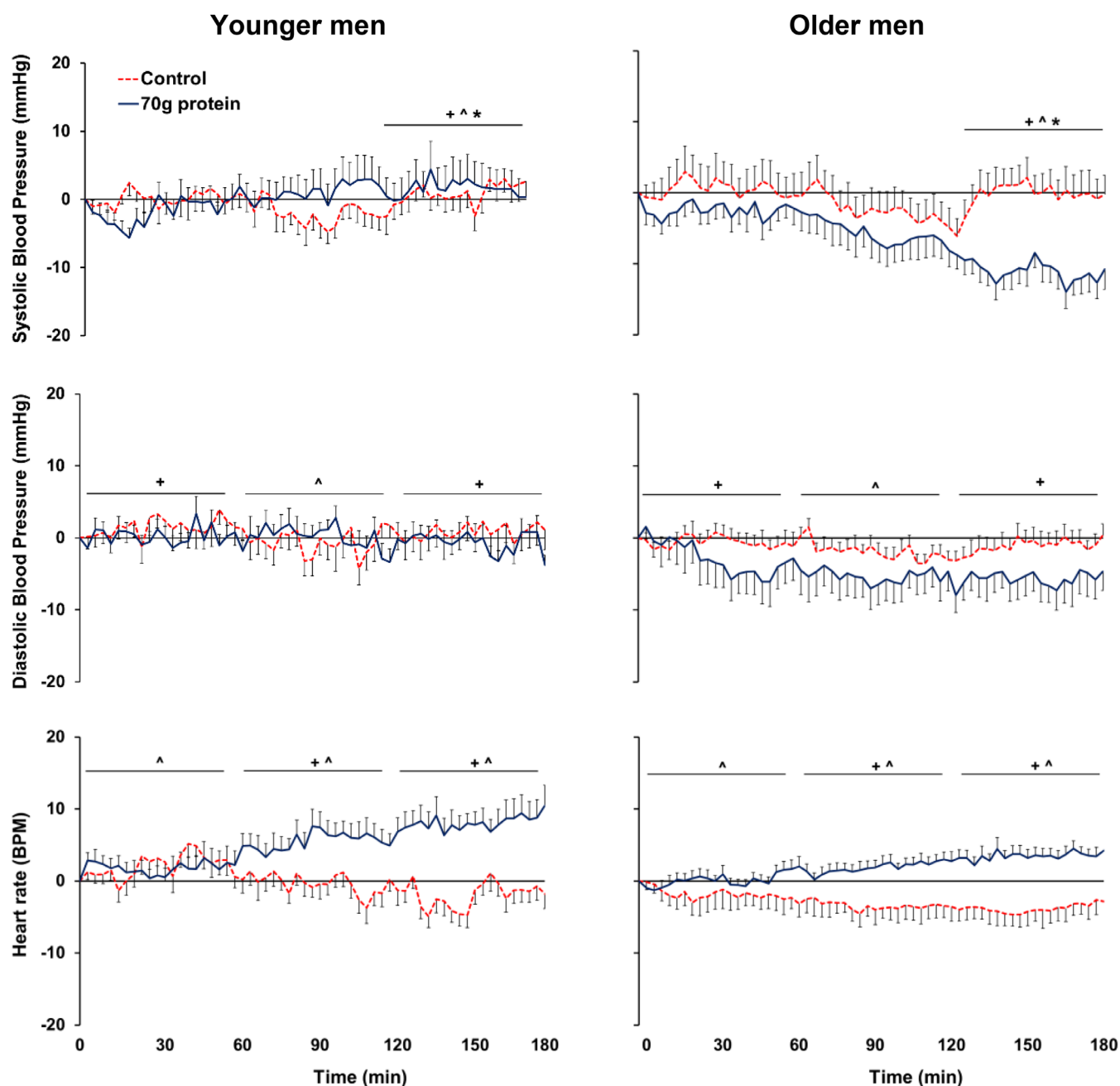
## RESULTS

The protocol was well tolerated in all participants. Ultrasound images were of poor quality in four older and two younger men and therefore all gastric emptying data were excluded from analyses for these participants.

## Systolic blood pressure

Baseline SBP was higher in older than younger men (older vs younger: control, protein drink:  $130 \pm 3$ ,  $131 \pm 3$  vs  $116 \pm 3$ ,  $120 \pm 4$  mmHg; age main effect  $p = 0.005$ ).

In older, but not younger men, there was a fall in SBP from baseline following the protein drink but not control.



**FIGURE 1** Mean ( $\pm$ standard error of mean [SEM]) cumulative changes from baseline of systolic and diastolic blood pressure (mmHg) and heart rate (beats per minute [BPM]) in 13 healthy younger and 19 healthy older men following control ( $\sim 2$  kcal), and protein (70 g whey protein, 280 kcal), drinks. Effects of drink condition, age, and the drink by age interaction effect were determined for cumulative changes from baseline between 0–60 min, 60–120 min, and 120–180 min by repeated-measures ANOVA with post hoc Bonferroni corrections.  $^+p < 0.05$ , the overall effect of drink condition;  $^{\wedge}p < 0.05$ , the overall effect of age.  $^*p < 0.05$ , post hoc study drink effect within the age group, control is significantly different from protein condition

As the older men had higher baseline SBPs than younger men, absolute SBPs remained higher after control (older vs younger:  $129 \pm 3$  vs  $115 \pm 3$  mmHg,  $p = 0.006$ ), but were similar after protein ( $123 \pm 3$  vs  $118 \pm 3$  mmHg,  $p = 0.27$ ), in older compared to younger men ( $AUC_{0-180\text{min}}$  interaction effect of age by drink  $p = 0.010$ ). The greatest difference in the SBP response to treatments between the two age groups occurred in the third hour after drink consumption: there was a fall in SBP (cumulative change from baseline 120 to 180 min; interaction effect of age by drink  $p = 0.015$ ) following the whey protein drink compared to control in the older (protein vs control:  $-11 \pm 2$  vs  $0 \pm 2$  mmHg,  $p = 0.001$ ), but not younger ( $2 \pm 3$  vs  $1 \pm 2$  mmHg,  $p = 0.84$ ), men.

In older (protein vs control nadir:  $-23 \pm 2$  vs  $-15 \pm 2$  mmHg,  $p = 0.001$ ), but not younger ( $-13 \pm 2$  vs  $-13 \pm 2$  mmHg,  $p = 0.96$ ), men SBP maximum decrease was larger after the protein compared to control drink (interaction effect of age by drink  $p = 0.033$ ; Figure 1). Furthermore, the nadir in SBP occurred later in the older than younger men, independent of the study drink (older vs younger:  $114 \pm 11$  vs  $62 \pm 14$  min; age main effect  $p < 0.001$ ), and SBP was still apparently falling at the end of the study period (3 h after drink ingestion) in the older men.

## Diastolic blood pressure

Baseline DBP was higher in older compared to younger men (older vs younger: control, protein drink:  $76 \pm 2$ ,  $76 \pm 2$  vs  $67 \pm 1$ ,  $67 \pm 2$  mmHg; age main effect,  $p < 0.001$ ).

In older, but not younger men, there was a fall in DBP from baseline in response to the protein drink but not control. Accordingly, absolute DBPs were higher after control (older vs younger:  $75 \pm 2$  vs  $67 \pm 2$  mmHg,  $p = 0.005$ ), but not after protein ( $71 \pm 1$  vs  $67 \pm 2$  mmHg,  $p = 0.09$ ), in older compared to younger men ( $AUC_{0-180\text{min}}$  interaction effect of age by drink,  $p = 0.037$ ).

The maximum fall in DBP was greater in older than younger men, independent of the study drink (older vs younger:  $-14 \pm 1$  vs  $-11 \pm 1$  mmHg, age main effect,  $p = 0.050$ ; Figure 1). Between 60 and 120 min, there was a further fall in DBP in the older (cumulative change from baseline 60 to 120 min:  $-4 \pm 1$  mmHg), but not younger ( $0 \pm 2$  mmHg), men, independent of study drink (age main effect,  $p = 0.047$ ).

## Heart rate

Baseline HR was not significantly different between age groups (older vs younger: control, protein drink:  $59 \pm 2$ ,

$59 \pm 2$  beats per minute [BPM] vs  $65 \pm 4$ ,  $65 \pm 3$  BPM; age main effect,  $p = 0.15$ ).

Independent of the study drink, older compared to younger men had lower absolute HRs (older vs younger:  $AUC_{0-180\text{min}}$   $58 \pm 2$  vs  $66 \pm 3$  BPM; age main effect,  $p = 0.013$ ). Regardless of the age group, absolute HR was higher after the protein drink compared to the control drink (control vs protein:  $60 \pm 2$  vs  $65 \pm 2$  BPM; drink main effect,  $p < 0.001$ ).

HR increased less from baseline in older than younger men during the first (cumulative change from baseline 0 to 60 min: older vs younger: control:  $-2 \pm 1$  vs  $2 \pm 1$  BPM, protein:  $0 \pm 1$  vs  $2 \pm 1$  BPM; age main effect,  $p = 0.021$ ), second (60–120 min: control:  $-3 \pm 1$  vs  $0 \pm 1$  BPM, protein:  $2 \pm 1$  vs  $6 \pm 2$  BPM);  $p = 0.016$ ), and third (120–180 min: control:  $-4 \pm 1$  vs  $-2 \pm 1$  BPM, protein:  $3 \pm 1$  vs  $8 \pm 2$  BPM;  $p = 0.029$ ) hour after drink consumption, independent of the study drink. The maximum increase in HR was less in older than younger men, independent of the study drink (older vs younger:  $6 \pm 1$  vs  $15 \pm 3$  BPM; age main effect,  $p < 0.001$ , Figure 1).

## Postprandial hypotension

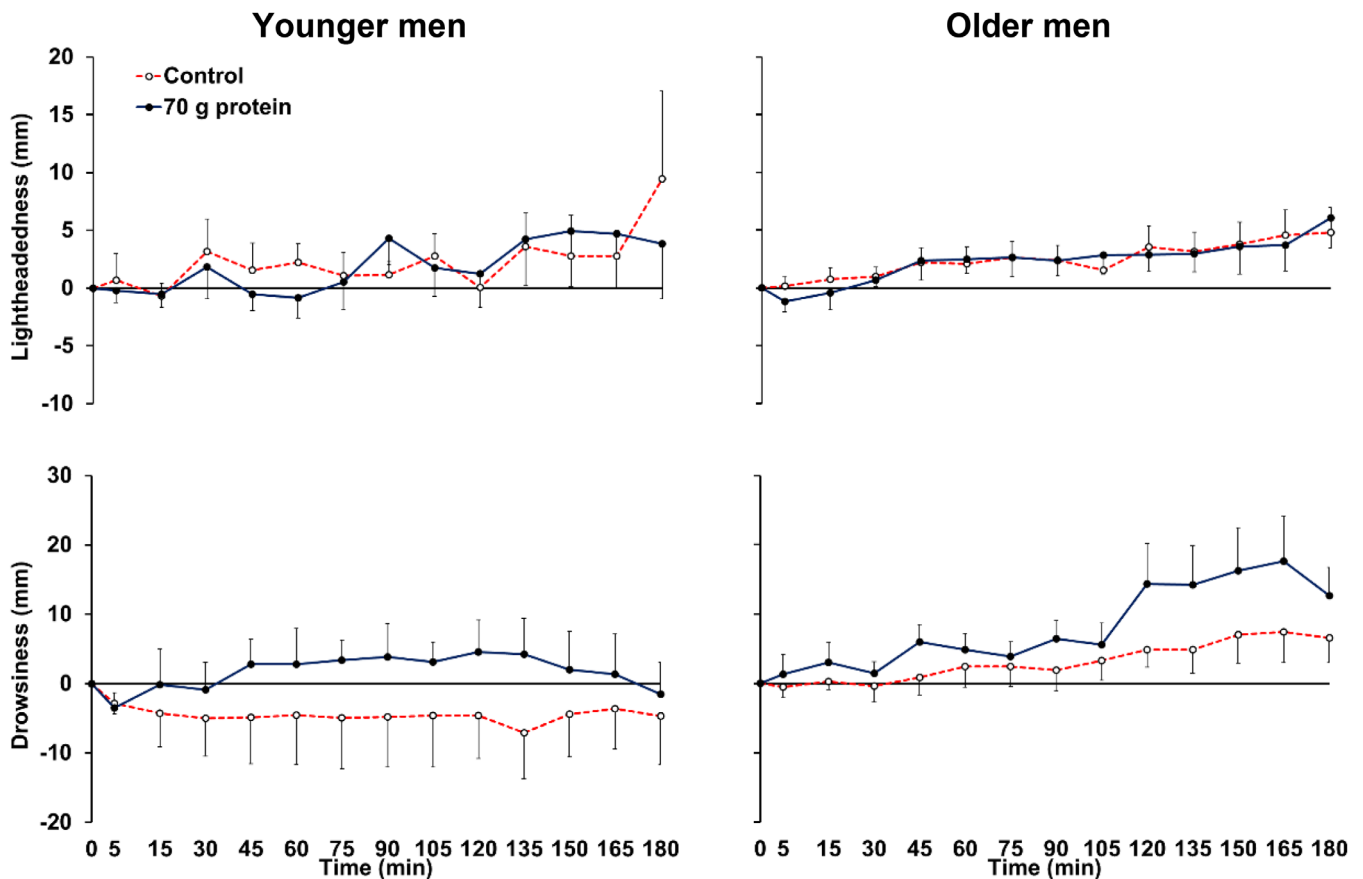
In response to the control drink, 26% of older (5/19) and 23% of younger (3/13) men experienced a  $\geq 20$  mmHg decrease from baseline in SBP at some time during the following 3 h. Following the definition of PPH as a decrease of  $\geq 20$  mmHg sustained for  $\geq 30$  min in SBP after nutrient ingestion; 10% of older (2/19) and 0% of younger men had PPH after control drink ingestion.

In response to the whey protein drink, 58% older (11/19) and 23% of younger (3/13) men demonstrated a fall of  $\geq 20$  mmHg in SBP at some time during the 3 h, and 10% of older (3/19) and 0% of younger men had PPH after whey protein drink ingestion. In two of those three older men, the onset of that fall was more than 120 min after whey drink consumption. In two additional older men, there was a fall of  $\geq 20$  mmHg in the six BP measurements before the end of the study period (from  $T = 165$  to 180 min after whey ingestion). As subjects were only followed until  $T = 180$  min, these two subjects may have had a sustained decrease in SBP  $\geq 20$  mmHg for  $\geq 30$  min.

## Perceptions of light-headedness and drowsiness

There were no age, treatment, or interaction effects on AUC or cumulative changes from baseline for





**FIGURE 2** Mean ( $\pm$ standard error of mean [SEM]) cumulative changes from baseline for perceptions of light-headedness and drowsiness in 13 healthy younger and 19 healthy older men following control ( $\sim 2$  kcal), and protein (70 g whey protein, 280 kcal), drinks. Effects of age, time, and age by time interaction effect within the study drink conditions were determined by repeated-measures ANOVA. Drowsiness: the overall effect of time:  $p = 0.031$ . Data are mean ( $\pm$ standard error of mean [SEM]) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

perceptions of light-headedness or drowsiness (Figure 2). Regardless of the age group, perceptions of drowsiness increased after administration of the protein drink (time main effect,  $p = 0.031$ ), and peak drowsiness was higher after the protein compared to the control drink ( $p = 0.011$ ).

### Gastric emptying

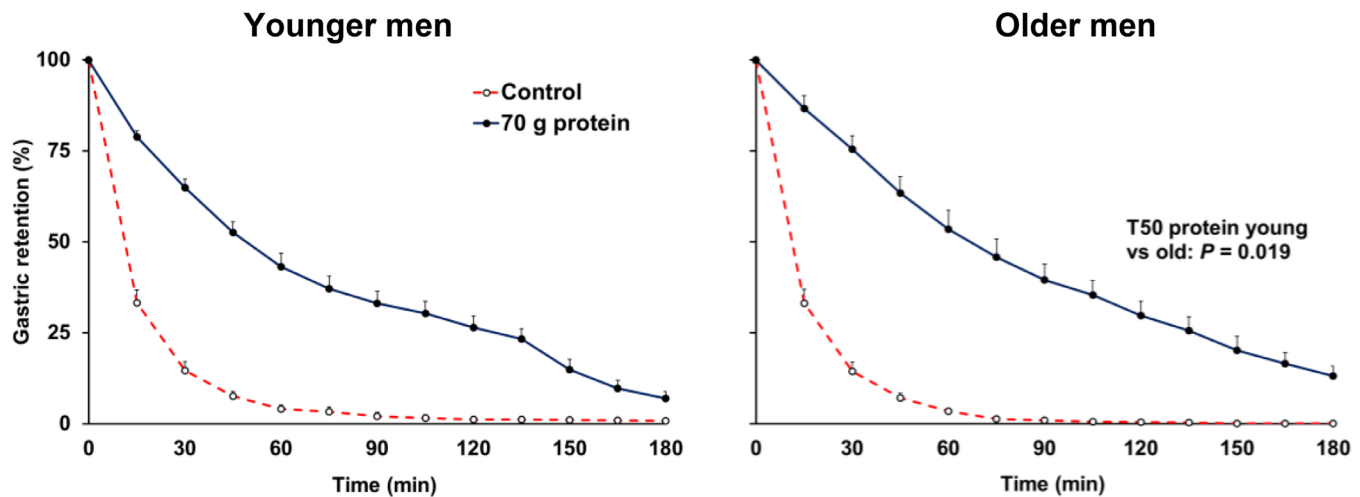
In older men, gastric emptying of the protein drink (T50; older vs younger:  $70 \pm 6$  min vs  $58 \pm 9$  min,  $p = 0.019$ ), but not control ( $12 \pm 1$  vs  $12 \pm 1$  min,  $p = 0.15$ ), was slower, when compared to the younger men (interaction effect of age by study drink,  $p = 0.027$ ; Figure 3).

## DISCUSSION

Our study has established that, in response to a 280 kcal (70 g) whey protein drink (450 ml) ingestion, healthy

older men exhibit a substantial decrease in SBP and DBP, whereas younger men maintained their BP at a level comparable to that after an iso-volumic, non-caloric, drink. Furthermore, in the older subjects, the fall in BP was sustained until at least 180 min after consumption of the drink. There was an increase in HR after the protein drink, but this increase in HR was greater in the younger than older men. The perception of drowsiness, but not light-headedness, was greater after protein irrespective of age.

The use of protein supplements to aid undernutrition in older people is increasing, and PPH is particularly common in institutionalized older patients, who are more likely to take nutritional supplements.<sup>18</sup> It is certainly not appreciated that PPH is a potential outcome of the use of protein supplements in this group; with emergent increased rates of falls, syncope, and death.<sup>1</sup> All our participants were seated, and orthostatic hypotension was not assessed. Posture likely affects postprandial BP<sup>27</sup> and it is possible that the lowering of BP that occurred in the older subjects may



**FIGURE 3** Mean ( $\pm$ standard error of mean [SEM]) gastric retention (%) in 11 healthy younger and 14 healthy older men following control ( $\sim$ 2 kcal), and protein (70 g whey protein, 280 kcal), drinks. Effects of drink-condition, age, and the drink-by-age interaction effect were determined by repeated-measures ANOVA with post hoc Bonferroni corrections. Interaction effect of age by drink condition:  $p = 0.027$  [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

have been caused partially by the upright seated position during the study.

Our observations also indicate that, in studies evaluating BP after protein administration, BP should be monitored for a minimum of 3 h. PPH is defined as a sustained fall in BP  $\geq 20$  mmHg within 2 h of a meal.<sup>4</sup> This definition is based on the outcome of studies using high-carbohydrate meals or glucose drinks to diagnose PPH, and our observations suggest that the definition should be modified to increase this time frame—at least after a high protein (i.e., more than 30 g) meal or supplement.

The current findings are consistent with our previous observations, which showed a decrease in BP in response to intraduodenal glucose infusion in older, but not younger, adults.<sup>10</sup> We have also reported a more delayed hypotensive response after an intraduodenal infusion of protein compared to glucose in healthy older people.<sup>16</sup> This difference may be attributed to differences in time for digestion of carbohydrates and protein<sup>22</sup> to stimulate an increase in SMA blood flow response<sup>23</sup>; that is, the fall in BP may be triggered by amino acids, the digestion products of protein. In the younger subjects, the rise in HR induced by the protein drink was greater than in the older subjects, which is likely to contribute to the maintenance of BP despite a substantial increase in splanchnic blood flow in both age groups.<sup>10</sup> The increase in splanchnic blood flow after the protein drink may be reflected by the increase in perceptions of drowsiness which occurs in both age groups. In contrast with our results, another study with a very similar study design, in which BP was measured every 5 min for 150 min after 75 g oral loads of glucose, whey protein, and cream, older hypertensive

patients showed a fall in SBP and DBP after glucose, but not after fat and protein. Furthermore, HR increased after glucose and fat but was not affected by protein intake.<sup>20</sup> In the current study, participants were seated throughout the study (i.e., 3 h), whereas the participants in the described study<sup>20</sup> were in a semi-recumbent position, reducing effects of potential orthostatic hypotension. In patients with autonomic failure, the fall in postprandial BP was also larger after carbohydrates and fat,<sup>28</sup> and in healthy young subjects, two iso-caloric loads containing 92 g of either carbohydrates or protein resulted in increased cardiovascular output and ventricular contractility after carbohydrates compared to protein.<sup>29</sup> These studies may suggest that even though we reported a fall in BP after protein, this fall may not be as large as a fall in response to carbohydrates.

As shown in this study, gastric emptying of protein was slower in the older compared to younger subjects.<sup>24,25</sup> Slower gastric emptying should, intuitively, be associated with increased, and more sustained, gastric distension which is known to attenuate the postprandial fall in BP.<sup>17</sup> In older people, this may, in part, represent a compensatory mechanism to reduce the magnitude of a fall in BP after a meal.

This study has several potential limitations. The study represents a pooled data analysis from two separate studies, and whereas the methodology in terms of inclusion criteria, timeline, and drink composition were identical in both studies, there is the inherent potential for bias. We evaluated the effects of a relatively large protein dose (70 g), representative of a normal daily intake of protein—a meal typically contains 15–30 g of protein. Protein supplements used to manage undernutrition in older

people typically contain 10–25 g protein, and therefore, use of these may not necessarily be associated with falls in BP as large as those observed in this study. We only studied whey protein, and therefore, the results may not apply to other protein sources. We only studied healthy men, and therefore, the results may not be translatable to women. Given that there was a fall in BP in response to whey protein in healthy older men, it is likely that the fall would be greater in populations at risk of PPH (e.g., diabetic, hospitalized and geriatric patients, and patients with neurological disorders). This warrants investigation as these are patient groups that are most likely to benefit from increased protein intake through the use of protein supplements. We did not measure autonomic nerve function or orthostatic BP, and therefore we were unable to determine whether nerve dysfunction may be an underlying factor in the age-related results on BP and gastric emptying reported in this study. We acknowledge that the inclusion of participants with hypertension may have affected the BP responses in older adults.

In summary, healthy older men exhibited a sustained fall in systolic and diastolic BP, despite an increase in HR, following ingestion of 70 g whey protein, whereas in younger men the increase in HR was greater and there was no change in BP. In future research, it should be investigated whether the substitution of carbohydrates and/or fat by protein slows gastric emptying, and thereby attenuates the postprandial fall in BP in older people. In conclusion, these observations suggest that postprandial BP after protein supplements or high protein meals may need to be monitored in older people, particularly those at particular risk of PPH.

## ACKNOWLEDGMENTS

## FINANCIAL DISCLOSURE

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## CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

## AUTHOR CONTRIBUTIONS


Caroline Giezenaar, Michael Horowitz, Ian Chapman, and Stijn Soenen conceptualized and designed the research. Caroline Giezenaar, Avneet Oberoi, and Stijn Soenen acquired the data. Caroline Giezenaar, Avneet Oberoi, Karen L. Jones, Michael Horowitz, Ian Chapman,

and Stijn Soenen analyzed and interpreted the data. Caroline Giezenaar and Stijn Soenen drafted the manuscript. Ian Chapman, Karen L. Jones, and Michael Horowitz critically revised the manuscript. Stijn Soenen has primary responsibility for the final content. The authors would like to thank Kylie Lange for her contribution to the statistical analyses in this manuscript.

## SPONSOR'S ROLE

Fonterra and the Royal Adelaide Hospital Research Fund did not have any input in the design, implementation, analysis, or interpretation of the data.

## ORCID

Caroline Giezenaar  <https://orcid.org/0000-0001-5612-1918>

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