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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
FACULDADE DE MEDICINA

ASSOCIAÇÃO DO ÁCIDO GRAXO POLI-INSATURADO ÔMEGA-3 COM A MASSA E A FORÇA MUSCULAR

LUANA THOMAZETTO ROSSATO

DOUTORADO
2020

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ASSOCIAÇÃO DO ÁCIDO GRAXO POLI-INSATURADO ÔMEGA-3 COM A MASSA E A FORÇA MUSCULAR

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do título de Doutora em Ciências da Saúde.

Área de concentração: Ciências da Saúde.
Orientador: Prof. Dr. Erick Prado de Oliveira.
Co-orientadora: Profª. Drª. Ana Elisa Madalena Rinaldi.

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Defesa de:	Tese de Doutorado Nº 003/PPCSA				
Data:	06 de março de 2020	Hora de início:	08:30h	Hora de encerramento:	13:30h
Matrícula do Discente:	11813CSD019				
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Reuniu-se no anfiteatro do bloco 4K, Campus Umuarama, da Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Ciências da Saúde, assim composta: Professores Doutores: Jaqueline Lopes Pereira França (USP) e Hamilton Roschel (USP) via *skype*, Luciana Saraiva da Silva (UFU), Cibele Aparecida Crispim (UFU) e Erick Prado de Oliveira orientador da candidata presentes no recinto.

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FOLHA DE APROVAÇÃO

Luana Thomazetto Rossato.

Associação do ácido graxo poli-insaturado ômega-3 com a massa e a força muscular

Presidente da banca: Prof. Dr. Erick Prado de Oliveira

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Área de concentração: Ciências da Saúde.

Banca Examinadora

Titular: Profª. Drª. Jaqueline Lopes Pereira França

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Instituição: Universidade Federal de Uberlândia

DEDICATÓRIA

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EPÍGRAFE

"É preciso ter o prazer como uma das referências para o trabalho, mas não como referência exclusiva. Sempre é necessário um desgaste para que você atinja um resultado."

Mário Sérgio Cortella

RESUMO

O envelhecimento está relacionado com a diminuição de força e massa muscular, o que pode provocar diversos malefícios ao indivíduo. Desta forma, estratégias nutricionais que possam impactar positivamente nessa situação são de grande importância. Nesse sentido, se inclui o ômega-3 (ω-3), o qual é uma gordura poli-insaturada que apresenta vários benefícios à saúde, e que, recentemente, tem sido apontado como potencial nutriente para impactar na força e massa muscular. Assim, o objetivo da presente tese foi avaliar a associação entre o ω-3 e a força muscular. Foram desenvolvidos três artigos, sendo uma revisão narrativa (artigo 1) e os demais com desenho transversal (artigos 2 e 3). A revisão narrativa mostrou que o ω-3 parece não promover aumentos na massa muscular em jovens e idosos sedentários, há resultados conflitantes entre os estudos quando ocorre associação de treinamento físico e não há consenso em relação à efeitos na função muscular de idosos. Assim sendo, a evidência científica ainda é limitada. Diante deste contexto, realizamos dois estudos transversais envolvendo dados do *National Health and Nutrition Examination Survey* (NHANES). No primeiro estudo transversal (NHANES 1999-2002), envolvendo indivíduos entre 50-85 anos, foi avaliada a associação entre a ingestão alimentar de ω-3 e força isocinética dos extensores do joelho (pico de força). Foi observado que o consumo de ω-3 foi positivamente associado com a força muscular em homens, mas não em mulheres. Além disso, após realizarmos análise de substituição isocalórica de outros tipos de gordura por ω-3, não foram observadas diferenças significativas. No segundo artigo transversal (NHANES 2011-2012), investigamos a associação dos níveis plasmáticos de ω-3 e a ingestão alimentar desta gordura com a força de preensão muscular em indivíduos adultos (acima de 20 anos). Foi observada associação positiva da força de preensão manual com o DHA plasmático (homens mais jovens) e com o ω-3 total do sangue para homens mais velhos. Com relação ao ω-3 da dieta, foi observada associação positiva entre o consumo de DHA e a força muscular em homens mais velhos. Para as mulheres, nenhuma associação significativa foi observada após a inserção dos ajustes tanto na avaliação do plasma quanto na análise dietética. Em conclusão, foram encontradas associações significativas apenas para o grupo masculino, mas não para mulheres. Desta forma, sugere-se que os próximos estudos avaliem esses grupos separadamente, uma vez que as associações foram sexo-dependente. Assim, mais estudos são necessários envolvendo esse tema, afim de melhor elucidar a relação entre o ω-3 e a saúde muscular.

Palavras-chave: ômega-3; força muscular; massa muscular; envelhecimento.

ABSTRACT

Aging is related to the decrease in strength and muscle mass, which can cause several health problems to the individual. Thus, nutritional strategies that can positively impact this situation are of great importance. In this sense, omega-3 (ω-3) is included, which is a polyunsaturated fat that has numerous health benefits, and which has recently been identified as a potential nutrient to impact muscle strength and mass. Thus, the objective of the present thesis was to evaluate the association between ω-3 and muscle strength. Three articles were developed, one being a narrative review (article 1) and the others with a cross-sectional design (articles 2 and 3). The narrative review showed that ω-3 does not seem to promote increases in muscle mass in sedentary young and elderly people, there are conflicting results between studies when there is an association between physical training and there is no consensus regarding the effects on muscle function in the elderly. Therefore, the scientific evidence is still limited. In this context, we conducted two cross-sectional studies involving data from the National Health and Nutrition Examination Survey (NHANES). In the first cross-sectional study (NHANES 1999-2002), involving individuals aged 50-85 years, the association between ω-3 food intake and isokinetic strength of the knee extensors (peak strength) was evaluated. It was observed that the consumption of ω-3 was positively associated with muscle strength in men, but not in women. In addition, after performing an isocaloric substitution analysis of other types of fat with ω-3, no significant differences were observed. In the second cross-sectional article (NHANES 2011-2012), we investigated the association of plasma levels of ω-3 and the food intake of this fat with muscle handgrip strength in adult individuals (over 20 years old). A positive association between handgrip strength and plasma DHA (younger men) and total blood ω-3 was observed for older men. Regarding dietary ω-3, a positive association was observed between DHA consumption and muscle strength in older men. For women, no significant association was observed after the insertion of adjustments in both plasma assessment and dietary analysis. In conclusion, significant associations were found only for the male group, but not for women. Thus, it is suggested that the next studies evaluate these groups separately, since the associations were sex-dependent. Thus, further studies are needed involving this topic, in order to better elucidate the relationship between ω-3 and muscle health.

Keywords: omega-3; muscle strength; muscle mass; aging.

LISTA DE ILUSTRAÇÕES

Revisão da literatura

Artigo 1 – Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults?

Artigo 2 – Association between omega-3 fatty acids intake and muscle strength in older adults: a study from National Health and Nutrition Examination Survey (NHANES) 1999-2002.

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Artigo 2 – Association between omega-3 fatty acids intake and muscle strength in older adults: a study from National Health and Nutrition Examination Survey (NHANES) 1999-2002.

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LISTA DE ABREVIATURAS E SIGLAS

ALA - Ácido alfa-linolênico

CDC - *Centers for Disease Control and Prevention*

CID-10 - Classificação Internacional de Doenças e Problemas Relacionados à Saúde

COX - Ciclo-oxigenase

DHA - Ácido docosahexaenoico

DPA - Ácido docosapentaenoico

DRI – *Dietary Reference Intake*

EPA - Ácido eicosapentaenoico

ETA - Ácido eicosatetraenoico

EUA - Estados Unidos da América

LOX - Lipo-oxigenase

NCHS - *National Center for Health Statistics*

NHANES - *National Health and Nutrition Examination Survey*

SDA - Ácido estearidônico

SPM – Síntese proteica muscular

Ω-3 – Ômega-3

Ω-6 - Ômega-6

SUMÁRIO

1 INTRODUÇÃO

A expectativa de vida tem aumentado na maioria dos países (HO; HENDI, 2018), inclusive no Brasil (IBGE, 2018), resultando no crescimento do número de pessoas mais velhas. Esse cenário pode influenciar a condição de saúde dos indivíduos, assim como outras variáveis, incluindo os hábitos de vida (REHM, 2011; WARBURTON; BREDIN, 2017; WEST, 2017) e o consumo alimentar (WILLETT; STAMPFER, 2013). Quando associados, esses fatores podem impactar negativamente sobre a condição da musculatura esquelética do indivíduo (TIELAND; TROUWBORST; CLARK, 2018).

Nesse sentido, a sarcopenia, situação em que ocorre redução da força, massa muscular e, em algumas ocasiões, da capacidade funcional (CRUZ-JENTOFT *et al.*, 2019; CRUZ-JENTOFT *et al.*, 2019), é frequentemente associada a pior qualidade de vida (SILVA NETO *et al.*, 2016), menor independência (DOS SANTOS *et al.*, 2017) e maior mortalidade (BROWN; HARHAY; HARHAY, 2016; SIPERS *et al.*, 2019).

É bem documentado que a determinação da composição corporal, força e capacidade funcional é multifatorial. No que diz respeito aos hábitos de vida, a inatividade física é associada com menor quantidade de massa muscular e maiores níveis de gordura (PIETILAINEN *et al.*, 2008), além de menor força (LANGHAMMER; BERGLAND; RYDWIK, 2018). Em relação aos hábitos alimentares, dietas com maior teor proteico quando comparadas as atuais recomendações parecem exercer efeito benéfico sobre a saúde muscular (GREGORIO *et al.*, 2014; VERLAAN *et al.*, 2017). Entretanto, outros nutrientes da dieta têm sido estudados por apresentarem associações e/ou efeito na massa muscular esquelética e função física, como o ácido graxo poli-insaturado ômega-3 (ω-3) (REINDERS *et al.*, 2015; ROBINSON *et al.*, 2008; SMITH *et al.*, 2015).

A literatura atual aponta evidência científica conflitante sobre a relação entre oω-3 e a força muscular (ROSSATO; SCHOENFELD; DE OLIVEIRA, 2020), sendo que um único estudo encontra associação positiva entre o ácido alfa-linolênico (ALA) plasmático e a força muscular (REINDERS *et al.*, 2015). Ensaios clínicos mostram efeitos benéficos sobre a massa muscular, força e capacidade funcional (LOGAN; SPRIET, 2015; NOREEN *et al.*, 2010; ROBINSON *et al.*, 2008; STRANDBERG *et al.*, 2015) apesar de não serem consenso (CORNISH; CHILIBECK, 2009; HARDEN *et al.*, 2014). Além disso, os estudos são heterogêneos e apresentam várias limitações, o que dificulta conclusões sobre o tema (ROSSATO; SCHOENFELD; DE OLIVEIRA, 2020).

Assim, diante desse contexto, o aumento do número de indivíduos idosos acometidos redução da força muscular é preocupante, uma vez que esses indivíduos podem sofrer efeitos deletérios sobre a saúde. Portanto, averiguar fatores dietéticos potencialmente associados à melhor condição de saúde dos mesmos, como o ω-3, é necessário.

2 FUNDAMENTAÇÃO TÉORICA

2.1 Envelhecimento populacional

O aumento da expectativa de vida da população tem sido observado em todo o mundo. No Brasil, por exemplo, a expectativa de vida ao nascer era de 45,5 anos no ano de 1940, aumentando a 76 anos em média (72,5 anos para homens e 79,6 anos para mulheres) em 2017 (IBGE, 2018). Essa situação pode ser explicada por vários fatores, incluindo a dinâmica do crescimento populacional (BOVOLENTA; FELICIO, 2017) e dos padrões de morbimortalidade (MCKEOWN, 2009).

Compreendido nesse contexto, se insere o conceito de transição demográfica, o qual diz respeito às variações do crescimento populacional. Vários pesquisadores propuseram essa teoria, sendo que Adolphe Landry e Warren Thompson foram pioneiros na apresentação de um padrão regular de mudança populacional (BLUE; ESPENSHADE, 2011). Ao redor do mundo, apesar das populações apresentarem diferenças quanto ao nível de desenvolvimento econômico e social (FREEDMAN, 2017), e ao momento da transição em que se encontram (BONGAARTS; WATKINS, 1996), elas exibem padrões semelhantes (BLUE; ESPENSHADE, 2011).

Para destacar os pontos mais importantes da transição demográfica, os pesquisadores demarcaram “estágios”, os quais são indicativos de alterações nos padrões de mortalidade e fertilidade (BLUE; ESPENSHADE, 2011). Quatro fases principais são relatadas, sendo elas: 1) pré-transição: altas taxas de óbitos e nascimentos, levando baixo crescimento populacional; 2) queda nas taxas de mortalidade e manutenção das altas taxas de natalidade, contribuindo para o rápido crescimento populacional; 3) queda nas taxas de natalidade, mas a qual se mantém bem superior à taxa de mortalidade, cooperando com o contínuo aumento da população; e 4) baixa mortalidade e fertilidade em queda, com fertilidade ligeiramente acima à mortalidade (BLUE; ESPENSHADE, 2011). Mais recentemente, têm sido sugerido uma próxima etapa (5ª fase), sendo ela caracterizada por queda da fertilidade para níveis inferiores à mortalidade, cujo padrão colabora com a diminuição da população (BLUE; ESPENSHADE, 2011).

Concomitantemente à transição demográfica, tem sido notada a mudança no padrão de morbimortalidade da população, cujo processo é denominado transição epidemiológica (MCKEOWN, 2009). No início do século XX, a principal causa de adoecimento e morte dos indivíduos eram as doenças infectocontagiosas (HAHN *et al.*, 2018). Em meados das décadas de 60, houve o aumento da mortalidade por doenças crônicas não transmissíveis e causas externas, as quais passaram a ser as maiores razões de adoecimento e morte dos indivíduos (HAHN *et al.*, 2018). No entanto, doenças com causas infecciosas ainda são observadas em número significativo, como câncer de colo de útero e úlcera péptica, por exemplo, indicando certa fragilidade no conceito da transição epidemiológica, provavelmente porque o modelo dessa transição reflete a falta de conhecimento na época sobre a patogênese e etiologia de doenças crônicas (MERCER, 2018).

Inseridas no contexto de envelhecimento e alteração do padrão de doenças, se encontram as desordens musculoesqueléticas, as quais são associadas com a qualidade de vida e mortalidade (BROWN; HARHAY; HARHAY, 2016; SILVA NETO *et al.*, 2016; SIPERS *et al.*, 2019). A sarcopenia é uma destas condições, a qual é frequentemente associada ao processo de envelhecimento (CRUZ-JENTOFT *et al.*, 2010). Frente aos efeitos deletérios que essa situação pode provocar ao indivíduo, estudar sua origem e fatores associados ao tratamento é de suma importância.

2.2 Sarcopenia

A sarcopenia é uma palavra derivada do grego, formada pela junção dos termos *sarx* (carne) e *penia* (pobreza, falta, carência) (MUSCARITOLI *et al.*, 2010). A primeira definição deste termo é datada de 2010, entretanto, o termo foi utilizado há cerca de 30 anos, em 1989, durante uma reunião sobre a epidemiologia do envelhecimento, realizada na cidade de Albuquerque, Novo México, Estados Unidos (GARRY, 1989). Entretanto, a perda de massa muscular esquelética e força relacionadas com o processo de envelhecimento já havia sido descrito vários anos antes, em 1931, pelo pesquisador Critchley, o qual observou redução de certos tipos de fibras musculares ao longo do tempo, mesmo em décadas iniciais da vida, após a realização de biópsias musculares (CRITCHLEY, 1931; LEXELL *et al.*, 1983).

No ano de 2010, quatro organizações europeias (Sociedade Europeia de Medicina Geriátrica, Sociedade Europeia de Nutrição Clínica e Metabolismo, Associação Internacional de Gerontologia e Geriatria e Associação Internacional de Nutrição e Envelhecimento) se

reuniram para formar o Grupo de Trabalho Europeu sobre Sarcopenia em Pessoas Idosas (EWGSOP), o qual definiu os critérios diagnósticos para a sarcopenia relacionada à idade (CRUZ-JENTOFT *et al.*, 2010). Segundo o consenso publicado no mesmo ano, a sarcopenia constitui uma síndrome caracterizada pela perda progressiva e generalizada da massa muscular esquelética e força e/ou função física. De acordo com esse documento a síndrome era classificada como: 1) pré-sarcopenia – perda de massa muscular; 2) sarcopenia – perda de massa muscular associada a redução da força ou função; e 3) sarcopenia grave – perda de massa muscular, força e função (CRUZ-JENTOFT *et al.*, 2010).

Diversos estudos apontam os efeitos deletérios à saúde resultantes da baixa quantidade de massa muscular no organismo, incluindo aumento do risco de aparecimento de osteoporose (KIM *et al.*, 2014; PAPAGEORGIOU; SATHYAPALAN; SCHUTTE, 2019), quedas e fraturas (REIJNIERSE *et al.*, 2019), além de mortalidade (ABRAMOWITZ *et al.*, 2018). Sabe-se que a redução da massa muscular também está relacionada à menor qualidade de vida (BALOGUN *et al.*, 2017; MENANT *et al.*, 2017; SZULC; FEYT; CHAPURLAT, 2016), entretanto, a força muscular reduzida parece ser um problema ainda mais grave, uma vez que é mais fortemente associada à mortalidade do que redução de musculatura esquelética (LI *et al.*, 2018).

Recentemente, o consenso europeu de diagnóstico da sarcopenia foi revisado pelo mesmo grupo, e uma nova versão foi publicada (CRUZ-JENTOFT *et al.*, 2019; CRUZ-JENTOFT *et al.*, 2019), uma vez que agora a sarcopenia é formalmente reconhecida como uma doença muscular (CID-10 M62.84) (_____, 2018). Nesse novo documento houve alteração no diagnóstico da sarcopenia. A massa muscular, a qual constituía a variável principal no diagnóstico, agora é substituída pela força muscular. Essa mudança ocorreu devido ao fato de a força muscular se mostrar uma melhor preditora de resultados adversos, como quedas, realização de atividades diárias (DOS SANTOS *et al.*, 2017) e mortalidade (LI *et al.*, 2018), do que a própria massa muscular. Desta forma, o diagnóstico, de acordo com o consenso europeu de 2018, ocorre da seguinte forma: 1) sarcopenia provável – redução de força muscular; 2) sarcopenia – redução de força e massa muscular; e 3) sarcopenia grave – redução de força, massa e função muscular (CRUZ-JENTOFT *et al.*, 2019; CRUZ-JENTOFT *et al.*, 2019).

Sabe-se que a prevalência de sarcopenia encontrada entre as pesquisas tem ampla variação, uma vez que ela é dependente da população avaliada (idosos, presença de alguma doença de base) (SU *et al.*, 2019; WAKABAYASHI *et al.*, 2017), idade dos voluntários (MOREIRA; PEREZ; LOURENÇO, 2019), e critério diagnóstico utilizado (LIMIRIO *et al.*,

2019; MAYHEW *et al.*, 2019). Além disso, é bem documentado que a sarcopenia é uma síndrome com gênese multifatorial, e envolve o aumento de gordura intramuscular (AKAZAWA *et al.*, 2017), proteólise (COMBARET *et al.*, 2009), resistência anabólica (PADDON-JONES *et al.*, 2008), desuso muscular (BELL *et al.*, 2016), consumo alimentar inadequado (GRANIC *et al.*, 2019; MOHSENI *et al.*, 2017; ROBINSON *et al.*, 2018), alteração de hormônios sexuais com o avançar da idade (KIM *et al.*, 2016), disfunção mitocondrial (JOHNSON; ROBINSON; NAIR, 2013) e inflamação crônica (DALLE; ROSSMEISLOVA; KOPPO, 2017), por exemplo. Assim, conhecer os fatores e mecanismos que levam à sarcopenia é de grande interesse, uma vez que isso possibilita o desenho de ensaios clínicos que busquem o tratamento dessa situação.

Além disso, outras síndromes associadas a maior tempo de hospitalização, menor mobilidade, maior risco de fraturas e morbimortalidade (CLEGG *et al.*, 2013; SOENEN; CHAPMAN, 2013; VON HAEHLING; ANKER, 2014), como a caquexia, a fragilidade e a desnutrição proteico-calórica, apresentam características semelhantes à sarcopenia, apesar de terem diagnóstico diferente (GINGRICH *et al.*, 2019). Seguem abaixo os critérios diagnósticos para essas outras três síndromes:

- Fragilidade (FRIED *et al.*, 2001): presença de três ou mais critérios seguintes: perda de peso não intencional, exaustão, baixo nível de atividade física, velocidade lenta da marcha e baixa força de preensão manual.
- Caquexia (EVANS *et al.*, 2008): perda de peso associada à doença, combinada com três ou mais dos cinco critérios a seguir: diminuição da força de preensão manual, fadiga, anorexia, baixo índice de massa livre de gordura e exames bioquímicos alterados (proteína C-reativa alta, hemoglobina ou albumina baixas).
- Desnutrição (CEDERHOLM *et al.*, 2015): indivíduos com score de 7 pontos ou menos de acordo com a Mini Avaliação Nutricional (MNA-SF) (GUIGOZ; VELLAS; GARRY, 1996).

É importante destacar que tanto a caquexia, como a desnutrição e a fragilidade são fatores que contribuem para a instalação da sarcopenia (CRUZ-JENTOFT *et al.*, 2010).

2.2.1 Força muscular

Com o envelhecimento, é observada perda natural de massa e força muscular, o que está associado com aumento do risco de fragilidade, incapacidade, quedas, perda de independência e mortalidade (CAO; MORLEY, 2016).

Nesse contexto, a força muscular, variável necessária para gerar forças que produzem ou estabilizam o movimento articular, é um importante componente de saúde (VOLAKLIS; HALLE; MEISINGER, 2015), uma vez que é independentemente relacionada às atividades da vida diária (REID *et al.*, 2008), além de ser o preditor mais importante da função física (LEES *et al.*, 2019) e de estar mais relacionada com a mortalidade do que a massa muscular (VOLAKLIS; HALLE; MEISINGER, 2015), podendo então, ser utilizada como potencial preditor de morbimortalidade na população (GARCIA-HERMOSO *et al.*, 2018).

A força muscular é gerada devido a vários fatores, sendo resultado da combinação de fatores morfológicos e neurais, como área de seção transversa do músculo, unidade motora e sua sincronização e recrutamento de fibras (SUCHOMEL *et al.*, 2018). Embora a relação entre força e massa muscular não seja completamente elucidada, observa-se que, com o envelhecimento, a redução de força pode ocorrer 2-5 vezes mais rápido que a perda de massa muscular (MITCHELL *et al.*, 2012).

O declínio da força muscular com a idade parece variar de acordo com o grupo muscular analisado (TRUDELLE-JACKSON; FERRO; MORROW, 2011). Em mulheres entre 20-55 anos, a força preensão manual e dos extensores do joelho diminuíram 10,3% e 8,2%, respectivamente; enquanto que entre 55-80 anos, a força de preensão diminuiu 28% e a força do quadríceps apresentou redução em 40,2% (SAMSON *et al.*, 2000).

Além do envelhecimento, a literatura sugere que outros fatores, incluindo sexo (HAIZLIP; HARRISON; LEINWAND, 2015) e raça/etnia (SILVA *et al.*, 2010) podem exercer influência sobre a saúde muscular. Com relação ao efeito que a ingestão dietética possa provocar, o tema é melhor explorado nos tópicos abaixo.

2.3 Influência da dieta na prevenção e tratamento da sarcopenia

De acordo com o Guia Alimentar para a População Brasileira (BRASIL, 2014), o consumo dietético dos indivíduos relaciona-se fortemente com seu estado geral de saúde. Nos últimos anos foram observadas grandes alterações no padrão dietético dos brasileiros, como a realização de um maior número das refeições fora de casa, maior utilização de alimentos

prontos para comer e uso de tecnologia no momento da ingestão alimentar (como televisão, tablet, computador e celular) (BRASIL, 2014). Além disso, o consumo de alimentos in natura estão cada vez mais sendo substituídos pelos alimentos processados e ultraprocessados, o que reduz drasticamente a ingestão de importantes nutrientes e, consequentemente, impacta de maneira negativa sobre a qualidade alimentar dos indivíduos (BRASIL, 2014). Assim, frente aos impactos deletérios à saúde que podem ser provocados, avaliar a ingestão alimentar e a composição nutricional da dieta é necessário.

Sabe-se que a ingestão alimentar de proteínas leva à estimulação da síntese proteica muscular (SPM); entretanto, indivíduos mais velhos apresentam SPM atenuada no período pós prandial, situação conhecida como resistência anabólica (MOORE *et al.*, 2015). Diversos estudos oferecem suporte à premissa de que a recomendação de ingestão proteica para idosos deveria ser superior aos 0,8 g/kg de peso/dia, propostos pela *Dietary Reference Intake* (DRI) (BAUER *et al.*, 2013; PHILLIPS, 2017; PHILLIPS; CHEVALIER; LEIDY, 2016). Concomitantemente, pesquisas têm proposto que a ingestão de aproximadamente 1,2 g de proteína/kg de peso/dia seria mais eficiente na manutenção da massa magra (RAFII *et al.*, 2015; TANG *et al.*, 2014). Esses estudos utilizaram a técnica de oxidação de aminoácido, um método superior ao balanço nitrogenado, o qual é utilizado para chegar no atual valor da recomendação da DRI (IOM, 2002).

Entretanto, essa nova proposta de ingestão ainda não é um consenso. Murphy e colaboradores (2016) avaliaram a SPM (após três dias de ingestão) comparando o consumo de 0,8 e 1,2 g de proteína/kg/dia em homens idosos, na presença e ausência de exercício. Não foi observada diferença na estimulação da SPM entre ambas ingestões de proteína (MURPHY *et al.*, 2016). Em um estudo conduzido por nosso grupo de pesquisa, com o intuito de avaliar cronicamente o efeito de uma maior ingestão de proteína (~1,2 vs. ~0,8 g de proteína/kg/dia) em mulheres na pós-menopausa associado ao treinamento de força, não encontrou diferenças significativas entre os grupos na hipertrofia muscular ou ganho de força (ROSSATO *et al.*, 2017).

Entretanto, foi observada uma pequena melhoria adicional na capacidade funcional (aumento da velocidade na execução dos testes de 6 minutos e 400 metros ao longo do tempo, com uma melhora adicional no grupo ~1,2 g de proteína/kg/dia) (NAHAS *et al.*, 2019).

Outro ponto importante diz respeito à avaliação da ingestão de proteína em cada refeição ao invés de se avaliar apenas a ingestão de proteína total diária (LOENNEKE *et al.*,

2016; MURPHY; OIKAWA; PHILLIPS, 2016). Uma distribuição mais uniforme de proteína ao longo do dia parece estimular a SPM mais efetivamente (MAMEROW *et al.*, 2014). Entretanto, várias pesquisas mostram um padrão desigual de ingestão de proteínas habitual ao longo do dia em diversas populações (ROSSATO *et al.*, 2017; TIELAND *et al.*, 2012; USDA, 2016; VALENZUELA *et al.*, 2013), onde geralmente, apenas uma única refeição teria a quantidade adequada de proteína (comumente o almoço ou o jantar). Além disso, ensaios clínicos randomizados mostram que parece não haver uma consonância entre estudos agudos (MAMEROW *et al.*, 2014) e crônicos (HUDSON *et al.*, 2017; KIM *et al.*, 2018) com esse foco, uma vez que a longo prazo, o conteúdo total do consumo proteico parece ser mais importante do que a distribuição (KIM *et al.*, 2015; KIM *et al.*, 2018).

Relacionado à distribuição do consumo de proteínas ao longo do dia, encontra-se a variável do *timing* (momento) de ingestão proteica, ao qual se baseia na existência de uma "janela de oportunidades" (VAN LOON, 2014) no pós-treino imediato (aproximadamente 45 minutos a 1 hora após a sessão de treino) (MOORE *et al.*, 2009). Recentemente, nosso grupo de estudos publicou uma pesquisa sobre esse tema (DE BRANCO *et al.*, 2019), onde mulheres na pós-menopausa foram submetidas, durante 8 semanas, a um protocolo de treino de força. Um grupo consumiu proteína (30g de *whey protein*) imediatamente após o treino e no lanche da tarde ingeriu um suplemento ausente em proteína (30g de maltodextrina), enquanto o outro grupo ingeriu maltodextrina imediatamente após o treino e o mesmo conteúdo proteico no lanche da tarde. As mulheres treinaram pela manhã, foram orientadas a não consumir proteína no café da manhã, bem como nenhum outro alimento junto com o suplemento e ambos os grupos apresentaram o mesmo consumo de proteínas total. Após a intervenção, não foram identificadas diferenças entre os grupos para variáveis de composição corporal, força ou capacidade funcional (DE BRANCO *et al.*, 2019), o que corrobora com a afirmação de que a quantidade total parece ser a variável mais importante.

Além disso, uma fonte proteica com boa qualidade depende de sua digestibilidade e composição de aminoácidos essenciais (FAO, 2011), e as proteínas de origem vegetal apresentam qualidade inferior quando comparadas as proteínas de origem animal, como carnes, ovos e produtos lácteos (VAN VLIET; BURD; VAN LOON, 2015). Em adição, as proteínas de origem animal têm um teor mais elevado do aminoácido essencial leucina (VAN VLIET; BURD; VAN LOON, 2015), o qual parece atuar na estimulação pós-prandial da SPM (MURPHY; OIKAWA; PHILLIPS, 2016), pois apresenta potencial anabólico, com capacidade

de estimular a SPM via sinalização da proteína-alvo da rapamicina em mamíferos (*Mammalian Target of Rapamycin* - mTOR) (DE BANDT, 2016). Apesar da recomendação de ingestão de leucina ainda não estar bem clara, a necessidade do indivíduo parece aumentar com o avanço da idade (KATSANOS *et al.*, 2006), tendo sido demonstrado que é necessário ingerir entre 2-3 g de leucina/refeição para a estimulação máxima da SPM (CASPERSON *et al.*, 2012). No entanto, mesmo a proteína animal apresentando melhor qualidade de aminoácidos e estudos agudos indicando que a proteína do soro de leite apresenta maior estímulo à síntese de proteínas musculares comparada com as proteínas da soja e caseína (DEVRIES; PHILLIPS, 2015; VAN VLIET; BURD; VAN LOON, 2015), uma meta-análise apontou que cronicamente proteínas vegetais (soja) levam a ganhos de massa magra e força em associação ao treinamento de força de maneira semelhante ao *whey protein* (MESSINA *et al.*, 2018).

Além da proteína, outro nutriente naturalmente presente na dieta e que tem sido recentemente destacado como interessante para a saúde muscular é o ω-3 (MCGLORY; CALDER; NUNES, 2019). Esse ácido graxo, através de diferentes mecanismos (MCGLORY; CALDER; NUNES, 2019), parece influenciar a SPM, hipertrofia e força muscular, apesar de resultados conflitantes serem observados (ROSSATO; SCHOENFELD; DE OLIVEIRA, 2020). Assim, mais estudos e pesquisas envolvendo essa temática são necessários, afim de traçar estratégias nutricionais que podem ser importantes para a saúde.

2.3.2 Ômega-3

Os ácidos graxos poli-insaturados ω-3 apresentam primeira dupla ligação entre o terceiro e o quarto átomos de carbono, a partir da extremidade metil da cadeia acil dos ácidos graxos. Essas gorduras são essenciais ao organismo humano, e uma vez que o corpo não as produz, elas devem ser adquiridas pela dieta. Além disso, esse nutriente é um potencial nutracêutico (CONNOR, 2000), apresentando benefícios inclusive à saúde mental (LIN *et al.*, 2017).

Diretrizes alimentares recomendam o consumo de pelo menos duas porções de peixe por semana (KRIS-ETHERTON *et al.*, 2007; SACN, 2004). Entretanto, sabe-se que algumas populações apresentam baixo consumo de ω-3 em função das suas características alimentares, como os ocidentais, vegetarianos e veganos (LANE; DERBYSHIRE, 2018; MEYER, 2011). Nesse sentido, os suplementos alimentares fontes de ω-3 se tornam a principal opção alternativa às fontes alimentares daqueles indivíduos que não conseguem atender às recomendações

(CATAPANO *et al.*, 2016). Entretanto, mesmo se advindo de fontes não-animais, o uso de suplementos se torna uma escolha inadequada para veganos e certos grupos religiosos devido ao encapsulamento, método cujo principal material utilizado é a gelatina (JAIN, 2012). O principal desconforto gastrointestinal associado ao consumo de cápsulas contendo ω-3 é a tendência a produzir desagradável refluxo, pois os óleos apresentam densidade menor que o suco gástrico e a liberação do conteúdo das cápsulas no estômago pode resultar em altas concentrações de lipídios nas camadas superiores do suco gástrico (FETTERMAN; ZDANOWICZ, 2009).

2.3.2.1 Tipos

O ω-3 pode ser obtido por meio de fontes vegetais (ácido alfa-linolênico - ALA) ou animais (ácido eicosapentaenoico - EPA e ácido docosahexaenoico - DHA). Outros ácidos graxos ω-3, como ácido docosapentaenoico (DPA) e o ácido estearidônico (SDA) estão presentes em quantidades muito baixas na dieta. Inicialmente, o ALA sofre reações de dessaturação enzimática (eficiência variando entre 1 a 5%), sendo posteriormente convertido em EPA e DHA. Na figura abaixo são apresentadas as sucessivas reações de dessaturação enzimática que ocorre com os ω-3.

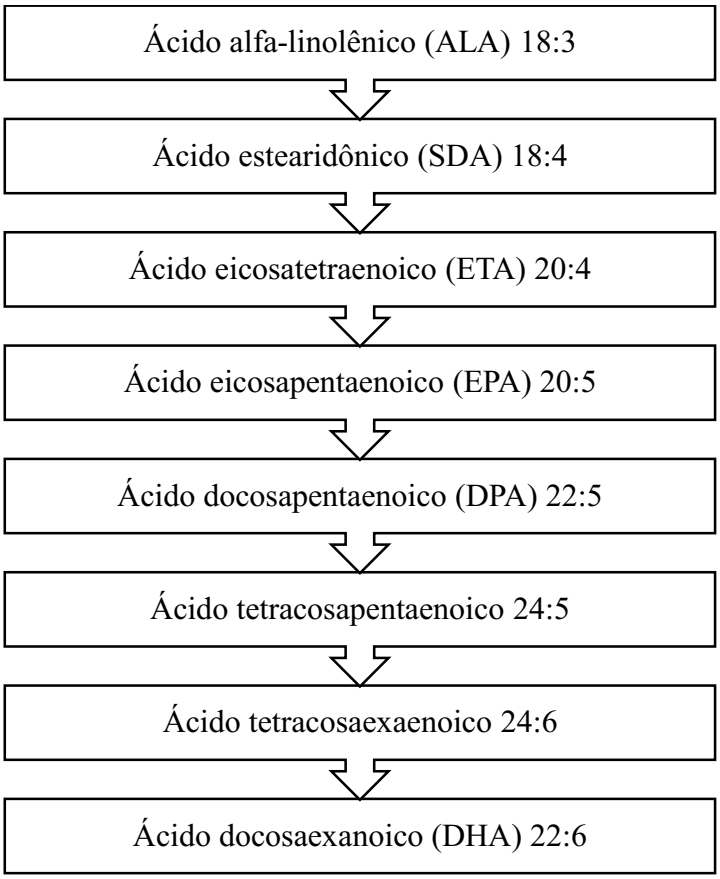

Figura 1 – Sequência de reações que leva a conversão de ácido alfa-linolênico (ALA) em ácido eicosapentaenoico (EPA) e ácido docosahexaenoico (DHA) (BURDGE; CALDER, 2005).
Notas: A conversão de ALA em SDA e a conversão de ácido tetracosapentaenoico em ácido tetracosaexaenoico são limitadas em humanos, devido a quantidade existente da enzima catalisadora delta-6-dessaturase (JAMES; URSIN; CLELAND, 2003).

2.3.2.2 Fontes

Entre os vários tipos de ω-3, os efeitos são advindos principalmente de EPA e DHA, os quais são metabolizados a partir do ALA. EPA e DHA são encontrados em peixes de água fria, os quais possuem maior quantidade de gordura corporal. Entretanto, o teor desses lipídeos depende de vários fatores, como o meio ambiente em que vivem os animais, o clima e a dieta (ADARME-VEGA *et al.*, 2012). Por outro lado, o ALA é encontrado primordialmente em sementes (como linhaça, chia, abóbora), nozes/derivados e em óleo vegetais (óleos de soja e canola). Outras fontes importantes de ω-3 provenientes da vida marinha incluem algas e microalgas, crustáceos e krill. Além disso, não há grandes fontes dietéticas de SDA e DPA. Entretanto, o ω-3SDA é encontrado em grande quantidade (comparado à outras fontes de ω-3)

no óleo de cânhamo e óleo de semente de echium. Devido ao baixo consumo proveniente da dieta, muitos suplementos alimentares fontes de ω-3 estão disponíveis no mercado. Óleo de linhaça e alguns óleos derivados de nozes são fontes de ALA, enquanto óleo de peixe, óleo de krill e óleo de algas são comumente fontes de EPA e DHA.

Quadro 1 – Teor de ácido graxo ômega-3 de acordo com a Tabela Brasileira de Composição de Alimentos (2011).

Alimento	Quantidade de ω-3 (g) em 100g de alimento
Sardinha, assada	0,27
Salmão, sem pele, grelhado	2,23
Atum, conserva em óleo	0,54
Linhaça, semente	19,81
Nozes, crua	8,82
Castanha do Pará, torrada, salgada	0,08
Azeite de Oliva, extravirgem	0,75

Fonte: Tabela Brasileira de Composição de Alimentos (2011).

2.3.2.3 Ação anti-inflamatória

Os lipídeos apresentam dois destinos principais no organismo, os quais incluem a produção de energia a partir da β-oxidação ou a incorporação nas membranas plasmáticas celulares, processo que permite alterar a fluidez da membrana e atuar como moléculas de sinalização para inúmeras reações (CALDER, 2012).

Nesse sentido, tanto o ω-3 quanto o ω-6 podem ser utilizados como substratos para a síntese de eicosanoides, os quais são uma subcategoria de oxilipinas (metabólitos produzidos pela oxidação de ácidos graxos insaturados). Os eicosanoides são moléculas sinalizadoras, podendo atingir vários sistemas fisiológicos. Dependendo do substrato, efeitos fisiológicos diferentes e frequentemente opostos são observados.

Os fosfolipídios da membrana são clivados pela enzima fosfolipase A2, permitindo a ação das enzimas lipo-oxigenase (LOX) e ciclo-oxigenase (COX) sobre os ácidos graxos livres, o que resultará na produção de mediadores pró ou anti-inflamatórios se o precursor for um ácido graxo ω-6 (prostaglandinas da série 2, leucotrienos da série 4 e tromboxano A2) ou ω-3 (prostaglandinas da série 3, leucotrienos de série 5 e tromboxano A3), respectivamente (NIE *et*

al., 2001). Desta forma, o tipo de gordura presente na membrana celular apresenta efeito sobre a síntese de mediadores da resposta inflamatória, exercendo influência sobre esse perfil. Os metabólitos produzidos a partir do ω-3 apresentam efeitos inflamatórios diminuídos em relação aqueles produzidos a partir do ω-6, o que pode ser responsável pelos efeitos clínicos benéficos associados ao ω-3.

2.4 Ômega-3 e massa muscular

Os benefícios associados à saúde proporcionados pelo ω-3 estão possivelmente relacionados a diversos mecanismos. Em relação ao músculo, essas gorduras, ao serem incorporadas às membranas celulares, parecem deixar a célula mais sensível à captação de aminoácidos, os quais aumentariam o estímulo da SPM (MCGLORY; CALDER; NUNES, 2019). Além disso, a ação anti-inflamatória do ω-3 poderia agir dentro da célula, diminuindo a ação de fatores inflamatórios que resultariam na quebra proteica (MCGLORY; CALDER; NUNES, 2019).

Ao avaliarem a SPM após a suplementação de ω-3, pesquisadores encontraram aumento na resposta anabólica, traduzida pelo aumento da expressão de proteínas relacionadas com a SPM, tanto em jovens (SMITH *et al.*, 2011) como em idosos (SMITH *et al.*, 2011). Curiosamente, ao avaliar o efeito de 5 g/dia de óleo de peixe (3,5g de EPA e 0,9g de DHA) ou de óleo de coco na SPM e na atividade de proteínas sinalizadoras da síntese, McGlory e colaboradores (MCGLORY *et al.*, 2016) observaram aumento da atividade de p70S6K1 após uma sessão de treino de força apenas no grupo óleo de coco, sugerindo uma atenuação da SPM relacionada com o ω-3. Entretanto, mesmo com esse resultado, não foram encontradas diferenças na taxa de SPM entre os grupos, o que pode sugerir influência do ω-3 na SPM através de vias metabólicas alternativas à via de SPM clássica (MCGLORY; CALDER; NUNES, 2019).

Em relação ao ganho de massa magra, evidências provenientes de estudos que não associaram a realização de exercícios em adultos apontam para resultados não conclusivos, principalmente devido à falta de controle da realização de exercícios ou mesmo da ingestão alimentar pela amostra durante a intervenção (ROSSATO; SCHOENFELD; DE OLIVEIRA, 2020). Embora alguns estudos mostrem aumentos modestos na massa magra nessa população, a falta de controle da atividade física e da ingestão alimentar impede a capacidade de inferir se os ganhos da massa magra ocorreram devido à suplementação de ω-3 ou a fatores de confusão

(COUET *et al.*, 1997; HARDEN *et al.*, 2014; NOREEN *et al.*, 2010; SNEDDON *et al.*, 2008). Resultados encontrados na população idosa apresentam a mesma tendência de resultados mistos (LOGAN; SPRIET, 2015; SMITH *et al.*, 2015; SNEDDON *et al.*, 2008), além de importantes limitações metodológicas que dificultam avaliar os efeitos da suplementação com ω-3 na massa muscular. Quando incluído o exercício no protocolo, dados provenientes de indivíduos jovens parecem não resultar em benefícios extras do ω-3 para a hipertrofia (HAYWARD *et al.*, 2016; HILL *et al.*, 2007), enquanto que para idosos, os resultados se mostram contraditórios (CORNISH; CHILIBECK, 2009; CORNISH *et al.*, 2018; DA BOIT *et al.*, 2017; STRANDBERG *et al.*, 2015; STRANDBERG *et al.*, 2018), destacando a importância da realização de novas pesquisas envolvendo essa temática.

2.5 Ômega-3 e força muscular

Apesar dos mecanismos de ação da ω-3 na força muscular ainda precisarem ser melhores descritos, foi postulado que oω-3 pode promover a fluidez da membrana e com isso, provocar o aumento da sensibilidade à acetilcolina, a qual torna a transmissão sináptica mais rápida na junção neuromuscular, resultando em uma contratilidade muscular mais rápida (PATTEN *et al.*, 2002).

Evidências advindas de estudos observacionais são mistas. Robinson e colaboradores (ROBINSON *et al.*, 2008) constataram que a ingestão de peixes gordurosos foi o maior preditor da força de preensão manual em ambos os sexos, e, embora os autores não tenham avaliado a ingestão propriamente dita de ω-3, sabe-se que peixes gordurosos são a principal fonte desse ácido graxo. A literatura aponta apenas para um estudo em que o ALA plasmático foi positivamente associado com a força de extensão do joelho de idosos ao longo de 5 anos de seguimento (REINDERS *et al.*, 2015). Alguns estudos investigaram a associação do conteúdo de ω-3 nos glóbulos vermelhos e a força muscular e não encontraram resultados significativos (FOUGERE *et al.*, 2018; FOUGERE *et al.*, 2017).

Mesmo o treinamento físico sendo de extrema importância para a força muscular (SUCHOMEL *et al.*, 2018), Smith e colaboradores (2015) (SMITH *et al.*, 2015) observaram aumento na força de preensão manual e 1-RM após 6 meses de suplementação com ω-3, mesmo sem realizar intervenção de exercícios. Devemos destacar que o nível de atividade física dos sujeitos durante a intervenção não foi avaliado, o que pode ser um potencial fator de confusão. No entanto, com base nesse resultado, podemos inferir que a suplementação com ω-3 poderia

ajudar a melhorar a função muscular em adultos mais velhos, mesmo sem a realização de exercícios. De acordo com McGlory e colaboradores (MCGLORY; CALDER; NUNES, 2019), indivíduos que não detêm os estímulos máximos (exercícios e dietéticos, por exemplo) para a saúde muscular, como é o caso de idosos, teriam maiores benefícios com a ingestão deω-3.

Estudos que incluíram a realização de exercícios em associação com a suplementação do ω-3 em seus protocolos também foram realizados, tanto com jovens (HAYWARD *et al.*, 2016) quanto com idosos (CORNISH; CHILIBECK, 2009; DA BOIT *et al.*, 2017; EDHOLM; STRANDBERG; KADI, 2017; RODACKI *et al.*, 2012). Em indivíduos jovens, não foram encontradas diferenças significativas entre os grupos controle (apenas exercício); dieta rica em proteína mais ω-3; e dieta rica em proteína mais ω-3 mais creatina monohidratada durante 4 semanas de suplementação, mostrando apenas um efeito do exercício no ganho de força muscular (HAYWARD *et al.*, 2016). Em relação aos mais velhos, alguns estudos apontaram efeitos positivos para a suplementação de ω-3 e ganhos na força muscular (DA BOIT *et al.*, 2017; EDHOLM; STRANDBERG; KADI, 2017; RODACKI *et al.*, 2012). No entanto, os resultados devem ser analisados com cautela, uma vez que limitações importantes são encontradas, como a ausência de um grupo placebo (RODACKI *et al.*, 2012) e alteração de outros tipos de gordura além do ω-3 (EDHOLM; STRANDBERG; KADI, 2017).

2.6 National Health and Nutrition Examination Survey

O *National Health and Nutrition Examination Survey* (NHANES) é um programa que abrange a realização de entrevistas e exames físicos, sendo realizado pelo *National Center for Health Statistics* (NCHS), o qual faz parte do *Centers for Disease Control and Prevention* (CDC). O objetivo do programa é avaliar a saúde e o estado nutricional de indivíduos dos Estados Unidos (EUA) (CDC, 2019).

O NHANES teve início na década de 60 e partir de 1999 se tornou um programa contínuo, o qual é realizado bienalmente, cujo foco abrange inúmeras variáveis demográficas, socioeconômicas, dietéticas e relacionadas à saúde, visando atender às necessidades emergentes. A amostra do NHANES é selecionada para representar a população dos EUA de todas as idades, inclusive idosos. Sabe-se que os EUA apresentaram um rápido crescimento do número de idosos nos últimos 100 anos, e frente as necessidades de cuidados de saúde relacionadas ao envelhecimento, o NHANES apresenta papel fundamental no aumento do

conhecimento do estado de saúde dos americanos mais velhos. Em geral, quanto mais velho o indivíduo, mais extenso o exame que é realizado (CDC, 2019).

O NHANES foi projetado para facilitar a realização das pesquisas e incentivar a participação da população, sendo que as entrevistas de saúde são realizadas nas casas dos participantes e as avaliações de saúde são realizadas em centros móveis, os quais viajam para todos os locais dos EUA. Um sistema avançado de computadores auxilia a coleta e processa todos os dados do NHANES, praticamente eliminando a necessidade de formulários em papel e operações de codificação manual. As informações do NHANES são disponibilizadas através vários documentos, disponíveis em publicações no próprio site do programa e em artigos em revistas científicas. Os dados são publicamente disponibilizados na internet em todo o mundo (CDC, 2019).

Espera-se que os resultados das avaliações realizadas sejam utilizados em pesquisas epidemiológicas da área das ciências da saúde e sirvam para a determinação da prevalência e fatores de risco ou protetores de doenças, possibilitando o desenvolvimento de políticas públicas de saúde que orientem a promoção da saúde e a prevenção de doenças (CDC, 2019).

3. OBJETIVOS

3.1 Objetivo geral

Avaliar a associação entre o ácido graxo poli-insaturado ω-3 e a força muscular.

3.2 Objetivos específicos

- Avaliar a atual evidência científica entre o consumo de ω-3 (via dieta ou suplementação) e sua associação ou efeito na massa muscular, função física e força em indivíduos adultos e idosos;

- Associar o consumo de ω-3 (total e tipos isolados) com a força muscular;

- Associar as concentrações plasmáticas de ω-3 (total e tipos isolados) com a força muscular.

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5 ARTIGOS PUBLICADOS OU SUBMETIDOS

Artigo 1: Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults?

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Review

Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults?

Short title: Omega-3 fatty acids, muscle mass and strength

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ABSTRACT

Omega-3 (ω-3) is a polyunsaturated fatty acid with anti-inflammatory properties that presents three main forms: alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. Recently, studies performed in both young and older adults suggest that ω-3 may improve gains in muscle mass and/or enhance physical function. Thus, the aim of this narrative review was to evaluate the current evidence of ω-3 intake/supplementation on muscle/lean mass (LM) and physical function in young and older adults, and draw research-based conclusions as to the practical implications of findings. We first assessed whether ω-3 intake is associated with muscle mass and strength (observational studies), and then sought to determine whether evidence shows that supplementation of ω-3 increases muscle protein synthesis, LM and strength in adults and older adults (interventional studies). The search was carried out in PubMed and Scopus databases for the periods between 1997 and November 2018. The following keywords were used alone and in combination: ω-3, fish oil, muscle protein synthesis, muscle mass, lean mass, body composition, and physical function. In general, ω-3 supplementation does not seem to promote increases in muscle mass in sedentary young and older adults; the hypertrophic effects of supplementation when combined with resistance training remain equivocal. Moreover, there is conflicting evidence as to whether supplementation confers a beneficial effect on muscle function in older adults. Importantly, this conclusion is based on limited data and more studies are needed before ω-3 supplementation can be recommended as a viable strategy for such purposes in clinical practice.

Keywords: omega-3, muscle protein synthesis, muscle mass, lean mass, physical function.

1- INTRODUCTION

Omega-3 fatty acids (ω-3) are polyunsaturated fatty acids (PUFA), which are a family of essential fatty acids that mediate numerous biological processes. There are three major dietary forms of ω-3: alpha-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3). ALA is considered an essential dietary fatty acid, meaning it cannot be synthesized in humans [1]. It is found in a relatively limited set of foods including nuts, seeds, and their oils (mainly in flaxseed and chia) [2]. Although there are some biochemical pathways to convert ALA into EPA and DHA, a limitation for this endogenous conversion is observed in humans (DHA conversion is even lower than EPA conversion)[3, 4]. Thus, circulating and tissue levels of EPA and DHA are mainly determined by dietary consumption [1, 5], with fish oil (FO) being the major dietary source of EPA and DHA [2]. Supplements containing FO are mainly composed of triglycerides, ethyl esters, and phospholipids, as well as frequently containing additional essential micronutrients such as vitamins D and E [6]. Various global recommendations indicate that ω-3 intake should be ~1 g per day [7-9]. Many expert committees in the primary prevention of coronary heart disease recommend approximately 2 servings of fatty fish per week, which represents a combined ~500 mg of EPA and DHA per meal [10, 11]. It is important to draw attention to the fact that the modern Western diet had several potentially detrimental effects on health as a result of high consumption of saturated fats and ω-6, with a corresponding low intake of ω-3 [12]. When the adequate consumption of a certain nutrient is not possible or does not occur through food consumption, supplementation is required for diet adequacy [13].

Adequate intake and/or supplementation of ω-3 has been associated with better control of lipid profile [14, 15], decreased inflammation [16], attenuation of metabolic syndrome [17]; and reduced risk of coronary heart disease, ischemic stroke, and sudden

cardiac death [18, 19], although these findings remain equivocal [20, 21]. Recently, ω-3 has been studied as a possible nutritional intervention to promote muscle mass and strength gains [22-27]. Some studies report positive effects of ω-3 intake on muscle mass and physical function [24-27], and these benefits are shown to occur in both young [24] and older [25-27] individuals, but this is not a consensus [22, 23]. Low muscle mass and strength are associated with an impairment in walking [28], increased risk of falls [29] and higher mortality [30-32]. Therefore, nutritional strategies, such as consumption of ω-3, aiming to increase or maintain muscle mass and physical function are important, regardless of age. Thus, the aim of this narrative review was to evaluate the current evidence of ω-3 intake/supplementation on muscle/lean mass (LM) and physical function in young and older adults, and draw research-based conclusions as to the practical implications of findings. We first assessed whether ω-3 intake is associated with muscle mass and strength (observational studies), and then sought to determine whether evidence shows that supplementation of ω-3 increases muscle protein synthesis, LM and strength in adults and older adults (interventional studies).

2 - EVIDENCE FROM OBSERVATIONAL STUDIES

In a cross-sectional and retrospective cohort study with 1519 men and 1414 women, Robinson et al. [25] found that fatty fish intake was the largest predictor of muscle strength (handgrip strength - HGS) both in men and women. Each additional portion of fatty fish consumed per week resulted in a 0.48 kg (95% CI 0.24 to 0.72) increase in HGS in women, and a 0.43 kg (95% CI 0.13 to 0.74) increase in men, whereas the consumption of white fish and shellfish did not correlate with HGS. Although the authors did not evaluate actual ω-3 intake, findings suggest that ω-3 may at least partially explain this association, since fatty fish intake is a primary source of this PUFA.

Several studies have investigated the association of ω-3 content in red blood cells or in the plasma (that may reflect the dietary pattern of ω-3 [33]) with muscle mass, strength and functional capacity [34-37]. Belury et al. (2016) did not find an association between ω-3 fatty acids composition in erythrocyte and LM in older adults [34]. Another study [35] investigated the association of plasma PUFA, including ω-3, with muscle size and strength in older adults at baseline and after 5 years of follow-up. Muscle size was not associated with total ω-3 PUFAs, ALA, DHA and EPA at baseline and over 5 years of follow-up. Total ω-3 PUFAs, DHA and EPA were positively associated with HGS at baseline; however, the associations were no longer significant after adjustments for confounding variables and no associations were found in longitudinal analysis. Alternatively, the longitudinal data showed that ALA was positively associated with increased knee extension strength.

Recently, it was observed that older adults with a lower percentage of total ω-3 fatty acid content in red cells presented reduced physical function; however, after adjustments for confounders, the association disappeared [36]. In a subsequent longitudinal study carried out over a 3-year period, the same research group evaluated the association between ω-3 fatty acid content in red cells and physical performance [37]. The authors' found that the individuals with lower ω-3 levels had lower gait speed in unadjusted model, but the significance was lost after adjustments for confounders. In addition, no association was found between ω-3 levels and short physical performance battery [37]. However, the study was limited by the fact that plasma ω-3 fatty acid content in red cell was assessed only at baseline, and hence this concentration may have changed over the follow-up period via food intake fluctuations. Multiple measurements of ω-3 in red cells at regimented intervals over time would be needed to more fully investigate the association

between plasma PUFA and muscle/function parameters; this gap in the literature should be explored in future studies.

In summary, cross-sectional studies do not seem to show that ω-3 is associated with muscle mass, but some studies indicate a possible association between ω-3 and muscle function. However, these associations seem to be indirect, since the relationship between variables disappeared after statistical adjustments in the majority of the studies. Limited longitudinal data show that ω-3 intake is not associated with muscle size and some muscle function parameters, such as grip strength and gait speed; but it is likely associated with knee extension strength. It is important to note that these studies were carried out in older adults and associations in young adults remain to be elucidated. Moreover, observational studies are inherently limited because they do not afford the ability to draw causality.

3 - Ω-3 AND MUSCLE PROTEIN SYNTHESIS

An important determinant of muscle loss with aging seems to be a decrease in muscle protein synthesis (MPS) [38], with older adults presenting lower MPS rates compared to young individuals with the same nutritional anabolic stimulus [39, 40]. Thus, nutritional interventions aiming to increase MPS potentially can be important for muscle loss prevention [41].

The exact mechanisms by which ω-3 could mediate an increase in MPS remain unknown, but may be involved with alterations in catabolic and anabolic pathways. It is known that ω-3 is incorporated into cellular membranes of various body tissues, including skeletal muscle [5], modulating lipid-protein interactions. This incorporation seems to be a chronic process that can be observed after just 2 weeks of supplementation [33]. In muscle cells (myocytes), EPA and DHA, may enhance membrane fluidity, improving the uptake

144 of amino acids and, consequently, making the cell more sensitive to MPS [42-45]. However,
145 studies evaluating ω-3 supplementation and MPS have shown contradictory results; some
146 studies found improvements in MPS and in anabolic response [43, 44], while others showed
147 no increase in MPS [5] or even an impairment in anabolic signaling [42].
148
149 ***3.1 - Ω-3 and protein synthesis in young adults***
150 Smith et al. [43] investigated the effect of ω-3 supplementation (1.86 g of EPA and
151 1.5 g of DHA) on MPS in 9 middle aged adults over an 8 week study period. Insulin and
152 amino acid infusion was obtained at baseline and after 8 weeks of ω-3 supplementation,
153 with results showing supplementation-induced pre- to post-study increases in Akt^{Thr308},
154 mTOR, p70s6k and MPS, translating into a ~50% greater anabolic response. However,
155 the absence of a control group may limit the interpretation of these data.
156 Recently, McGlory et al. [42] evaluated the effect of 5 g/day of FO (3.5 g EPA and
157 0.9 g DHA) or coconut oil on MPS and the activity of kinases involved in anabolic
158 signaling. After 8 weeks of supplementation, the individuals performed an acute bout of
159 unilateral resistance exercise followed by the intake of 30 g of whey protein. MPS
160 increased similarly between conditions post-exercise. However, the activity of p70S6K1
161 was elevated 3h after the resistance exercise following protein ingestion only in the
162 coconut oil group. Interestingly, despite the apparent attenuation in anabolic signaling,
163 there was no detrimental effect on MPS in the FO group. The contradictory findings
164 between these studies may be explained by differences in methodologies, such as the
165 studied population (untrained vs. resistance trained) and the mode of amino acid
166 administration (oral vs. intravenous). While the provision of amino acids by Smith et al.
167 [43] was continuous (infusion), McGlory et al. [42] provided a bolus of whey, which is known
168 to promote a peak of aminoacidemia (by ingestion) followed by a rapid decrease in blood

levels. Another important difference to take into account is that Smith et al. [43] clamped the plasma when a leucine concentration of ~65-175 μmol/L was achieved, which would represent a submaximal dose, while peak of plasma leucine concentrations in McGlory et al. [42] were ~250-300 μmol/L, which equates to ~0.35 g of protein/kg; a value sufficient to maximize the rate of MPS in young men. Thus, it can be speculated that a greater amount of ω-3 in the cell appears to enhance anabolism when the dose of protein is insufficient to stimulate a maximum MPS response. However, when a maximal MPS response is achieved by protein stimulus, supplementation with ω-3 seems to promote no increase in MPS response to resistance training. This hypothesis is based on limited data and further research is needed to draw more concrete inferences.

3.2 - Ω-3 and protein synthesis in older adults

Smith et al. [44] conducted a RCT with 16 older adults that compared the effect of FO supplementation (1.86 g of EPA and 1.5g of DHA) versus placebo (4 g of corn oil) on MPS. After 8 weeks of supplementation, subjects underwent a hyperaminoacidemia-hyperinsulinemia clamp to assess the rate of MPS and phosphorylation of various anabolic signaling elements. Results showed that supplementation with FO enhanced the rate of MPS as well as increasing activation of mTOR and p70s6k concentration, although no change in Akt^{Thr308} was observed. Lalia et al [46] also aimed to evaluate the influence of ω-3 supplementation on MPS and anabolic response to an acute exercise bout in healthy older adults. Twelve volunteers received 3.9 g/day of ω-3 (2.7 g EPA and 1.2 g of DHA) for 16-week in an open-label intervention. Small, non-significant increases in myofibrillar protein synthesis were noted in the pre-exercise post-absorptive state following 16 weeks of ω-3 supplementation; however, the rates of myofibrillar fractions were significantly

higher after exercise. Intriguingly, the resistance training-induced increase in MPS following ω-3 supplementation was greater in older versus younger individuals.

Although there is a relative dearth of studies evaluating the effect of ω-3 supplementation on MPS in older adults, it seems that ω-3 can promote anabolic increases in these individuals. These findings persist despite heterogeneity in methodological designs, with an amino acid infusion employed in one study [44], and consumption of a mixed meal and an exercise bout in the other [46].

In summary, the current data shows promise for a beneficial anabolic effect of ω-3 in older adults, but further research is needed to draw stronger conclusions on the topic. Areas of interest include comparing the MPS response to ω-3 supplementation after different protein doses, both with and without exercise, as well as during bed rest conditions. Future studies are also needed to elucidate the effect of ω-3 supplementation on the attenuation of anabolic resistance in older adults.

4 - EVIDENCE FROM INTERVENTIONAL STUDIES

4.1 - Ω-3 AND MUSCLE MASS (WITHOUT EXERCISE)

4.1.1 - Young adults

Although MPS is recognized as the primary driver of muscle hypertrophy [47], the acute MPS response does not always correlate with long-term muscle hypertrophy [48]. Thus, longitudinal studies are needed to determine whether ω-3 consumption promotes actual changes in muscle mass. One of the first studies on the topic investigated the influence of FO on body composition in 6 adults, whereby participants initially ingested an *ad libitum* control diet for 3 weeks [49]. After a 10-12 weeks washout period, the participants ingested an ad libitum diet over a 3-week period with the substitution of 6

g/d of FO for an equal amount of other dietary lipids. No change in fat free mass (FFM) was found for either condition, although FO group presented a higher decrease in body fat. These results should be interpreted with caution due to the small sample size, absence of a parallel control group, and short study duration. In agreement with these results, Harden et al. [22] investigated the effect of supplementation of DHA (2.8 g/day) or oleic acid (olive oil) on body composition in obese women. The study employed double-blinded, 2-way, parallel design, with no differences reported in LM between conditions following the 12-week intervention. It should be noted that the study by Harden et al. [22] is specific to consumption of DHA; there is evidence that EPA has differential biological effects from DHA [50], and it is not clear whether their combined intake promotes synergistic benefits.

However, other studies [24, 51] found a possible effect of ω-3 supplementation on LM. Noreen et al [24] carried out a double-blind study whereby 44 adults were randomly assigned into one of two groups: a placebo group that received 4 g/day of safflower oil, or group that received the same dose of FO (equating to 1.6 g of EPA and 800 mg of DHA). After the 6-week intervention period an increase in FFM and a decrease in fat mass were observed in the FO group, which were both statistically greater compared to the safflower oil supplement. Although these results are intriguing, they should be interpreted with circumspection as it would seem unlikely that an isolated nutritional intervention can promote a concomitant gain in LM and loss in fat mass in the absence of regimented resistance training, as shown in this study. Moreover, the absence of dietary control may have influenced the results. A possible explanation for the findings is the use of air displacement plethysmography for body composition analysis, which may have been unduly influenced by changes in hydration status. In a double-blind, placebo-controlled, crossover study [51], lean and obese young and older adults were submitted to

12 weeks of supplementation, followed by a washout period of the same duration. Subjects consumed either 6 capsules of conjugated linoleic acid (CLA; C18:2n-6) + ω-3 (2.28 g of CLA, 900 mg of EPA, and 630 mg of DHA) or 6 capsules of control (4.8 g of palm oil and 1.2 g of soya bean oil) per day. Results showed CLA + ω-3 treatment increased FFM (1.3%) in young obese men, but supplementation had no effect in lean young adults. The reasons for discrepancies between populations is not clear, but an important limitation is that the study did not directly control for food intake and physical activity levels. Moreover, the addition of CLA to the ω-3 treatment confounds the ability to draw causality with respect to the effects of EPA and DHA.

When evaluating the current evidence, it remains equivocal as to whether ω-3 supplementation enhances LM in young adults who do not perform exercise. Although some studies show modest increases in LM in this population, the lack of control for physical activity and dietary intake precludes the ability to draw inferences as to whether LM gains occurred due to ω-3 supplementation per se or to confounding factors.

4.1.2 Older adults

Several studies have endeavored to determine the long-term effects of ω-3 in older adults. In the study by Sneddon et al. [51] discussed above, the combination of CLA + ω-3 supplementation did not augment LM compared to oleic acid in both lean and obese older adults following a 12-week intervention period. Similarly, Krzymińska-Siemaszko et al. [52] randomized 50 older adults with low baseline muscle mass to either a PUFA-treated group (660 mg of EPA, 440 mg of DHA, 200 mg of other ω-3, plus 10 mg of vitamin E) or control (11 mg of vitamin E). After 12 weeks of supplementation, no changes were observed in muscle mass and fat-free mass. Lending further support to these findings, Tardivo et al [53] found that changes in muscle mass were not significantly different in

postmenopausal women receiving a dietary intervention plus ω-3 supplementation (3 capsules/day, each one containing 180 mg of EPA and 120 mg of DHA) versus a dietary intervention alone (control group) over a 6-month study period.

In contrast to the aforementioned studies, Logan et al. [26] randomized 24 community-dwelling older women into one of two groups: FO (5 g/day; 2 g of EPA and 1 g of DHA) or placebo (3 g/day of olive oil). Both groups were instructed to maintain their current physical exercise and dietary regimen. After 12 weeks of supplementation, an increase in LM (~4%) was noted in the FO group whereas no significant changes were found in placebo. In a double-blind, placebo-controlled trial, Smith et al. [54] randomly assigned a cohort of older men to receive either ω–3 supplementation (4 pills/day of 1.86 g EPA and 1.50g of DHA) or placebo (4 pills/day of corn oil). At the end of the 6-month intervention period, results showed a significant increase in thigh muscle volume for subjects supplemented with ω–3, as determined by magnetic resonance imaging, widely considered the gold standard criterion.

In summary, the evidence is mixed as to the effects of ω–3 supplementation on muscle mass in older, sedentary individuals, with some studies demonstrating beneficial changes [26, 54] and others failing to show a benefit [51-53]. The current literature is, in general, limited by a lack of control for dietary intake and physical activity levels. Moreover, many of the studies employed bioelectrical impedance analysis to measure FFM, which may lack the accuracy to detect subtle changes in this parameter over relatively short time frames.

4.2 - Ω-3 AND MUSCLE MASS (WITH EXERCISE)

4.2.1 Young adults

To the best of our knowledge, only two studies have endeavored to investigate the combined effects of ω-3 supplementation and physical training on body composition changes in young individuals. Hill et al. [55] conducted a 12-week double-blind RCT whereby young adults were allocated into 4 groups. Two groups performed aerobic exercise (running or walking, 3 times per week, 45 min, at a heart rate of 75% of their age-predicted maximum). One of these groups received capsules containing FO (1.56 g of DHA and 360 mg of EPA), while the other received placebo (6 g of sunflower oil). The two groups that did not perform aerobic exercise also received the same supplementation protocol (treatment or placebo). Although the FO plus exercise group showed a greater decrease in body fat, no differences were observed on LM across all groups. The lack of change in LM could be expected since steady-state aerobic exercise protocols have minimal hypertrophic effects.

More recently, Hayward et al. [56] randomized 28 healthy untrained young females into one of three groups, all of whom performed a supervised resistance exercise protocol: 1) control (only exercise); 2) higher-protein diet plus ω-3; and 3) higher-protein diet plus ω-3 plus creatine monohydrate. The study protocol lasted 8 weeks, with 4 weeks devoted to pre-training and 4-weeks of resistance training plus dietary intervention. Results showed no beneficial effects on LM gains for ω-3 supplementation.

The limited data to date does not support a hypertrophic benefit for ω-3 supplementation when combined with structured exercise in young adults. However, conclusions must be interpreted with caution as one study [55] employed low-intensity aerobic exercise (walking), which would not be expected to promote LM gains; and the other study that did employ resistance training [56] involved only 4 weeks of ω-3 supplementation, which may not be of sufficient duration to observe a full incorporation of n-3 PUFA into membrane cells[57] and consequently increase biological function.

317 Clearly, more studies are needed to elucidate whether ω-3 supplementation enhances the
318 accretion of LM/muscle mass in exercising young adults.
319
320 **4.2.2 Older adults**
321 Several studies have investigated the effect of ω-3 supplementation in
322 combination with exercise on muscle mass in older adults. Cornish et al. [23] randomized
323 51 older men and women to receive a supplement consisting of either 30 g of corn oil
324 (placebo) or flaxseed oil (~14 g of ALA) for 12 weeks. All subjects performed a
325 periodized total-body RT program 3 times per week. Significant increases in LM were
326 found in both groups with no differences observed between conditions.
327 Similarly, Da Boit [5] failed to demonstrate a beneficial effect of ω-3 (3 g fish oil/d)
328 on muscle mass compared to placebo (3 g safflower oil/d) in older men and women
329 performing resistance training twice weekly for 18 weeks. Curiously, none of the groups
330 significantly increased muscle cross sectional area following the lengthy study period.
331 These findings run contrary to the compelling body of literature, which shows that older
332 individuals achieve robust gains in markers of muscle mass from structured resistance
333 training [58]. This raises questions as to whether the program was sufficiently challenging
334 to bring about hypertrophic adaptations. In addition, the analysis of quadriceps muscle
335 anatomical cross- sectional area was performed on only 5 slices (the midpoint slice and
336 2 slices immediately inferior and superior to the midpoint); it therefore is possible that
337 non-uniform changes between conditions may have occurred across the muscle that went
338 undetected by the employed methodology.
339 Most recently, Cornish et al[59] carried out a double-blind study, whereby 23 older
340 men were randomly assigned to consume either 3.0 g of a combined EPA/DHA
341 supplement (1.98 g of EPA and 0.99 g of DHA) or an equal amount of an omega fatty

342 acid blend containing alpha linolenic acid (1.35 g), linoleic acid and gamma linolenic acid
343 (0.795 g), oleic acid (0.525 g). Both groups completed a 12-week total body resistance
344 training program carried out on 3 nonconsecutive days per week. Post-study results
345 showed that both groups similarly increased lean tissue mass as measured by dual x-ray
346 absorptiometry. A possible confounding issue is that the relatively high alpha linolenic
347 acid content (45%) in the control supplement may have unduly influenced findings.

348 In contrast to the aforementioned null findings, Strandberg et al. [27] conducted a
349 three-armed RCT in older women that included a diet and resistance exercise intervention.
350 Subjects were randomly allocated to either control, RT, or RT plus a healthy diet with ω-
351 6/ω-3 ratio < 2. The control and RT groups were advised to maintain their nutritional
352 habits, whereas the RT plus healthy diet increased their ω-3, PUFA and MUFA intakes
353 and decreased their saturated fat and ω-6 intakes. At the end of the 24-week intervention,
354 only the RT plus healthy diet group demonstrated an increase in leg LM (~ 2%). It should
355 be noted that the study did not aim to evaluate the effect of ω-3 supplementation alone,
356 as the ratio of other fats were altered as well. Therefore, it is only possible to conclude
357 that a "healthier" fat intake, which includes an increase of ω-3 intake, promoted benefits
358 for older individuals involved in resistance exercise.

359 In a follow up study from the same lab, Strandberg et al. [60] randomized
360 recreationally active older women to one of three groups: resistance training and ω-3 rich
361 diet; resistance training only; or controls. Increased ω-3 intake was achieved by
362 consumption of ≥ 500 g/wk of fatty fish including salmon, mackerel, and herring.
363 Subjects realized resistance training twice a week with exercises for all the major muscle
364 groups. After 24 weeks, only the group consuming higher amounts of ω-3 significantly
365 increased type 2 fiber hypertrophy as determined by muscle biopsy. As with their
366 previous study, the ratio of other dietary fats was altered in the nutritional prescription,

which in turn confounds the ability to draw causality as to the specific effects of ω-3 alone on muscular gains.

In sum, the literature remains equivocal as to whether ω-3 supplementation enhances increases in LM/muscle mass when consumed in conjunction with a regimented resistance exercise program. Further research is needed in this area to draw relevant inferences.

4.3 Ω-3 AND PHYSICAL FUNCTION

The mechanisms that explain the improvement in physical function remain to be fully elucidated, but it has been speculated that ω-3 may promote benefits on this outcome by increasing acetylcholine sensitivity and membrane fluidity [61]. Acetylcholine is a neurotransmitter that supports muscle contraction, making synaptic transmission faster at the neuromuscular junction and thus resulting in a faster contractility [61]. With respect to the cellular membrane, there may be an effect on endocytosis, exocytosis, membrane fusion, and neurotransmitter uptake and release [62]. Given that neuronal function declines with ageing, ω-3 can be an important interventional strategy for staving off these detrimental effects [26]. Considering the logical rationale for a potential benefit of ω-3 on muscle function, the following sections look at the evidence from interventional studies on the topic to determine if there is actual efficacy for supplementation.

4.3.1 Young adults (without exercise intervention)

Only one study to date investigated the effect of ω-3 supplementation on physical performance in young individuals [63]. Competitive soccer players were randomized into a group that supplemented with ω-3 (70% of EPA, 20% of DHA and 0.02 mg of vitamin E per gram) or placebo (7% of caprylic acid, 92% of capric acid, 0,9% of lauric acid, and

392 0.3% of palmitic acid). Although the study did not employ a specific exercise
393 intervention, training session intensity, competitive games, and nutritional intake were
394 monitored. After 4 weeks of supplementation, only the ω-3 group improved in a test of
395 anaerobic endurance capacity (i.e. the Yo-Yo test). Although the study's objective was to
396 evaluate the effect of ω-3 supplementation on physical function, a controlled exercise
397 intervention together with the supplementation was not performed.
398
399 **4.3.2 Older adults (without exercise intervention)**
400 Several studies have sought to investigate the effect of ω-3
401 supplementation on physical function without exercise intervention in older adults.
402 Hutchins-Wiese et al. [64] randomly assigned 118 postmenopausal women to supplement
403 with either FO (720 mg of EPA and 480 mg of DHA) or placebo (1.8 g of olive oil) for 6
404 months. Post-study evaluation of physical function revealed significant improvements in
405 walking speed for the FO group compared to placebo. The previously mentioned study
406 by Logan and Spriet [26] found that 12 weeks of FO supplementation improved functional
407 capacity by 7%, while no changes were observed in placebo group; and another study [54]
408 reported an increase in handgrip strength and 1-RM following 6 months of ω-3
409 supplementation, despite the absence of a regimented exercise intervention. It is
410 important to note that neither study [26, 54] attempted to control subjects' physical activity
411 levels during the intervention, which may have confounded results.
412 Based on limited data, the evidence shows that ω-3 supplementation may help to
413 enhance muscle function in older adults, even without an exercise component. More
414 research is need with better control of physical activity and dietary intake to confirm these
415 conclusions.
416

4.4 - Ω-3 AND PHYSICAL FUNCTION (WITH EXERCISE)

4.4.1 - Young adults

To the best of our knowledge, only one study [56] investigated the effect of ω-3 supplementation on the physical function of young adults who performed an exercise intervention. Participants were randomized into three groups that performed regimented resistance exercise: 1) control (only exercise); 2) higher-protein diet plus ω-3; and 3) higher-protein diet plus ω-3 plus creatine monohydrate for 4 weeks of supplementation. All groups showed an increase in 1-RM strength for the bench press, squat, deadlift, and hip thruster, with no differences between the interventions. This isolated finding indicates that the ω-3 supplementation does not promote greater gains in muscle strength during resistance training, although additional research is needed to better evaluate the effect of ω-3 supplementation on physical function in young adults.

4.4.2 - Older adults

Cornish et al [23] compared the effect of 30 g of corn oil (placebo) or flaxseed oil (~14 g of ALA) for 12-weeks in individuals who performed RT three times per week. Both groups increased 1-RM strength, with no additional effects in the ALA group. Contrary to these findings, Rodacki et al. [65] randomly allocated 45 older women to one of three groups: RT alone, RT + FO for 90 days, or RT + FO for 150 days (supplementation began after day 60). The FO groups received two capsules of FO (containing 0.8 g of EPA and 0.6 g of DHA) per day. Training comprised 3 sets of 8 repetitions of multiple exercises for the lower limbs performed 3 times per week. Participants were instructed to maintain their usual diet and physical activity levels, and had their eating habits evaluated by FFQ. At study's end, all groups increased their muscle

function; however, both FO groups realized greater improvements in muscle strength and functional capacity. Importantly, the absence of a placebo group is a limitation of this study, since a placebo effect can occur for muscle function improvements.

Recently, da Boit et al. [5] evaluated the effect of ω-3 (3 g fish oil/d) or placebo (3 g safflower oil/d) plus lower-limb resistance exercise training carried out twice per week for 18 weeks in older men and women. Women who supplemented with ω-3 showed greater improvements in maximal isometric torque and in muscle quality (strength per unit of muscle area). However, no beneficial effects on muscle function were observed in men after ω-3 supplementation. These sex-related differences may have be occurred because older women do not seem to increase muscle strength to the same magnitude as older men [66]; however, this is highly speculative since other research [67] failed to observe differences in strength gains between sexes.

The possible improvements in muscle function induced by ω-3 supplementation were also observed by a recent study[68]. Three groups were compared: control, RT, and RT plus a healthy diet high in ω-3 on muscle function, similar to the previous design employed by previous study performed by the same laboratory [27]. Results showed greater improvements in dynamic explosive capacity during isolated lower limb movements and multijoint exercises in the group consuming high intakes of ω-3 and MUFA and lower amounts of saturated fat and ω-6 compared to the group that only performed RT without any dietary modifications. Alternatively, the recent study by Cornish et al [59] found that supplementation with EPA and DHA had no ergogenic effect on the timed-up-and-go and 6-minute walk tests following 12 weeks of regimented resistance exercise.

Collectively, the evidence remains conflicting as to whether ω-3 supplementation promotes greater improvements in muscle function induced by resistance exercise in

older adults. This conclusion is based on somewhat limited data and more studies are needed to elucidate potential nuances and mechanisms of action.

5 - POTENTIAL LIMITATIONS OF THE CURRENT STUDIES AND SUGGESTIONS FOR THE FUTURE

We should highlight that a large number of studies included in this review did not control for food intake and physical activity levels. This confounds the ability to draw causality as to the effect of ω-3 on body composition and/or muscle function. It is important to control nutritional intake during studies focused on muscular adaptations, and particularly protein consumption, since it influences the accretion of muscle mass and physical function. Moreover, it is well-established that exercise is a primary modulator of muscle mass [69], and thus controlling physical activity levels is paramount in this regard.

The use of ω-3 supplements may cause adverse effects in gastrointestinal tract and few studies reported this information. The "fish taste" after the consumption of the supplement may characterize the study as open-label. Thus, any difference in taste, smell, mode of administration or appearance could interfere with blinding [70].

Another limitation for comparing results among studies is the high variability of the placebo provision, which includespalm oil, soya bean oil, corn oil, olive oil, coconut oil, safflower oil and ALA. Moreover, other studies compared the effects of ω-3 supplementation with a control group that had no placebo provision. Therefore, standardization of the placebo used in future studies can help to conclude the true effect of ω-3 supplementation on muscle mass and strength, since differences in placebo content can promote differential changes in fatty acid incorporations into cell membrane.

In addition, many of the studies evaluated changes in muscle mass/LM by bioimpedance, which may not have the precision to detect subtle increases in muscle mass

over short-term interventions. Thus, more studies using more accurate body composition methodologies are needed to detect changes in LM or muscle, such as CT or MRI. However, even when MRI is used, a better standardization in methodology is needed for more accurate comparison.

Therefore, these factors highlight the importance of adequate assessment of dietary intake and physical activity in future studies, as well as the correct blinding and use of gold standard methods of body composition.

6 - CONCLUSIONS

The observational studies do not show significant associations between ω-3 intake and muscle mass. The associations between ω-3 intake and muscle function do not seem to be significant after adjustments for confounders, with exception of one observational study (longitudinal design) that showed that ALA was associated with knee extension strength (Figure 1). Thus, the clinical relevance of the association between ω-3 intake and muscle function is questionable. Importantly, these studies are relegated to older individuals and thus cannot be generalized to young adults.

In addition, ω-3 supplementation does not seem to promote increases in muscle mass in sedentary young and older adults; the hypertrophic effects of supplementation when combined with resistance training remain equivocal. Moreover, there is conflicting evidence as to whether supplementation confers a beneficial effect on muscle function in older adults (Figure 1). Importantly, this conclusion is based on limited data and more studies are needed before ω-3 supplementation can be recommended as a viable strategy for such purposes in clinical practice.

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Table 1 – Studies assessing the effect of ω-3 on muscle protein synthesis (MPS), lean/fat-free mass and physical function in young individuals.

Author	Year	Study design	n (m/w)	Intervention	Control	Diet	Exercise	Time	Mainly results
Smith et al.	2011	RCT	9 (5/4)	1.86g EPA + 1.5g DHA	NC	NC	NC	8wk	ω-3 increased MPS, and also doubled the anabolic response to amino acid and insulin infusion. The concentration of Akt^{Thr308}, mTOR, and p70s6k were greater after supplementation.
McGlory et al.	2016	RCT, double-blind, controlled	19 (19/0)	3.5g EPA + 900mg DHA + 100mg DPA + 0.1mg vitamin E	5g coconut oil	3-d food diary	1 acute session	8wk	pan PKB was significantly suppressed at REST compared to before supplementation in ω-3, but not in coconut oil group. The activity of pan PKB and AMPKα2 were significantly increased REST at post exercise, and the activity of p70S6K1 was also elevated 3h after FEDEX from REST only in coconut oil group. MPS increased similarly between conditions post-exercise.
Couet et al.	1997	Clinical trial	6 (5/1)	6g fish oil	6g other fats	7-d food diary	NC	3wk of each oil	No change in FFM was found for either condition.
Sneddon et al.	2008	Crossover, double-blind, placebo-controlled	59 (59/0)	2.28g CLA + 900mg EPA + 630mg DHA	4.8g palm oil + 1.2g soya bean oil	NC	NC	12wk	Increase in FFM in young obese men of treatment group compared to control.
Noreen et al.	2010	RCT, double-blind, controlled	44 (14/30)	1.6g EPA + 800mg DHA	4g safflower oil	NC	NC	6wk	Increase in FFM and reduction in BF of treatment group compared to control.

Gravina et al.	2017	Clinical Trial	26 (19/7)	0.1 of ω-3/kg/day	0.1 of placebo/kg /day	3-d weighed food diary	Training diary		Only ω-3 group improve Yo-Yo test from pre to post supplementation (mean difference 203; 95%CI: 66 to 340; p<0.001; effect size 0.52)
Harden et al.	2014	RCT, double-blind, controlled	27 (0/27)	2.8g DHA	2.8g oleic acid	3-d food diary	NC	12wk	Any change in LM.
Hayward et al.	2016	RCT, open label, controlled	28 (0/28)	60g whey protein + 540mg EPA + 360mg DHA or 60g whey protein + ω-3 + 5g creatine	One group only in RT	7-d diary	RT 3x/wk	9wk	Significant time effects for all groups on decrease in fat mass, increase in LM, and 1-RM. No beneficial effects on LM gains for ω-3 supplementation.
Hill et al.	2007	RCT, double-blind, controlled	68 (24/44)	1.56g DHA + 360mg EPA	6g safflower oil	Weighted food record	AT 3x/wk	12wk	FO plus exercise group showed a greater decrease in BF, no differences were observed on LM across all groups.

Notes: RCT = randomized clinical trial; m = men; w = women; NA = not applicable; CLA = conjugated linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; wk = weeks; mo = months; NC = not controlled; RT = resistance training; AT = aerobic training; MPS = muscle protein synthesis; FFM = fat free mass; BF = body fat; LM = lean body mass; TUG = time up and go test; HGS = handgrip strength; 1-RM = one repetition maximum.

Table 2 – Studies assessing the effect of ω-3 on muscle protein synthesis (MPS), body composition and function in older adults.

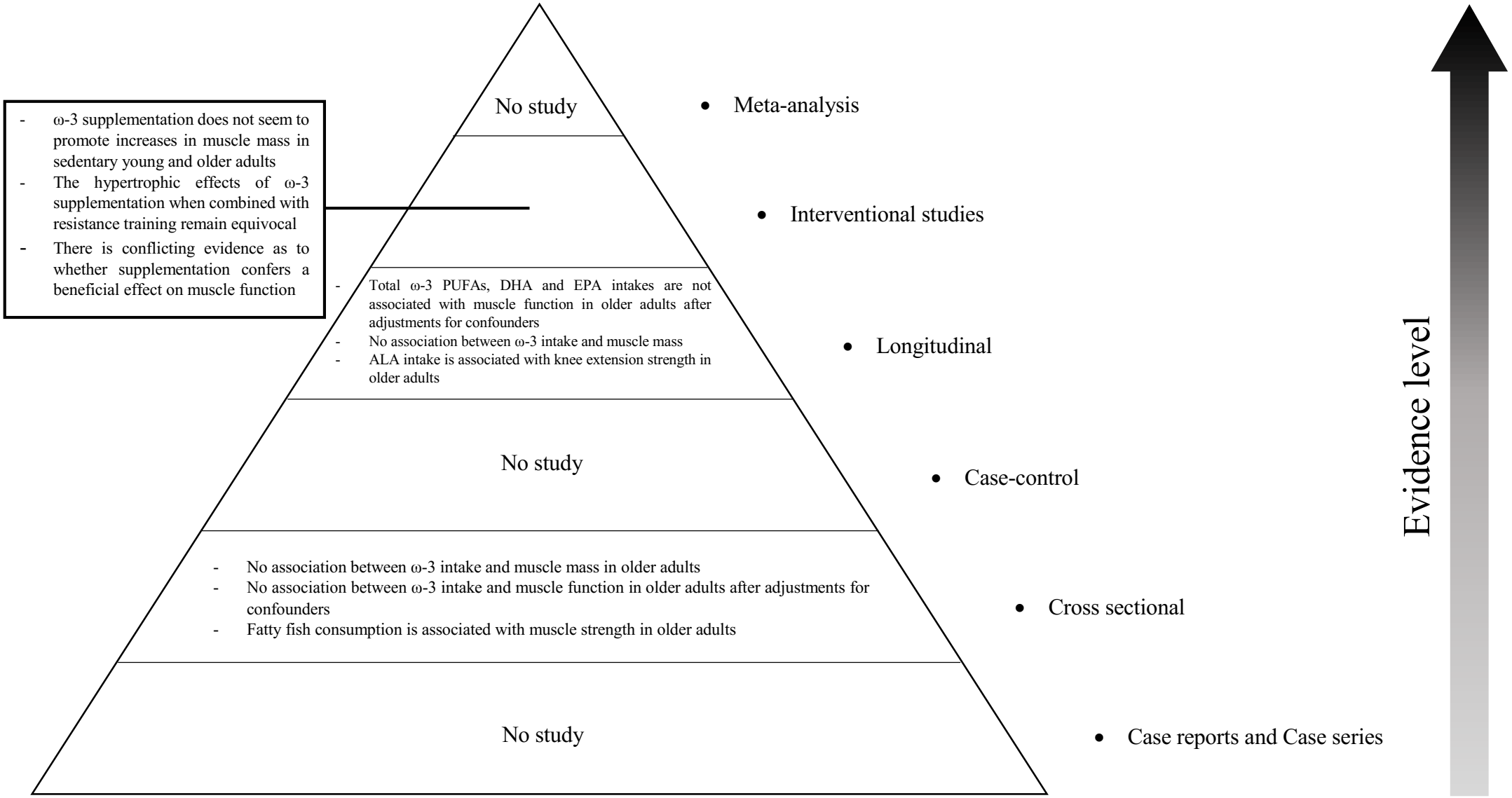
Author	Year	Study design	n (m/w)	Intervention	Placebo	Diet	Exercise	Time	Main results
Observational studies									
Robinson et al.	2008	Cross-sectional and retrospective cohort	2933 (1519/1414)	NA	NA	FFQ	NC	NA	Fatty fish was the largest predictor of HGS in men and women.
Reinders et al.	2013	Cross-sectional / Longitudinal	836 (348/488) 459 (210/249)	NA	NA	FFQ	Self-reported	5y	Muscle size and HGS were not associated with total ω-3 PUFAs , ALA, DHA and EPA at baseline and over 5 years of follow-up.. The longitudinal data showed that ALA was positively associated with increased knee extension strength.
Belury et al.	2016	Cross-sectional (baseline data from two crossover studies)	139 (40/99)	NA	NA	Fatty acid content at red blood cell membrane	Questionnaire not identified	NA	No association between ω-3 content at red blood cell membrane and LM.
Fougère et al.	2017	Longitudinal	400 (128/272)	NA	NA	ω-3 content at red blood	NC	3 y	Individuals with high levels of baseline ω-3 content at red blood cell membrane present a slower decline

						cell membrane			on gait speed over a 3-year follow-up only when not adjusted for confounders.
Fougère et al.	2017	Cross-sectional	1449 (515/934)	NA	NA	ω-3 content at red blood cell membrane	NC	NA	Low ω-3 index was associated with worse performance-based test scores of physical function only when not adjusted for confounders.
Interventional studies									
Sneddon et al.	2008	Crossover, double-blind, placebo-controlled	59 (59/0)	2.28g CLA + 900mg EPA + 630mg DHA	4.8g palm oil + 1.2g soya bean oil	NC	NC	12wk	No change in body composition.
Smith et al.	2011	RCT, double-blind, controlled	16 (10/6)	1.86g EPA + 1.5g DHA	4g corn oil	NC	NC	8wk	FO enhanced the rate of MPS as well as increasing activation of mTOR and p70s6k concentration, although no change in Akt^{Thr308} was observed.
Lalia et al.	2017	Clinical trial, open-label	12 (5/7)	2.7g EPA + 1.2mg DHA	NC	NC	1 acute session	16wk	Non-significant increases in myofibrillar protein synthesis were noted in the pre-exercise post-absorptive state; however, the rates of myofibrillar fractions were significantly higher after exercise.
Hutchins-Wiese et al.	2013	RCT, double-blind, controlled	124 (0/124)	720mg EPA + 480mg DHA	1.8g olive oil	2 food recall	NC	6mo	At baseline, frailty status was negatively correlated with serum DHA. Walking speed presented an increase in ω-3 group compared to placebo.
Smith et al.	2015	RCT, double-blind, controlled	44 (15/29)	1.86g EPA + 1.5g DHA	4g corn oil	NC	NC	6mo	Increase in thigh muscle volume, HGS, and 1-RM in ω-3 therapy compared to control group.

Logan and Spriet	2015	RCT, single-blind, controlled	24 (0/24)	2g EPA +1g DHA	3g olive oil)	3 food recall	PASE Questionaire	12wk	Increase in LM and decrease in TUG speed in ω-3 group, while no significant changes in placebo were observed.
Strandberg et al.	2015	RCT, open label, controlled	55 (0/55)	Health diet (ω-6/ω-3 ratio < 2)	One with only RT and one control group	6-day food record 3 times	RT 2x/wk	24wk	RT plus healthy diet group presented significant increase in leg lean mass, compared to both resistance training group or control.
Edholm; Strandberg and Kadi, 2017	2017	RCT, open label, controlled	63 (0/63)	Health diet (ω-6/ω-3 ratio < 2	One with only RT and one control group	6-day food record 3 times	RT 2x/wk	24wk	RT plus healthy diet group presented significant increase RT gains in dynamic explosive capacity during isolated lower limb movements and multijointed exercises in older women.
da Boit et al.	2017	RCT, double-blind, controlled	50 (27/23)	2.1g EPA + 600mg DHA	3g of safflower oil	NC	RT 2x/wk	18wk	Women showed an increase in maximal isometric torque and muscle quality in ω-3 groups, with no changes in placebo group after exercise training. No change in MPS or muscle mass.
Rodacki et al.	2012	RCT, open label, controlled	45 (0/45)	0.8g EPA + 0.6 of DHA	Group with just exercise	FFQ	RT 3x/wk	12wk	FO supplementation improved peak torque, muscle activation level, and chair-rising test.
Krzymińska-Siemaszko et al.	2015	RCT, open label, controlled	50 (17/33)	660mg EPA + 440 mg DHA + 200 mg other ω-3 + 10mg vitamin E	10mg vitamin E	NC	NC	12wk	No change in body composition, muscle strength, or function.

Tardivo et al.	2015	RCT, open label, controlled	63 (0/63)	540mg EPA + 360mg DHA	Only diet	3 food recall	NC	6mo	No change in body composition.
Cornish et al.	2018	Randomized, double-blind, controlled	23 (23/0)	1.98 grams of EPA and 0.99 of DHA	alpha linolenic acid, linoleic acid and gamma linolenic acid, oleic acid	3-day food diary	RT 3x/wk	12wk	No ergogenic effect on the timed-up-and-go, 6-minute walk tests and LM induced by omega-3 supplementation
Cornish and Chilibeck	2009	RCT, double-blind, controlled	51 (28/23)	14g ALA	30ml of corn oil	FFQ	RT 3x/wk	12wk	No change in body composition or muscle strength.

Notes: RCT = randomized clinical trial; m = men; w = women; NA = not applicable; CLA = conjugated linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; y = years; wk = weeks; mo = months; FFQ = food frequency questionnaire; NC = not controlled; RT = resistance training; AT = aerobic training; MPS = muscle protein synthesis; FFM = fat free mass; BF = body fat; LM = lean body mass; TUG = time up and go test; HGS = handgrip strength; KES = knee extension strength; 1-RM = one repetition maximum.


- ω-3 supplementation does not seem to promote increases in muscle mass in sedentary young and older adults
- The hypertrophic effects of ω-3 supplementation when combined with resistance training remain equivocal
- There is conflicting evidence as to whether supplementation confers a beneficial effect on muscle function
No study
• Meta-analysis
• Interventional studies
- Total ω-3 PUFAs, DHA and EPA intakes are not associated with muscle function in older adults after adjustments for confounders
- No association between ω-3 intake and muscle mass
- ALA intake is associated with knee extension strength in older adults
• Longitudinal
No study
• Case-control
- No association between ω-3 intake and muscle mass in older adults
- No association between ω-3 intake and muscle function in older adults after adjustments for confounders
- Fatty fish consumption is associated with muscle strength in older adults
• Cross sectional
No study
• Case reports and Case series
Evidence level

Artigo 2: Association between omega-3 fatty acids intake and muscle strength in older adults: a study from National Health and Nutrition Examination Survey (NHANES) 1999-2002.

Original Article

Association between omega-3 fatty acids intake and muscle strength in older adults: a study from National Health and Nutrition Examination Survey (NHANES) 1999-2002.

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Abstract

Background: Muscle strength is a predictor of mortality in older adults and some dietary components are associated with this variable; however, little is known about the association between omega-3 fatty acids intake (ω-3) and strength in older adults.

Objective: To assess whether ω-3 dietary intake is associated with muscle strength in individuals over 50 years. We also aimed to evaluate whether an isocaloric replacement of dietary fatty acids types by ω-3 intake could be associated with higher muscle strength

Methods: This study included older adults aged from 50 to 85 y, from National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2001-2002. A total of 2141 individuals (1119 men and 1022 women) were evaluated and provided complete and reliable dietary intake and isokinetic strength of the knee extensors (peak force) data. Linear regression analysis was conducted without (Model 1) and with adjustments (Model 2). Isocaloric substitution analysis were performed to evaluate the substitution of other fatty acids (polyunsaturated (excluding ω-3), ω-6, monounsaturated, saturated) by total ω-3, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA).

Results: Total ω-3, DHA, EPA and ALA intakes were positively associated with peak force in men (Model 1). However, after the adjustments for confounders (Model 2), only total ω-3 intake remained significant. Ω-3 intake was not associated in women. The isocaloric substitution of saturated, polyunsaturated, monounsaturated fats and ω-6 by ω-3 were not associated with peak force.

Conclusion: The intake of total ω-3 was positively associated with muscle strength in older men, but not in older women. In addition, the substitution of other fatty acids by ω-3 intake were not associated with higher strength.

Keywords: Omega-3; Muscle strength; Aging.

Introduction

Aging leads to a decrease in muscle strength [1, 2], which may occur 2–5 times faster than the muscle mass loss [3]. Low muscle strength is associated with higher risk of falls [4], lower ability to perform activities of daily living [5] and higher risk of death [6, 7], being a better predictor of risk of mortality than the amount of muscle mass [8-10]. Several factors can predict the low muscle strength, such as smoking, cardiovascular disease, hypertension, diabetes mellitus [11], physical inactivity [11, 12] and low protein intake [13, 14].

Few studies have evaluated the association between omega-3 fatty acids (ω-3) intake and muscle strength in older adults [15-17]. The first study to raise a hypothesis about the relationship between ω-3 and muscle strength showed that the consumption of fatty fish, a ω-3 food source, was the largest predictor of handgrip strength in older adults [16]. However, this study did not evaluate the ω-3 intake per se [16], which limits the conclusion of a direct association with strength. To the best of our knowledge, only one study evaluated the association between omega-3 (blood markers of ω-3 intake) and muscle strength [17]. Reinders et al. [17] investigated the association of plasma total ω-3 polyunsaturated fatty acids, alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) with muscle strength in older adults at baseline and after 5 years of follow-up. Total ω-3, ALA, DHA and EPA were not associated with handgrip strength in cross-sectional and longitudinal data. However, ALA was positively associated with increased knee extension strength after 5 years of follow-up. These studies suggest that ω-3 intake might be associated with muscle strength in older adults, but this conclusion is based on limited data and the clinical relevance of this association is still questionable [15]. Therefore, more studies evaluating the association between ω-3 and strength in other populations are needed.

One of the possible explanations for muscle strength losses during aging can be the increase of pro-inflammatory markers, such as interleukin-6 and C-reactive protein [18]. Thus, considering that ω-3 presents anti-inflammatory properties [19], while other fatty acids, such as saturated fat [20] and ω-6 [21] may increase the inflammation [22], it is possible to speculate that a substitution of saturated fat and ω-6 by ω-3 could decrease the inflammation and increase the chance to present higher muscle strength. However, these dietary fatty acids substitutions were not still evaluated.

Therefore, considering the health problems that can be caused by low muscle strength, it is important to conduct studies investigating whether higher ω-3 intake or the

substitution of other types of fat by ω-3 are associated with strength in older individuals. Thus, the aim of our study was to investigate whether ω-3 dietary intake is associated with muscle strength in individuals over 50 years derived from National Health and Nutrition Examination Survey (NHANES) 1999-2002. In addition, our second aim was to evaluate whether an isocaloric replacement of dietary fatty acids types by ω-3 intake could be associated with higher muscle strength. We hypothesized that individuals with higher consumption of ω-3 and the isocaloric replacement of other types of fatty acids by ω-3 would be associated with higher strength.

Methods

Participants

This study included older adults aged from 50 to 85 y, from NHANES 1999-2000 and 2001-2002 [23]. A total of 2141 individuals (1119 men and 1022 women) were evaluated and provided complete and reliable dietary intake and isokinetic strength of the knee extensors (peak force) data. The National Center for Health Statistics of the Centers for Disease Control and Prevention conducted a series of cross-sectional surveys using a multistage, stratified sampling design to assess the nutritional status and health of a nationally representative sample of the non-institutionalized U.S. population.

In this survey, participants complete in-home interviews, physical examinations, dietary interviews, and post examination [23]. Individuals over 50 years, who had demographic, anthropometric, body composition, physical activity, smoke, diabetes, hypertension and dietary data; and performed strength tests were included in the analyzes. Pregnant women and who present any amputation, those with implausible energy intake (<800 and >4000 kcal or <500 and >3500 kcal for men and women, respectively) [24] or those with implausible peak force velocity [25], and also who did not perform at least 4 trials in the strength test were excluded (Figure 1).

Dietary intake

Dietary intake data were collected by an interviewer who administered one 24h dietary recall for each volunteer. NHANES 1999–2000 and 2001 survey were evaluated through a 4-step multiple pass approach [26, 27]. In NHANES 2002, the dietary intake was assessed according to the U.S. Department of Agriculture (USDA) Automated Multiple-Pass Method, which uses a 5-step procedure to quantify 24-hour food and

beverage intake [27, 28]. Total ω-3 intake was estimated by the sum of ALA (18:3n-3), DHA (22:6n-3), EPA (20:5n-3), stearidonic acid (SDA, 18:4n-3), docosapentaenoic acid (DPA, 22:5n-3) and eicosatetraenoic (ETA, 20:4n-3). Linoleic acid (18:2n-6) was considered as total ω-6, since this was the only ω-6 fatty acid available in NHANES data. To calculate ω-6/ω-3 ratio, total ω-6 was divided by total ω-3 intake.

Food Intake Analysis System (FIAS) version 3.99 with the USDA 1994-98 Survey Nutrient Database was used to code and report the NHANES 1999-2000 dietary data. The USDA Food and Nutrient Database for Dietary Study, version 1, was used for processing the intakes for 2001-2002.

Muscle strength

Kinetic Communicator isokinetic dynamometer (Kin Com MP, Chattecx Corp., Chattanooga, TN) was used to evaluate voluntary peak isokinetic knee extensor strength. The individuals performed 6 measurements of muscle strength of the right quadriceps, at a speed (60 degrees/second). Individuals who presented peak force velocity with extreme values (<55 degrees/second or >65 degrees/second) were excluded from the analysis [25]. In the first 3 trials, the individuals were encouraged to not exert the maximal effort, since this part of the test was used for movement learning and warm-up. In the last 3 trials, they were strongly encouraged to perform the maximal effort for muscle strength measurement. If the individual completed 4-6 trials, the highest peak force value was used. The individuals who completed fewer than 4 trials were excluded. Individuals who presented history of myocardial infarction within the past six weeks, knee surgery or knee replacement surgery, chest or abdominal surgery within the past three weeks, history of brain aneurysm or stroke, or severe back pain did not perform the muscle strength evaluation.

Body composition

Whole body dual-energy x-ray absorptiometry (DXA) scans were taken with a Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts). Due to invalid and missing data (50-59 years: 75% of valid DXA;60-69 years: 72% of valid DXA; 70-79 years: 70% of valid DXA; over 80 years: 59% of valid DXA), multiple imputation was performed using the sequential regression imputation method [29]. Survey Methodology Program at the University of Michigan's Institute of Survey Research developed a SAS-callable imputation and variance estimation software, which

was used to impute the NHANES DXA data [30]. The Muscle Mass Index (MMI) was calculated by dividing appendicular lean mass (kg) to height squared [31].

Covariates of interest

Demographic characteristics evaluated in this study were age (years), sex (men or women), race/ethnicity (non-Hispanic white or other), marital status (single/divorced/widowed/never married or married/living as married), education level (under/high school graduate and some college or over) and annual family income (until $19999, from $20000 to 54999 or over $55000). Morbidities and lifestyle conditions included were hypertension (yes or no), diabetes (pre-diabetes, yes or no), menopausal (yes or no) and smoke status (yes or no). Physical activity was evaluated in the past 30 days and was classified as moderate (at least ten minutes that caused light sweating or a slight to moderate increase in heart rate or breathing) or vigorous (at least 10 minutes that caused heavy sweating, or large increases in breathing or heart rate) (yes or no); whether the individuals performed strength exercises (yes or no) was also evaluated. In the adjustments, physical activity was considered as yes or no. For this, a new variable (physical activity) was created considering the 3 types of exercise. If the individual performed at least one activity, i.e., if the response was yes for any type of physical activity (moderate, vigorous or strength), the variable physical activity was rated as "yes". If the individual did not perform any type of physical activity, i.e. answered no to all the 3 types, he was classified as "no". For dietary supplementation (yes or no), all types of supplements were included as adjustments, including those containing ω-3 in its composition. Regarding dietary intake, total energy intake (kcal/day), protein intake (g/day) and alcohol intake (g/day) were used as adjustments. Body weight (kg) was also inserted in the adjustments.

Statistical analyzes

U.S. adult population-based estimates for demographic characteristics, health conditions and habits, physical activity, anthropometric and body composition, strength, muscle quality, and dietary habits were generated for participants by quartiles of total ω-3 intake. Quartiles were compared using linear regression. For the association between peak force and ω-3 consumption (total and subtypes), the total ω-3 and the isolated subtypes were divided into their respective quartiles. Analyzes were performed without (Model 1) and with adjustments for confounders, such as age, sex, race/ethnicity, marital

status, annual family income, diabetes (pre-diabetes/yes/no), hypertension (yes/no), smoke (yes/no), physical activity (yes/no), energy (kcal/day), protein intake (g/day), alcohol intake (g/day), supplement intake (yes/no) and body weight (Model 2). We run analyses stratified by sex, and in the analyzes performed for women we also included menopause in the adjustments. Linear regressions were used to identify the trends for the association between peak force and ω-3 consumption.

We estimated the effect of isocaloric substitution of saturated, monounsaturated and polyunsaturated (excluding ω-3) fats, and ω-6 by total ω-3, ALA, EPA and DHA through regression analysis. In this way, energy and nutrient densities of macronutrients were included in isocaloric substitutions models. The percentage of replacement (0.5% or 2.0%) of other types of fat by ω-3 were chosen by the researchers taking into account the physiological translation of these values. On average, an increase of 0.5% in the total caloric intake from ω-3 simulates an increase in consumption of ~1.0 g, whereas an increase of 2.0% represents a greater consumption of ω-3 (~8 g per day).

Analyzes were performed using Stata 14 software (StataCorp, College Station, TX, USA). Data are presented as mean or percentage ± standard deviation or confidence interval. Significant difference was defined by $p<0.05$. All statistical analyzes were performed taking into account the survey design characteristics of NHANES (strata, cluster and sample weights) [23] through Stata SVY commands.

Results

Individual's characteristics

Individuals' characteristics are presented in Table 1. Individuals with higher ω-3 intake were predominantly women, younger, non-Hispanic white, with a higher annual income, education level and percentage of moderate and vigorous physical activity practicing. The individuals with higher ω-3 consumption presented higher body weight, height, lean mass, MMI and muscle strength; and lower body fat percentage. For food intake, the individuals that ingested greater amount of ω-3 consumed more calories, carbohydrate, protein, lipids and fiber; and lower ω-6/ω-3 ratio.

In older men, a higher proportion of non-Hispanic white, higher income and education level was noted according to the progression of quartiles of ω-3 intake. In addition, the older men who ingested more ω-3 presented higher height, total lean mass, MMI and strength (Supplementary Table 1). In relation to women, a higher proportion of

non-Hispanic white and individuals performing moderate physical activity was noted according to the progression of quartiles of ω-3 intake (Supplementary Table 2).

Peak force and ω-3

Table 2 presents the linear regression analyzes between ω-3 intake and peak force. We found specific associations for men. Total ω-3, DHA, EPA and ALA intakes were positively associated with peak force among men in unadjusted analyzes (Model 1). However, after the adjustments for confounders (Model 2), only total ω-3 intake remained significant. No associations were observed for women.

Substitution analyzes

The isocaloric substitution of saturated (Figure 2A), polyunsaturated (Figure 2B), monounsaturated (Figure 2C) fats and ω-6 (Figure 2D) by total ω-3, EPA, DHA and ALA were not associated with peak force in men and women.

Discussion

The main result of the present study was that the intake of total ω-3 was positively associated with peak force in older men, but not in older women. To the best of our knowledge, this is first observational study showing these results. In addition, the replacement of saturated, monounsaturated and polyunsaturated (excluding ω-3) fats, and ω-6 by ω-3 were not associated with higher muscle strength. These results show that the association observed between ω-3 and muscle strength seems to be related to an increase of ω-3 intake per se, and not due to the substitution of other types of fat by ω-3.

Although other studies evaluated the association between ω-3 intake and muscle function, such as gait speed [32, 33]; only one study [17] associated ω-3 intake with strength, which is comparable with our findings. Reinders and colleagues [17] evaluated 836 older adults (aged 66–96 y) with cross-sectional measures of muscle strength parameters (grip strength and knee extension strength) and plasma phospholipid ω-3 polyunsaturated fatty acids (blood markers of ω-3 intake). After adjustments for sex, age and physical activity, EPA was associated with knee extension strength; and total ω-3 polyunsaturated fatty acids, DHA and EPA were associated with grip strength. However, after the inclusion of education level, smoking status, BMI, diabetes, chronic obstructive pulmonary disease, coronary heart disease, microalbuminuria, and C-reactive protein as adjustments, the associations were no longer significant [17]. These results show that

plasma ω-3 was only indirectly associated with muscle strength. In the present study, we observed that total ω-3, DHA, EPA and ALA intakes were positively associated with peak force (all individuals and men) in crude model. However, after the adjustments for confounders (Model 2), total ω-3 intake remained significant only for men, suggesting a sex-specific association. The differences in the results observed between the study of Reinders et al [17] and ours can be possible explained due to three main factors. First, while the present study evaluated the ω-3 intake by 24-hour dietary recall, Reinders et al [17] estimated it by plasma phospholipid ω-3 polyunsaturated fatty acids. Second, different variables were included as adjustments in statistical analysis. Third, Reinders et al [17] evaluated men and women together, while we evaluated the total sample, and also men and women separately. Because we found a sex-dependent association, we suggest that future studies that will assess the association between ω-3 intake and strength evaluate men and women separately.

The sex-dependent association observed in the present study can be probably explained due to sex-differences in ω-3 metabolism. We noted that men and women ingested similar amounts of total ω-3, being the most part consisted of ALA. In men, 8% and 4% of ALA are converted to EPA and DHA, respectively [34]; while the conversion of ALA to EPA and DHA is more efficient in women (21% and 9%, respectively) [35]. Therefore, it is possible to speculate that the older men evaluated in the present study may have more ALA in the plasma derived from ALA intake, when compared to women. In a longitudinal study, Reinders et al [17] showed that only ALA plasma phospholipids were associated with knee extension strength after 5-years follow-up. Therefore, it seems that ALA can have effects on muscle strength; however, more studies are needed evaluating the effects of different ω-3 types on muscle strength to confirm this hypothesis, since it is only speculative.

The mechanisms that explain the association between ω-3 and muscle strength are not fully elucidated, but it has been suggested that ω-3 may promote benefits on strength by increasing acetylcholine sensitivity and membrane fluidity [36]. Acetylcholine is a neurotransmitter that supports muscle contraction, making synaptic transmission faster at the neuromuscular junction and thus resulting in a faster contractility [36]. With respect to the cellular membrane, there may be an effect on endocytosis, exocytosis, membrane fusion, and neurotransmitter uptake and release [37]. Another possible mechanism can be related with inflammation, since strength losses during aging seems to be partially caused by increases of pro-inflammatory markers [18]. Thus, considering that ω-3 presents anti-

inflammatory properties [19], a greater ω-3 intake could decrease inflammation and affect the muscle strength.

The present study showed that an increased intake of ~2.7 g of ω-3 (last vs. first quartile in men; Supplemental Table 1) was associated with an increase of 21.0 Newtons, which is equivalent to approximately 2.1 kg of strength (Table 2). These results seem to be physiologically relevant since an increase of 1 kg of strength can decrease the risk of multiple falls by 17% [38]. Future longitudinal studies should be performed to evaluate the association between ω-3 intake, strength and risk of falls.

We also performed isocaloric substitution analyzes, which comprises a statistical technique in which some nutrient or food group is replaced by another [39]. Several types of fat (polyunsaturated, monounsaturated, saturated and ω-6) were replaced by ω-3 in both men and women. The substitution analyzes did not show an association with strength, suggesting that the increase of ω-3 while decreasing another type of fat is not associated with strength. Thus, evaluating all the data of the present study, it is possible to suggest that the increase of ω-3 intake is associated with muscle strength, independently of the intake of other type of fat.

This study presented limitations. First, dietary data was evaluated by one 24 h dietary recall for each volunteer, which may be a limitation to assess ω-3 dietary intake fluctuations. Second, we did not measure plasma or membrane phospholipid ω-3 polyunsaturated fatty acids, which is an effective blood marker to estimate long-term ω-3 consumption [40]. Third, the present data refers only to ω-3 intake from food sources and individuals may have consumed dietary supplements containing this nutrient. However, to minimize this limitation, the analyzes were adjusted for supplement intake (yes/no). Fourth, some covariables were not included in the analyzes (such as presence/absence of some diseases and use of medication that can influence muscle strength) due to the absence of data for all the volunteers. Fifth, the database survey contains dietary data for only one type of ω-6 (linolenic), and other important types, such as arachidonic acid, were not evaluated; which may result in underestimation of ω-6 intake. Finally, due to the cross-sectional design, causality cannot be stablished. As strengths, the analyzes were weighted conducted, which allows to evaluate a representative data from United States of America population. Additionally, all analyses were adjusted for important confounders. Furthermore, the muscle strength was accurately measured, which reduced the possibility of bias.

In conclusion, the intake of ω-3 was positively associated with peak force in older men, but not in older women. Therefore, these findings suggest that the association between ω-3 and muscle strength seems to be sex-dependent. In addition, the substitution of other fatty acids by ω-3 intake were not associated with higher strength. These results show that the association between ω-3 and muscle strength seems to be related to an increase of ω-3 intake per se, and not by the substitution of other types of fat by ω-3.

Conflicts of interest

The authors declare no conflicts of interest.

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Authorship

LTR participated in interpretation of the data, performed statistical analysis, and wrote the manuscript; FMSB participated in analysis and interpretation of the data. CMA and AEMR: participated in the configuration of datasets, organization of the statistical analysis and contributed with the revision of the manuscript. EPO participated in the interpretation of the data, wrote, and contributed with the revision of the manuscript. All authors read and approved the final manuscript.

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Table 1. Sociodemographic, healthy conditions and habits, physical activity, anthropometric and body composition, strength and dietary habits of older adults by quartile of omega-3 intake. NHANES, 1999-2002.

Variables	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value
Demographic						
Age, y	62.56 (9.47)	63.44 (10.00)	62.99 (9.84)	61.43 (9.02)	62.56 (8.93)	0.050
Sex, %						<0.001
Male	51.55 (48.84 - 54.25)	62.55 (57.13 – 67.67)	55.00 (49.61 – 60.27)	46.45 (41.28 – 51.69)	42.85 (37.39 – 48.50)	
Female	48.44 (45.74 – 51.15)	37.44 (32.32 – 42.86)	44.99 (39.72 – 50.38)	53.54 (48.30 – 58.71)	57.14 (51.49 – 62.60)	
Race, %						<0.001
Non-Hispanic white	82.06 (80.22 – 83.76)	77.43 (73.08 – 81.26)	79.70 (75.771 – 83.14)	82.90 (79.14 – 86.09)	88.19 (85.25 – 90.60)	
Marital status, %						0.062
Single/ Divorced/ Widowed/ Never Married	27.12 (24.85 – 29.51)	29.43 (24.74 – 34.60)	29.65 (25.13 – 34.61)	25.41 (21.33 – 29.98)	24.12 (19.77 – 29.07)	
Married/ Living as married	72.87 (70.48 – 75.14)	70.56 (65.39 – 75.25)	70.34 (65.38 – 74.86)	74.58 (70.01 – 78.66)	75.87 (70.92 – 80.22)	
Annual Family Income, %						0.003
$0-19999	26.78 (24.52 – 29.18)	32.21 (27.41 – 37.42)	30.07 (25.48 – 35.09)	21.15 (17.41 – 25.45)	24.43 (19.95 – 29.55)	
$20000-54999	38.27 (35.70 – 40.91)	36.64 (31.50 – 42.10)	37.74 (32.742 – 43.01)	40.47 (35.55 – 45.59)	37.92 (32.70 – 43.42)	
Over $55000	34.93 (32.319 – 37.64)	31.13 (26.04 – 36.73)	32.19 (27.17 – 37.64)	38.37 (33.27 – 43.73)	37.64 (32.39 – 43.19)	
Education level						0.005
Under high school graduate	47.51 (44.82 – 50.22)	51.06 (45.52 – 56.58)	51.51 (46.12 – 56.87)	46.33 (41.21 – 51.53)	41.12 (35.82 – 46.64)	
Some college or over	52.48 (49.77 – 55.17)	48.93 (43.41 – 54.47)	48.48 (43.12 – 53.87)	53.66 (48.46 – 58.78)	58.87 (53.35 – 64.17)	
Health conditions and habits						
Hypertension, %						0.086
Yes	40.65 (38.02 – 43.33)	45.82 (40.36 – 51.398)	40.73 (35.59 – 46.08)	36.51 (31.71 – 41.58)	40.20 (34.85 – 45.79)	
No	59.34 (56.66 – 61.97)	54.174 (48.60 – 59.63)	59.26 (53.91 – 64.40)	63.49 (58.41 – 68.28)	54.20 (54.20 – 65.14	
Diabetes, %						0.878
Pre-diabetes	1.91 (1.32 – 2.74)	2.11 (0.93 – 4.72)	0.95 (0.39 – 2.30)	2.74 (1.60 – 4.65)	1.75 (0.79 – 3.84)	
Yes	9.56 (8.15 – 11.11)	10.27 (7.51 – 13.90)	9.70 (7.17 – 13.01)	6.93 (5.01 – 9.53)	11.72 (8.49 – 15.96)	
No	88.52 (86.79 – 90.06)	87.60 (83.63 – 90.72)	89.33 (85.941 – 91.98)	90.31 (87.34 – 92.65)	86.51 (82.31 – 89.96)	
Smoke, %						0.339
Yes	15.11 (13.30 – 17.12)	17.61 (13.81 – 22.19)	12.73 (9.65 – 16.62)	17.01 (13.14 – 21.34)	12.94 (9.77 – 16.95)	
No	84.88 (82.870 - 86.69)	82.38 (77.80 – 86.18)	87.26 (83.37 – 90.34)	82.89 (78.65 – 86.58)	87.05 (83.04 – 90.22)	
Physical activity						
Moderate PA in past 30 days, %						0.012
Yes	50.58 (47.87 – 53.29)	46.68 (41.20 – 52.25)	49.93 (44.56 – 55.30)	48.07 (42.89 – 53.29)	58.06 (52.48 – 63.44)	
No	49.41 (46.70 – 52.12)	53.31 (47.74 – 58.79)	50.06 (44.69 – 55.43)	51.92 (46.70 – 57.113)	41.93 (36.55 – 47.51)	
Vigorous PA in past 30 days, %						0.038

Yes	27.03 (24.63 – 29.58)	25.40 (20.76 – 30.68)	23.86 (19.37 – 22.02)	26.50 (22.04 – 31.50)	32.62 (27.59 – 38.09)	
No	72.96 (70.41 – 75.36)	74.59 (69.32 – 79.24)	76.13 (70.97 – 80.62)	73.49 (68.49 – 77.95)	67.37 (61.90 -72.41)	
Strength PA in past 30 days, %						0.164
Yes	20.59 (18.44 – 22.92)	19.01 (15.02 – 23.77)	19.59 (15.53 – 24.42)	20.10 (16.22 – 24.64)	23.477 (19.23 – 29.00)	
No	79.40 (77.07 – 81.55)	80.98 (76.22 – 84.97)	80.403 (75.58 – 84.46)	79.89 (75.35 – 83.77)	76.22 (70.99 – 80.76)	
Anthropometric and body composition						
Weight, kg	80.24 (17.97)	78.08 (18.40)	79.31 (18.34)	81.44 (17.08)	81.98 (17.86)	0.003
Height, m	1.67 (0.09)	1.65 (0.10)	1.66 (0.10)	1.68 (0.09)	1.69 (0.09)	<0.001
Body mass index, kg/m^2	28.39 (5.51)	28.26 (5.72)	28.51 (5.667)	28.51 (5.35)	28.27 (5.32)	0.975
Total lean mass, kg	49.17 (11.65)	46.52 (11.04)	48.19 (11.85)	50.34 (11.04)	51.51 (12.01)	<0.001
Muscle mass index, kg/m^2	7.37 (1.41)	7.09 (1.35)	7.30 (1.43)	7.52 (1.36)	7.57 (1.46)	<0.001
Total fat mass, kg	29.41 (10.25)	29.98 (10.90)	29.49 (10.52)	29.42 (10.12)	28.785 (9.39)	0.154
Total fat mass, %	36.05 (7.90)	37.60 (7.95)	36.595 (8.05)	35.465 (7.99)	34.62 (7.22)	<0.001
Strength						
Peak force, Newtons	375.56 (123.21)	345.72 (118.59)	364.62 (113.09)	391.11 (124.76)	398.84 (127.16)	<0.001
Time to peak force, seconds	1.07 (0.53)	1.08 (0.62)	1.09 (0.62)	1.05 (0.43)	1.06 (0.44)	0.546
Angle of peak force, degree	122.26 (7.32)	122.93 (7.27)	122.02 (7.40)	122.35 (6.93)	121.73 (7.65)	0.769
Peak force velocity degree/second	60.68 (0.62)	60.67 (0.66)	60.68 (0.58)	60.70 (0.60)	60.66 (0.62)	0.315
Dietary Intake						
Energy, kcal/day	1906 (697)	1331 (5153)	1755 (551)	2146 (586)	2361 (651)	<0.001
Carbohydrate, g/day	236.71 (97.57)	185.43 (81.43)	225.70 (86.86)	264.25 (96.38)	267.48 (99.52)	<0.001
Carbohydrate, %	50.15 (11.20)	55.71 (11.29)	51.32 (10.58)	48.86 (10.18)	44.88 (10.05)	<0.001
Protein, g/day	73.37 (31.36)	51.49 (24.11)	68.51 (25.41)	81.56 (27.20)	90.81 (33.22)	<0.001
Protein, %	15.64 (4.55)	15.64 (4.84)	15.89 (4.64)	15.46 (4.15)	15.59 (4.59)	0.597
Protein, g/kg/day	0.94 (0.41)	0.69 (0.36)	0.89 (0.36)	1.03 (0.37)	1.13 (0.42)	<0.001
Lipids, g/day	72.29 (33.92)	41.42 (18.17)	61.46 (22.03)	83.17 (25.98)	101.85 (33.00)	<0.001
Lipids, %	33.88 (9.16)	28.66 (8.90)	31.97 (7.58)	35.45 (8.17)	39.28 (8.51)	<0.001
Total Ω3, g/day	1.676 (1.261)	0.608 (0.170)	1.094 (0.149)	1.704 (0.208)	3.319 (1.509)	<0.001
EPA, g/day	0.042 (0.153)	0.005 (0.015)	0.012 (0.032)	0.024 (0.061)	0.130 (0.281)	<0.001
DHA, g/day	0.077 (0.211)	0.014 (0.023)	0.033 (0.052)	0.057 (0.084)	0.210 (0.381)	<0.001
ALA, g/day	1.413 (1.092)	0.522 (0.167)	0.936 (0.190)	1.467 (0.266)	2.7418 (1.402)	<0.001
Total Ω6, g/day	13.693 (8.566)	6.264 (3.460)	10.018 (3.790)	15.149 (5.299)	23.280 (9.020)	<0.001
Ω6/ Ω3 ratio	9.05 (4.20)	10.70 (6.59)	9.19 (3.35)	8.87 (2.90)	7.468 (2.28)	<0.001
Saturated fat, g/day	22.87 (12.01)	14.03 (7.28)	20.41 (9.38)	26.97 (11.44)	29.53 (12.45)	<0.001
Polyunsaturated fat, g/day	15.51 (9.55)	6.92 (3.55)	11.25 (3.85)	17.04 (5.46)	26.75 (9.71)	<0.001
Monounsaturated fat, g/day	26.53 (13.53)	15.52 (7.87)	23.29 (10.47)	30.82 (11.74)	35.94 (13.57)	<0.001
Fiber, g/day	15.93 (9.59)	12.39 (7.36)	14.81 (8.65)	17.29 (10.09)	19.07 (10.33)	<0.001
Alcohol, g/day	7.82 (23.03)	6.24 (22.16)	8.60 (23.22)	8.08 (24.09)	8.23 (22.24)	0.336

Notes: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ALA: alpha linolenic acid. Data described as mean (standard deviation) or percentage (confidence interval).

Table 2. Weighted linear regression between quartiles of omega-3 intake and peak force (Newtons). NHANES, 1999-2002.

			Model 1		***p-trend***			**Model 2**		***p-trend***
			β (95%CI)					**β (95%CI)**		
	Q1	**Q2**	**Q3**	**Q4**		**Q1**	**Q2**	**Q3**	**Q4**	
Total Ω3										
Total	1	18.89 (0.97; 36.81)	45.39 (26.48; 64.30)	53.11 (32.90; 73.33)	**<0.001**	1	3.79 (-8.33; 15.92)	7.79 (-4.65; 20.59)	13.44 (-0.44; 27.32)	0.057
Men	1	-2.83 (-31.72; 26.04)	34.05 (5.84; 62.26)	43.86 (15.67; 72.06)	**<0.001**	1	-8.43 (-30.10; 13.22)	14.14 (-7.08; 35.36)	20.85 (-1.90; 43.61)	**0.012**
Women	1	18.64 (2.41; 34.88)	12.94 (-4.11; 30.00)	5.10 (-13.80; 24.01)	0.585	1	14.78 (0.76; 28.80)	3.83 (-11.24; 18.92)	4.96 (-12.14; 22.08)	0.842
DHA										
Total	1	-2.61 (-20.78; 15.56)	9.35 (-9.24; 27.94)	30.31 (10.85; 49.77)	**0.001**	1	-9.785 (-21.75; 2.18)	-2.11 (-13.38; 9.16)	5.43 (-7.18; 18.05)	0.256
Men	1	-4.60 (-29.20; 19.98)	14.64 (-9.99; 39.27)	37.20 (12.08; 62.32)	**0.001**	1	-18.40 (-37.79; 0.97)	-8.67 (-26.95; 9.60)	1.67 (-18.11; 21.47)	0.664
Women	1	-1.80 (-19.17; 15.56)	5.34 (-11.71; 22.39)	11.91 (-5.92; 29.75)	0.145	1	-1.18 (-16.03; 13.65)	-0.54 (-13.84; 12.74)	6.91 (-8.81; 22.65)	0.431
EPA										
Total	1	-3.39 (-26.73; 19.93)	5.91 (-10.85; 22.68)	22.29 (4.83; 39.76)	**0.018**	1	7.88 (-7.70; 23.47)	-5.71 (-16.09; 4.65)	-0.17 (-11.42; 11.08)	0.789
Men	1	15.47 (-13.74; 44.69)	11.06 (-10.39; 32.52)	25.59 (3.37; 47.80)	**0.030**	1	11.06 (-11.53; 33.65)	-5.48 (-22.73; 11.77)	-3.21 (-21.04; 14.61)	0.719
Women	1	-5.75 (-24.55; 13.05)	2.51 (-13.91; 18.95)	7.88 (-8.72; 24.49)	0.358	1	5.63 (-14.26; 25.53)	-3.76 (-16.37; 8.83)	2.48 (-11.15; 16.12)	0.888
ALA										
Total	1	12.55 (-5.82; 30.93)	38.59 (19.22; 57.97)	44.97 (24.72; 65.22)	**<0.001**	1	-0.58 (-12.84; 11.66)	0.59 (-12.52; 13.72)	12.39 (-1.83; 26.61)	0.113
Men	1	-15.21 (-44.41; 13.97)	18.05 (-9.89; 46.00)	30.92 (2.31; 59.53)	**0.002**	1	-13.83 (-35.58; 7.92)	-1.38 (-23.29; 20.52)	15.18 (-7.78; 38.14)	0.070
Women	1	15.04 (-1.14; 31.22)	7.68 (-10.45; 25.81)	8.70 (-9.25; 26.65)	0.486	1	14.08 (0.17; 27.98)	4.74 (-10.75; 20.25)	9.02 (-7.83; 25.88)	0.584
Ω6/ Ω3 ratio										
Total	1	2.83 (-16.80; 22.47)	-2.11 (-21.83; 17.60)	4.78 (-14.49; 24.60)	0.761	1	-0.57 (-12.95; 11.80)	-8.91 (-21.12; 3.29)	-4.43 (-16.87; 7.99)	0.403
Men	1	-13.11 (-37.64; 11.41)	-10.76 (-35.47; 13.94)	-10.34 (-34.81; 14.13)	0.495	1	-9.43 (-28.37; 9.51)	-22.29 (-41.62; -2.96)	-10.32 (-28.80; 8.14)	0.164
Women	1	12.52 (-5.62; 30.67)	10.74 (-6.65; 28.13)	16.66 (-0.31; 33.64)	0.085	1	4.39 (-10.73; 19.53)	-1.31 (-16.45; 13.82)	-2.26 (-17.78; 13.25)	0.774

Notes: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ALA: alpha linolenic acid. Model 1: crude analysis; Model 2: adjusted for protein (g), energy (kcal) and alcohol intake (g/d), age (years), physical activity, family income, marital status, race, education level, diabetes, hypertension, body weight (kg), supplementation. Women was also adjusted for menopausal status. The analysis for total sample was also adjusted for sex in Model 2.

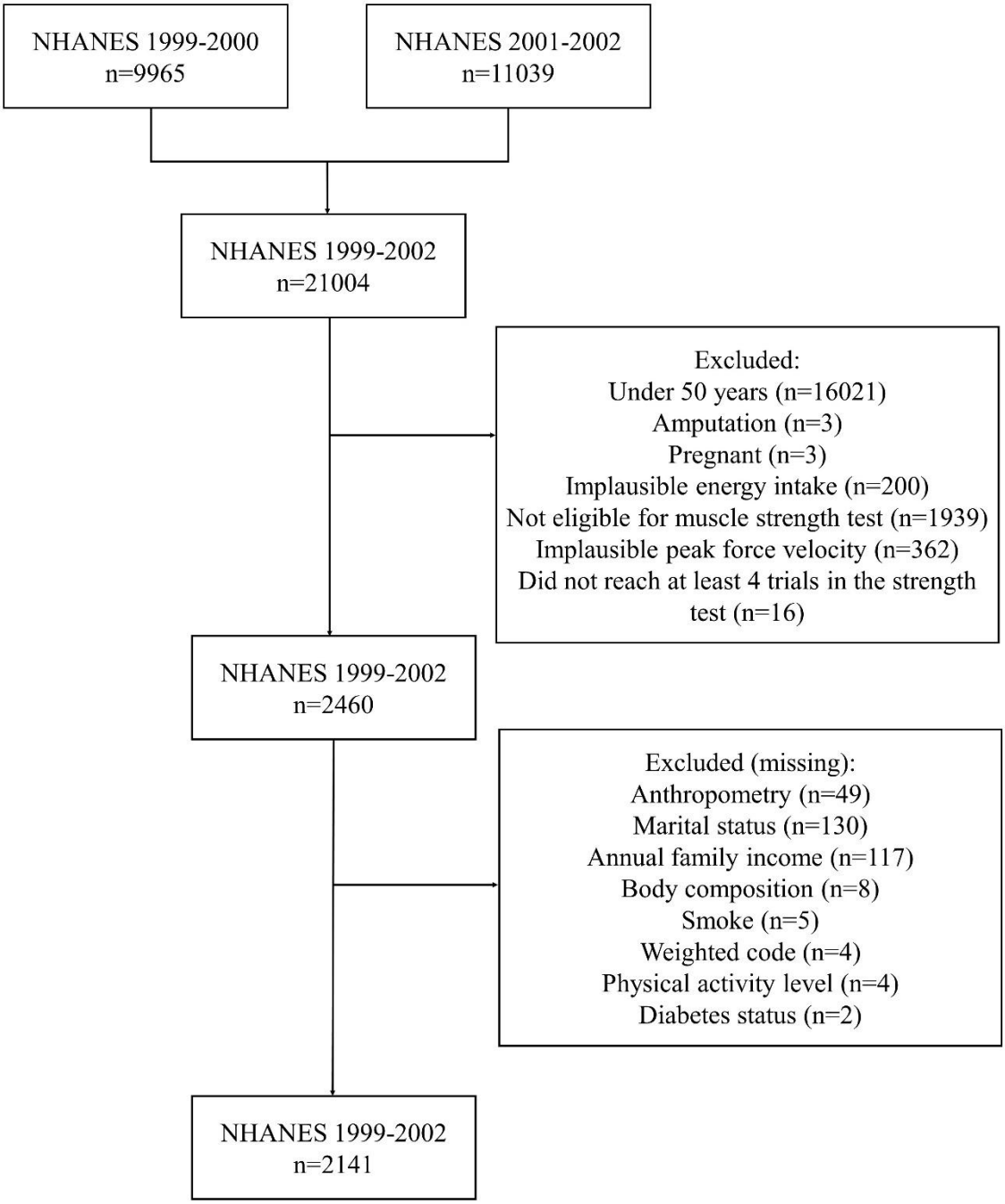
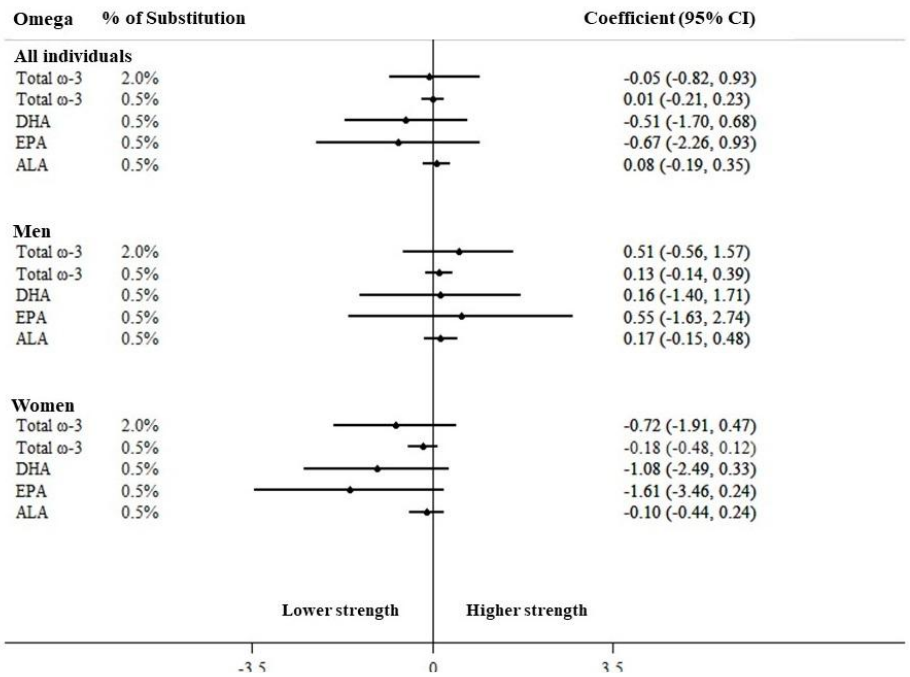
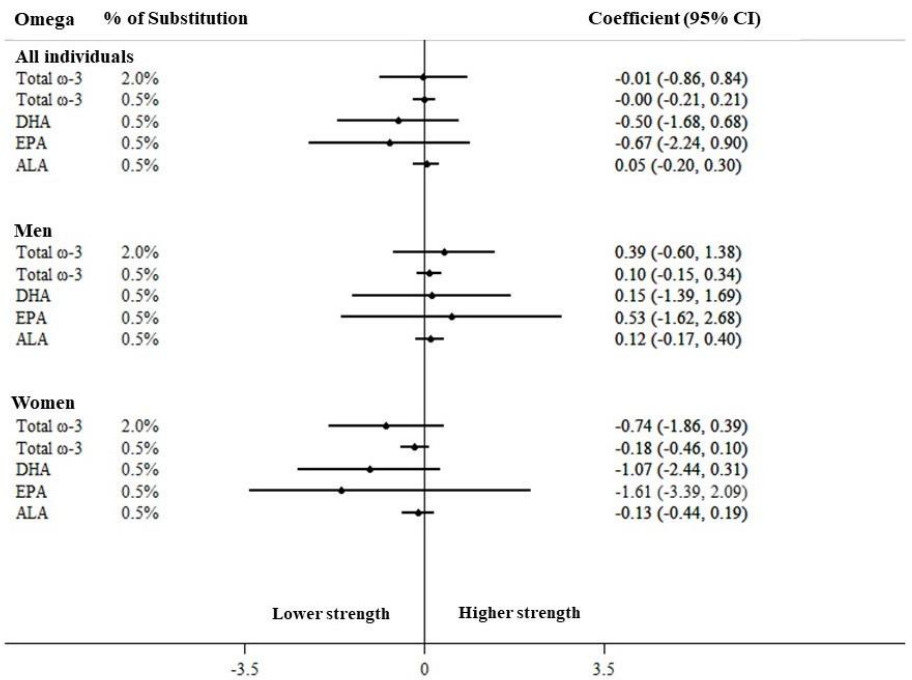


Figure 1 - Flowchart of the sample selection from NHANES 1999-2002.

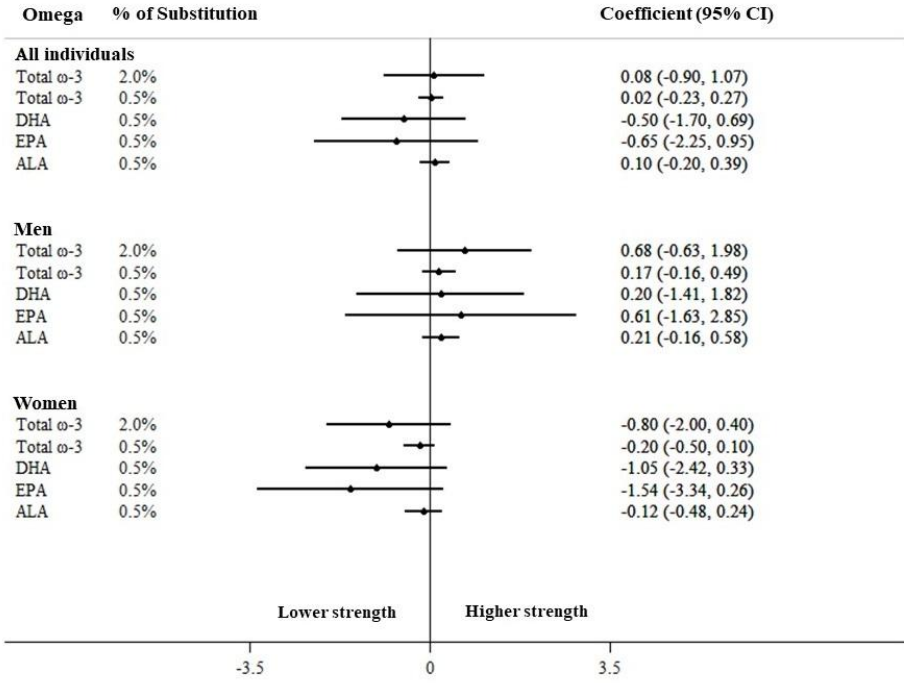
A) Saturated fat



B) Polyunsaturated fat (excluding ω-3)



C) Monounsaturated fat



D) Ω-6

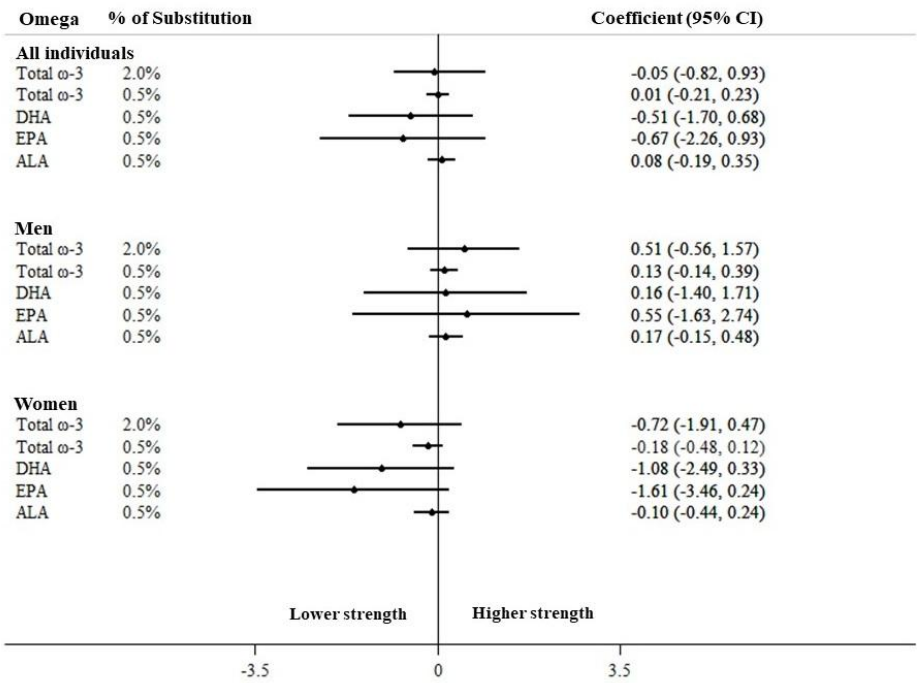


Figure 2 - Weighted associations between increasing specific doses of total omega-3 or subtypes with peak force. NHANES, 1999-2002.

Notes: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ALA: alpha linolenic acid. Analysis were adjusted for protein (g), energy (kcal), alcohol (g/d), age (years), physical activity, family income, marital status, race, education level, sex (analysis for total individuals), diabetes, hypertension, body weight (kg), supplementation. Women was also adjusted for menopausal status. The analysis for total sample was also adjusted for sex.

Supplementary table 1. Weighted sociodemographic, healthy conditions and habits, physical activity, anthropometric and body composition, strength and dietary habits of older men by quartile of omega-3 intake. NHANES, 1999-2002.

Variables	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value
Demographic						
Age, y	62.28 (9.26)	63.15 (9.75)	63.05 (9.77)	61.32 (8.95)	62.11 (8.73)	0.118
Race, %						0.002
Non-Hispanic white	84.73 (82.42 – 86.79)	81.19 (74.97 – 86.15)	81.35 (75.45 – 86.09)	84.96 (80.61 – 88.46)	89.61 (86.12 – 92.29)	
Marital status, %						0.146
Single/ Divorced/ Widowed/ Never Married	14.49 (12.24 – 17.08)	15.49 (10.28 – 22.67)	18.01 (13.14 – 24.17)	13.58 (9.96 – 18.24)	11.91 (8.37 – 16.68)	
Married/ Living as married	85.50 (82.91 – 87.75)	84.50 (77.32 – 89.71)	81.98 (75.82 – 86.85)	86.41 (81.75 – 90.02)	88.08 (83.31 – 91.62)	
Annual Family Income, %						0.007
$0-19999	22.19 (19.37 – 25.29)	28.03 (21.17 – 36.09)	30.49 (23.90 – 37.99)	13.74 (10.282 – 18.14)	20.63 (15.62 – 26.75)	
$20000-54999	37.88 (34.33 – 41.56)	36.82 (29.05 – 45.35)	36.93 (29.71 – 44.79)	42.02 (35.47 – 48.86)	34.87 (28.49 – 41.84)	
Over $55000	39.92 (36.18 – 43.78)	35.13 (26.94 – 44.30)	32.57 (25.37 – 40.69)	44.22 (37.40 – 51.27)	44.48 (37.49 – 51.70)	
Education level						0.001
Under high school graduate	44.70 (41.01 – 48.45)	52.01 (43.28 – 60.61)	51.076 (43.31 – 58.91)	43.07 (36.53 – 49.87)	36.40 (30.07 – 43.24)	
Some college or over	55.29 (51.54 – 58.98)	47.98 (39.38 – 56.71)	48.92 (41.08 – 56.82)	56.92 (50.12 – 63.46)	63.59 (56.75 – 69.92)	
Health conditions and habits						
Hypertension, %						0.791
Yes	36.46 (32.93 – 67.06)	39.32 (31.29 – 47.97)	34.68 (27.73 – 42.35)	35.79 (29.55 – 42.55)	36.82 (30.16 – 44.04)	
No	63.53 (59.84 – 40.15)	60.67 (52.02 – 68.70)	65.31 (57.64 – 72.26)	64.21 (57.44 – 70.44)	63.17 (55.95 – 69.83)	
Diabetes, %						0.853
Pre-diabetes	2.08 (1.32 – 3.26)	0.48 (0.10 – 2.20)	1.68 (0.60 – 4.63)	3.48 (1.83 – 6.54)	1.92 (7.65 – 4.76)	
Yes	10.77 (8.67 – 13.30)	12.05 (7.47 – 18.87)	10.45 (6.72 – 15.91)	8.09 (5.35 – 12.05)	13.09 (8.74 – 19.15)	
No	87.14 (84.48 – 89.40)	87.45 (80.64 – 92.10)	87.85 (82.20 – 91.88)	88.41 (83.90 – 91.78)	84.97 (78.81 – 89.58)	
Smoke, %						0.083
Yes	15.41 (81.72 – 87.06)	20.72 (14.47 – 28.77)	14.38 (10.04 – 20.18)	15.82 (11.42 – 21.51)	12.36 (8.50 – 17.65)	
No	84.58 (12.93 – 18.27)	79.27 (71.22 – 85.53)	85.61 (79.81 – 89.95)	84.17 (78.48 – 88.57)	87.63 (82.34 – 91.49)	
Physical activity						
Moderate PA in past 30 days						0.346
Yes	53.08 (49.31 – 56.83)	46.59 (38.02 – 55.38)	58.50 (50.73 – 65.87)	50.12 (43.27 – 56.97)	56.01 (48.83 – 62.95)	
No	46.91 (43.16 – 50.68)	53.40 (44.61 – 61.97)	41.49 (34.12 – 49.26)	49.87 (43.02 – 56.72)	43.98 (37.04 – 51.16)	
Vigorous PA in past 30 days						0.099
Yes	30.83 (27.36 – 34.53)	28.14 (20.72 – 36.99)	26.18 (19.54 – 34.12)	32.11 (25.88 – 39.06)	35.06 (28.55 – 42.17)	
No	69.16 (65.46 – 72.63)	71.85 (63.00 – 79.27)	73.81 (65.87 – 80.45)	67.88 (60.93 – 74.11)	64.93 (57.82 – 71.44)	

Strength PA in past 30 days						0.210
Yes	21.38 (18.37 – 24.74)	16.70 (11.33 – 23.93)	22.62 (16.36 – 30.41)	21.02 (15.86 – 27.31)	23.79 (18.13 – 30.56)	
No	78.61 (75.25 – 81.62)	83.29 (76.06 – 88.66)	77.37 (69.58 – 83.63)	78.97 (72.68 – 84.13)	76.02 (69.43 – 81.86)	
Anthropometric and body composition						
Weight, kg	87.08 (16.13)	85.83 (16.41)	86.49 (17.10)	86.59 (15.68)	88.90 (15.46)	0.088
Height, m	1.75 (0.07)	1.74 (0.07)	1.74 (0.07)	1.75 (0.064)	1.76 (0.06)	0.038
Body mass index, kg/m^2	28.29 (4.60)	28.04 (4.88)	28.33 (4.79)	28.16 (4.50)	28.57 (4.34)	0.387
Total lean mass, kg	58.12 (8.64)	56.75 (8.53)	57.69 (9.18)	57.91 (8.08)	59.57 (8.63)	0.004
Muscle mass index, kg/m^2	8.25 (1.09)	8.07 (1.13)	8.22 (1.14)	8.27 (1.00)	8.39 (1.10)	0.009
Total fat mass, kg	27.00 (8.73)	27.13 (9.18)	26.85 (8.99)	26.72 (8.96)	27.34 (7.92)	0.805
Total fat mass, %	30.16 (5.17)	30.69 (5.67)	30.19 (5.05)	29.93 (5.46)	30.06 (4.54)	0.264
Strength						
Peak force, Newtons	449.84 (116.77)	427.86 (131.39)	425.02 (110.73)	461.92 (113.20)	471.73 (109.15)	<0.001
Time to peak force, seconds	1.05 (0.53)	1.09 (0.72)	1.08 (0.62)	1.06 (0.46)	1.00 (0.38)	0.083
Angle of peak force, degree	120.61 (7.31)	121.12 (7.24)	120.36 (7.57)	121.20 (6.81)	119.83 (7.55)	0.262
Peak force velocity degree/second	60.71 (0.66)	60.78 (0.63)	60.71 (0.63)	60.71 (0.66)	60.66 (0.69)	0.113
Dietary habits						
Energy, kcal/day	2170 (707)	1554 (611)	2016 (581)	2318 (586)	2541 (674)	<0.001
Carbohydrate, g/day	264.25 (104.98)	211.33 (97.18)	252.88 (94.07)	282.39 (102.45)	288.53 (106.39)	<0.001
Carbohydrate, %	48.90 (11.44)	54.42 (12.24)	50.00 (11.11)	48.34 (10.65)	44.99 (10.38)	<0.001
Protein, g/day	84.08 (32.89)	59.47 (26.62)	77.87 (26.81)	89.02 (27.79)	99.93 (35.05)	<0.001
Protein, %	15.74 (4.55)	15.63 (4.76)	15.75 (4.84)	15.62 (3.98)	15.94 (4.73)	0.624
Protein, g/kg/day	0.99 (0.42)	0.72 (0.34)	0.93 (0.36)	1.05 (0.37)	1.15 (0.44)	<0.001
Lipids, g/day	82.02 (35.15)	47.73 (20.92)	69.24 (23.56)	87.93 (25.86)	108.60 (35.28)	<0.001
Lipids, %	33.93 (9.13)	28.39 (9.25)	31.36 (7.82)	34.75 (8.01)	38.79 (8.43)	<0.001
Total Ω3, g/day	1.835 (1.364)	0.618 (0.173)	1.115 (0.149)	1.700 (0.205)	3.375 (1.632)	<0.001
EPA, g/day	0.045 (0.154)	0.004 (0.018)	0.010 (0.029)	0.024 (0.059)	0.125 (0.261)	<0.001
DHA, g/day	0.083 (0.219)	0.011 (0.023)	0.029 (0.048)	0.055 (0.082)	0.205 (0.368)	<0.001
ALA, g/day	1.544 (1.181)	0.531 (0.168)	0.948 (0.190)	1.456 (0.255)	2.793 (1.495)	<0.001
Total Ω6, g/day	14.970 (9.062)	6.790 (4.173)	10.411 (4.201)	15.381 (5.278)	23.648 (9.822)	<0.001
Ω6/ Ω3 ratio	9.08 (4.03)	11.22 (6.47)	9.41 (3.81)	9.04 (2.96)	7.44 (2.25)	<0.001
Saturated fat, g/day	26.12 (12.44)	16.41 (8.76)	23.190 (9.78)	28.67 (11.16)	32.11 (13.05)	<0.001
Polyunsaturated fat, g/day	16.96 (10.05)	7.46 (4.25)	11.71 (4.21)	17.28 (5.42)	27.16 (10.57)	<0.001
Monounsaturated fat, g/day	30.54 (14.34)	18.01 (9.03)	27.15 (11.76)	33.03 (12.20)	38.84 (14.48)	<0.001
Fiber, g/day	17.53 (10.59)	13.34 (8.55)	16.35 (9.95)	18.18 (10.64)	20.54 (11.07)	<0.001
Alcohol, g/day	11.71 (28.33)	10.86 (31.26)	15.63 (31.22)	12.19 (30.72)	8.48 (19.64)	0.144

Notes: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ALA: alpha linolenic acid. Data described as mean (standard deviation) or percentage (confidence interval).

Supplementary table 2. Weighted sociodemographic, healthy conditions and habits, physical activity, anthropometric and body composition, strength and dietary habits of older women by quartile of omega-3 intake. NHANES, 1999-2002.

Variables	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value
Demographic						
Age, y	62.83 (9.66)	63.61 (10.26)	62.94 (9.95)	61.56 (9.02)	63.16 (8.99)	0.329
Race, %						0.013
Non-Hispanic white	79.55 (76.67 – 82.16)	75.18 (69.17 – 80.36)	78.35 (72.81 – 83.04)	80.52 (73.93 – 85.77)	86.30 (80.89 – 90.36)	
Marital status, %						0.660
Single/ Divorced/ Widowed/ Never Married	38.99 (35.34 – 42.76)	37.78 (31.23 – 44.79)	39.18 (32.38 – 46.42)	39.06 (31.08 – 46.83)	40.39 (32.13 – 49.23)	
Married/ Living as married	61.00 (57.23 – 64.65)	62.21 (55.20 – 68.76)	60.81 (53.57 – 67.61)	60.94 (53.16 – 68.19)	59.60 (50.76 – 67.86)	
Annual Family Income, %						0.318
$0-19999	31.10 (27.68 – 34.74)	34.72 (28.41 – 41.61)	29.72 (23.60 – 36.67)	29.69 (23.11 – 37.24)	29.50 (21.93 – 38.38)	
$20000-54999	38.64 (34.97 – 42.44)	36.53 (29.90 – 43.71)	38.39 (31.65 – 45.62)	38.68 (31.44 – 46.47)	41.97 (33.55 – 50.89)	
Over $55.000	30.25 (26.68 – 34.06)	28.74 (22.50 – 35.91)	31.87 (25.16 – 39.43)	31.61 (24.37 – 39.87)	28.52 (21.32 – 36.99)	
Education level						0.583
Under high school graduate	49.84 (45.96 – 53.71)	49.49 (42.37 – 56.64)	48.12 (40.85 – 55.47)	49.90 (42.03 – 57.78)	52.57 (43.71 – 61.28)	
Some college or over	50.15 (46.28 – 54.03)	50.50 (43.35 – 57.62)	51.87 (44.52 – 59.14)	50.09 (42.21 – 57.96)	47.42 (38.71 – 56.28)	
Health conditions and habits						
Hypertension, %						0.139
Yes	44.58 (40.76 – 48.46)	49.72 (42.59 – 56.85)	45.68 (38.50 – 53.04)	37.33 (30.14 – 45.14)	44.69 (36.13 – 53593)	
No	55.41 (51.53 – 59.23)	50.27 (43.14 – 57.40)	54.31 (46.95 – 61.49)	62.66 (54.85 – 69.86)	55.30 (46.40 – 63.86)	
Diabetes, %						0.777
Pre-diabetes	1.75 (0.97 – 3.11)	3.09 (1.27 – 7.28)	0.35 (0.06 – 1.93)	1.88 (0.71 – 4.88)	1.52 (0.35 – 6.40)	
Yes	8.42 (6.66 – 10.58)	9.20 (6.05 – 13.74)	9.096 (5.97 - 13.60)	5.60 (3.29 – 9.387)	9.89 (5.76 – 16.47)	
No	89.82 (87.44 – 91.79)	87.70 (82.42 – 91.55)	90.54 (86.01 – 93.72)	92.50 (88.27 – 95.29)	88.57 (81.68 – 93.09)	
Smoke, %						0.909
Yes	14.83 (12.29 - 17.78)	15.75 (11.29 – 21.56)	11.38 (7.40 – 17.11)	18.37 (12.92 – 25.45)	13.71 (8.91 – 20.52)	
No	85.16 (82.21 – 87.70)	84.24 (78.43 – 88.70)	88.16 (82.88 – 92.59)	81.62 (74.54 – 87.07)	86.28 (79.47 – 91-08)	
Physical activity						
Moderate PA in past 30 days						0.028
Yes	48.23 (44.37 – 52.11)	46.73 (39.69 – 53.91)	42.91 (35.88 – 50.25)	45.69 (37.91 – 53.69)	60.79 (51.91 – 69.01)	
No	51.76 (47.88 – 55.62)	53.26 (46.08 – 60.30)	57.08 (49.74 – 64.11)	54.30 (46.30 – 62.08)	39.20 (30.98 – 48.08)	
Vigorous PA in past 30 days						0.471
Yes	23.46 (20.24 – 27.02)	23.75 (18.08 – 30.54)	21.96 (16.22 – 29.04)	20.03 (14.22 – 27.45)	29.37 (21.86 – 38.20)	
No	76.53 (72.97 – 79.75)	76.24 (69.45 – 81.91)	78.03 (70.95 – 83.77)	79.96 (72.54 – 85.77)	70.62 (61.79 – 78.13)	

Strength PA in past 30 days						0.518
Yes	19.84 (16.88 – 22.18)	20.40 (15.14 – 26.90)	17.12 (12.21 – 23.47)	19.04 (13.58 – 26.04)	23.75 (16.80 – 32.45)	
No	80.15 (76.81 – 83.11)	79.59 (73.09 – 84.85)	82.87 (76.52 – 87.78)	80.95 (73.95 – 86.41)	76.24 (67.54 – 83.19)	
Anthropometric and body composition						
Weight, kg	73.81 (17.23)	73.44 (18.12)	73.44 (17.15)	75.50 (16.64)	72.76 (16.52)	0.890
Height, m	1.60 (0.06)	1.60 (0.07)	1.60 (0.06)	1.61 (0.06)	1.61 (0.05)	0.054
Body mass index, kg/m^2	28.49 (6.25)	28.39 (6.22)	28.66 (6.32)	28.66 (6.13)	27.87 (6.23)	0.695
Total lean mass, kg	40.77 (6.88)	40.39 (7.11)	40.41 (6.62)	41.61 (6.98)	40.75 (6.60)	0323
Muscle mass index, kg/m^2	6.55 (1.16)	6.51 (1.12)	6.54 (1.15)	6.65 (1.22)	6.48 (1.15)	0.790
Total fat mass, kg	31.67 (11.03)	31.68 (11.57)	31.66 (11.22)	32.52 (10.46)	30.62 (10.55)	0.674
Total fat mass, %	41.59 (5.72)	41.743 (5.99)	41.83 (5.71)	41.84 (5.41)	40.70 (5.58)	0.206
Strength						
Peak force, Newtons	305.76 (81.12)	296.55 (77.17)	3154.20 (86.61)	309.49 (80.93)	301.66 (77.39)	0.585
Time to peak force, seconds	1.09 (0.52)	1.08 (0.56)	1.11 (0.62)	1.05 (0.40)	1.14 (0.48)	0.546
Angle of peak force, degree	123.81 (6.99)	124.02 (7.16)	123.38 (6.99)	123.67 (6.79)	124.28 (6.92)	0.769
Peak force velocity degree/second	60.65 (0.57)	60.60 (0.67)	60.67 (0.54)	60.69 (0.51)	60.65 (0.50)	0.315
Dietary habits						
Energy, kcal/day	1658 (587)	1198 (400)	1541 (411)	1948 (517)	2120 (530)	<0.001
Carbohydrate, g/day	210.82 (82.06)	169.94 (67.19)	203.46 (73.11)	243.43 (83.45)	239.42 (80.87)	<0.001
Carbohydrate, %	51.33 (10.84)	56.48 (10.77)	52.40 (10.05)	49.47 (9.49)	44.73 (9.43)	<0.001
Protein, g/day	63.31 (26.12)	46.72 (21.46)	60.85 (21.22)	72.96 (23.62)	78.65 (25.96)	<0.001
Protein, %	15.55 (4.55)	15.65 (4.94)	16.00 (4.49)	15.29 (4.28)	15.11 (4.26)	0.172
Protein, g/kg/day	0.89 (0.40)	0.67 (0.36)	0.87 (0.36)	1.00 (0.37)	1.11 (0.38)	<0.001
Lipids, g/day	63.14 (29.98)	37.64 (15.40)	55.10 (18.30)	77.67 (24.85)	92.85 (26.96)	<0.001
Lipids, %	33.83 (9.20)	28.82 (8.81)	32.46 (7.39)	36.27 (8.22)	39.92 (8.40)	<0.001
Total Ω3, g/day	1.526 (1.136)	0.602 (0.170)	1.078 (0.148)	1.709 (0.210)	3.243 (1.307)	<0.001
EPA, g/day	0.038 (0.153)	0.005 (0.013)	0.013 (0.035)	0.026 (0.063)	0.137 (0.299)	<0.001
DHA, g/day	0.071 (0.204)	0.015 (0.023)	0.036 (0.055)	0.058 (0.087)	0.217 (0.389)	<0.001
ALA, g/day	1.290 (0.986)	0.516 (0.168)	0.924 (0.190)	1.481 (0.276)	2.672 (1.246)	<0.001
Total Ω6, g/day	12.493 (7.889)	5.949 (2.976)	9.697 (3.395)	14.881 (5.269)	22.790 (7.691)	<0.001
Ω6/ Ω3 ratio	9.02 (4.35)	10.39 (6.72)	9.00 (2.92)	8.68 (2.79)	7.49 (2.29)	<0.001
Saturated fat, g/day	19.82 (10.73)	12.61 (5.93)	18.12 (8.37)	25.00 (11.35)	26.09 (10.57)	<0.001
Polyunsaturated fat, g/day	14.14 (8.84)	6.60 (3.09)	10.88 (3.49)	16.76 (5.45)	26.21 (8.29)	<0.001
Monounsaturated fat, g/day	22.75 (11.50)	14.02 (6.78)	20.13 (7.92)	28.26 (10.547)	32.08 (11.05)	<0.001
Fiber, g/day	14.43 (8.27)	11.81 (6.62)	13.56 (7.18)	16.26 (9.23)	17.12 (8.80)	<0.001
Alcohol, g/day	4.14 (15.73)	3.46 (14.21)	2.85 (9.98)	3.34 (10.49)	7.89 (24.76)	0.117

Notes: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ALA: alpha linolenic acid. Data described as mean (standard deviation) or percentage (confidence interval).

Artigo 3: Association of plasma and dietary omega-3 fatty acids with muscle strength: a study from National Health and Nutrition Examination Survey (NHANES) 2011-2012.

Original Article

Association of plasma and dietary omega-3 fatty acids with muscle strength: a study from National Health and Nutrition Examination Survey (NHANES) 2011-2012.

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Abstract

Background: The decrease in muscle strength is associated with negative health outcomes and increased risk of mortality. There is conflicting evidence as to whether omega-3 fatty acids (ω-3) intake is associated with strength, both in young and older adults. **Objective:** To investigate the association of plasma (dietary biomarker) and dietary ω-3 with muscle strength in young and older adults. **Methods:** This study included 1390 individuals (702 men and 688 women) from the National Health and Nutrition Examination Survey (NHANES) 2011-2012, being 50.14% (n=697) young (<50 years) and 49.85% (n=693) older adults (≥50 years). Dietary evaluation was performed by two 24h dietary recalls. Plasma fatty acids was evaluated by gas chromatography - mass spectrometry. Muscle strength was assessed by isometric handgrip strength. Linear regression was performed adjusting for the confounders. **Results:** For young men, docosahexaenoic acid (DHA) in plasma was positively associated with muscle strength, while no associations were found between dietary ω-3 and handgrip strength. For older men, total ω-3 in plasma and DHA intake were positively associated with strength. No significant associations were observed in women. **Conclusion:** We concluded that, in young men, plasma DHA was positively associated with strength. In older men, total ω-3 in plasma and DHA consumption were positively associated with handgrip strength. No associations were observed in women, suggesting a sex-dependent association.

Keywords: Omega-3; Plasma fatty acids; Dietary intake; Muscle strength.

Introduction

Muscle strength predicts important health outcomes, such as quality of life [1], risk of falls [2], hospital costs [3, 4] and mortality [5-8]. It can be affected by several factors; for instance, physical activity level [9], aging [10] and dietary intake [11, 12]. Regarding dietary factors, omega-3 fatty acids (ω-3) has been recently studied as a potential beneficial factor for muscle mass and strength [13]; however, the results are conflicting, since some studies showed benefits [14-17], while others did not [18, 19].

To the best of our knowledge, only one cross-sectional study [20] evaluated the association between ω-3 and muscle strength. Reinders and colleagues [20] investigated the association between plasma ω-3 and muscle strength and found no significant associations. However, it is important to highlight that only older individuals (66-96 years old) of both sexes (evaluated together) were assessed. Thus, it is not yet known whether there are specific sex or age-dependent associations between ω-3 and strength, since differences in ω-3 metabolism is observed in men compared with women [21, 22].

The evaluation of ω-3 through blood fatty acids is a method with greater accuracy than dietary assessment [23, 24], since plasma levels involve the result of chronic consumption (~1 month) [23] as well as the metabolic process after food intake [25]. However, making associations using data from dietary ω-3 evaluation is also important, since this method is more accessible to conduct other epidemiological studies and also to professionals in clinical practice [26].

Therefore, the objective of the present study was to investigate the association of plasma and dietary intake ω-3 with muscle strength in young and older adults (according to sex) participating in the National Health and Nutrition Examination Survey (NHANES) 2011-2012.

Methods

Study population

NHANES assesses a representative sample of non-institutionalized U.S. civilians, being conducted by the National Center for Health Statistics (NCHS), including data collection and ethics approval [27]. This program uses a stratified multistage sampling to investigates association between nutritional status and health [27]. The present study included individuals over to 20 years old, derived from NHANES 2011-2012 [28]. Figure 1 demonstrated the

participants' flowchart. Those individuals without handgrip strength test, who did not perform plasma fatty acids evaluation, pregnant women, who presented implausible energy intake (<800 and >4000 kcal or <500 and >3500 kcal for men and women [29], respectively) and under 20 years old were excluded from the analysis. Volunteers who presented missing data in demographic, anthropometric, lifestyle or health conditions were also excluded. In this way, a total of 1390 individuals (702 men and 688 women) were evaluated. From the sample, 50.14% (n=697) were classified as young (<50 years) and 49.85% (n=693) as older adults (≥50 years).

Plasma fatty acids

Approximately 0.5-mL of plasma or serum fasting sample was obtained, which was dispensed into a Nalge 2.0-mL cryovial or another plastic screw-capped vial labeled with the specimen identification and stored at -70ºC. Profile of 30 fatty acids were evaluated by gas chromatography – mass spectrometry. The saturated fatty acids evaluated were: capric acid (C10:0), lauric acid (C12:0), myristic acid (14:0), pentadecanoic acid (C15:0), palmitic acid (16:0), margaric acid (C17:0), stearic acid (18:0), arachidic acid (20:0), docosanoic acid (22:0), tricosanoic acid (C23:0) and lignoceric acid (24:0). Monounsaturated fatty acids evaluation involved myristoleic acid (14:1n-5), palmitoleic acid (16:1n-7), cis-vaccenic acid (18:1n-7), eicosenoic acid (20:1n-9), nervonic acid (24:1n-9), oleic acid (18:1n-9) and eicosatrienoic acid (C20:3n-9). Polyunsaturated fatty acids were divided into ω-3 and ω-6. About ω-3, alpha-linolenic (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), docosahexaenoic acid (DHA; 22:6n-3), docosapentaenoic acid (DPA; 22:5n-3) and stearidonic acid (SDA; C18:4n-3) were assessed. In relation to ω-6 fatty acids, were measured linoleic acid (18:2n-6), arachidonic acid (20:4n-6), eicosadienoic acid (20:2n-6), docosapentaenoic acid (22:5n-6), homo-gamma-linolenic acid (20:3n-6), docosatetraenoic acid (22:4n-6) and gamma-linolenic acid (18:3n-6). All fatty acids were expressed in μmol/L. More details about method evaluation from plasma fatty acids are provided by the manual available on the NHANES website [30]. For the total plasma ω-3, the sum between ALA, EPA and DHA was considered. Although there are other ω-3 fatty acids evaluated from plasma samples, only these three types were considered because they were also evaluated by dietary intake.

Dietary intake

The dietary interview was conducted with a partnership between the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (DHHS). DHHS' National Center for Health Statistics (NCHS) was responsible for the survey sample design, while USDA's Food Surveys Research Group (FSRG) was responsible for the dietary data collection methodology, maintenance of the databases and data process. Two 24h dietary recalls were conducted, being the first done in person and the second collected by telephone. The in-person interview was conducted in a private room in the NHANES mobile examination center. Measuring guides (available on NHANES website [31]), containing glasses, spoons, bottles, bowls, and others, were used for better estimation of food intake. Telephone dietary interviews were collected 3 to 10 days following and in a different day of the week from the in-person interview. A toll-free number was supplied for participants who did not have a telephone. Dietary data were collected using USDA's dietary data collection instrument, the Automated Multiple-Pass Method [32], which is a fully computerized recall that uses a 5-step method (quick list, forgotten foods, time and occasion, detail cycle and final probe). USDA's Food and Nutrient Database for Dietary Studies (FNDDS) 2011-2012, which are based on values in the USDA National Nutrient Database for Standard Reference, release 26, produced by USDA's Nutrient Data Lab was used for processing the 2011-2012 food consumption. In our study, total ω-3 dietary intake was considered by the sum of ALA, EPA and DHA.

Muscle strength

A detailed description about the isometric handgrip strength procedure is found in NHANES Muscle Strength Procedures Manual, which is available on the NHANES website [33]. Initially, the equipment used (Takei Digital Grip Strength Dynamometer, Model T.K.K.540, Takei, Niigata, Japan) was adjusted to the grip size and calibrated. Before the beginning of the test, individuals were asked a series of questions in order to investigate whether they should be excluded from the test or if the result could have been influenced by some condition. Also, the volunteer was asked to remove hand and wrist jewelry. After the explanation of the protocol, the individual performed a practical test in the opposite hand tested first, which was performed only with submaximal effort. After the ending of practical test, the evaluation of the isometric strength was performed. The volunteer was asked to squeeze the

dynamometer as hard as possible in a standing position. They were instructed to maintain their feet apart (hip width), toes forward, shoulders back, chest up, arm extended at the side of the body with elbow fully extended, wrist in neutral position and eyes straight ahead. The exam was performed in the seated position only when the participant could not be stand unassisted. Each hand was tested three times, alternating hands between trials. An interval of 60-second rest was taken between measurements on the same hand. Best values (kilograms) were recorded for each hand. For our analysis, muscle strength was considered as the sum of the maximum strength value obtained in each hand.

Covariates of interest

Demographic covariates included were age (years), sex (men or women), education level (under high school graduate and some college or over), family income (until $19999, from $20000 to 54999 or over $55000), marital status (single/divorced/widowed/never married or married/living as married) and race/ethnicity (non-Hispanic white or other). For lifestyle and comorbidities, smoke status (yes or no), diabetes (pre, yes or no), hypertension (yes or no) and physical activity (yes or no) were included in the analysis. NHANES provides data about moderate or vigorous physical activity practice (yes or no) in the last 30 days. To include this covariate in the analyzes, a new variable (physical activity) was created, which was marked as "yes" if the individual had performed moderate or vigorous intensity physical activity in the last 30 days and "no" if it did not had performed any of these activities. Additionally, body weight (kg) was used as anthropometric measure. In relation to dietary intake, total energy intake (kcal/day), protein (g/day) and alcohol (g/day) were included. For women, adjustment for menopausal status was performed and the analysis for total sample was adjusted for sex.

Data analyzes

U.S. adult population-based estimates for demographic characteristics, lifestyle, health conditions, anthropometric measures, muscle strength, plasma fatty acids and dietary habits were generated for participants by terciles of total plasma ω-3 and total dietary ω-3 intake, according to sex and age (<50 years and ≥50 years old). Terciles were compared using linear regression. For the association between muscle strength (considered the sum of best values from each hand) and plasma or dietary ω-3, the total ω-3 and fractions (from plasma or diet) were divided into their terciles, according to the classification for sex and age. Linear regressions

were performed without adjustments (Model 1) or after the adjustments for the following confounders: age (years), education level, family income, marital status, race/ethnicity, physical activity (yes or no), diabetes (pre, yes or no), hypertension (yes or no), smoke status (yes or no), body weight (kg), energy intake (kcal/day), protein intake (g/day), and alcohol consumption (g/day) (Model 2). In addition, linear regression analyzes between plasma ω-3 and muscle strength were adjusted by total plasma saturated fat, while linear regression analyzes between dietary ω-3 and muscle strength were adjusted by dietary saturated fat. Women was also adjusted for menopausal status while the analyses including total sample (men and women) were also adjusted for sex.

Data were described as mean ± standard deviation or percentage ± 95% confidence interval (95%CI) when appropriated. It was adopted as significance level p-value <0.05. Statistical analyzes were conducted using Stata 14 software (StataCorp, College Station, TX, USA) and according to survey design characteristics of NHANES (strata, cluster and sample weights) [34] through Stata SVY commands.

Results

Individual's characteristics according to plasma ω-3

Individual's characteristics according to sex and age by tercile of total plasma ω-3 are shown in Table 1. Young men with higher plasma ω-3 presented higher age, all plasma fatty acids and EPA, DHA and fiber intake, while a lower proportion of vigorous physical activity and dietary fat percentage were observed. For young women, those with higher plasma ω-3 had higher age, annual familiar income, pre-diabetes and diabetic proportion, ω-3 and saturated fat in plasma, and EPA, DHA, fiber, and alcohol intake; and lower height.

For older men in the third tercile, it was observed lower proportion of married/living as married individuals, and caloric, carbohydrate (g), protein (g/kg), lipids (g), saturated and monounsaturated fat intakes; while they presented a higher ω-3 and plasma saturated fat levels. Older women in the last tercile presented higher proportion of pre-diabetic and diabetic individuals, plasma fatty acids, and caloric, carbohydrate (g and %), protein (g), total ω-3, ALA, EPA, DHA, linoleic fatty acid, polyunsaturated fat and fiber intake.

Individual's characteristics according to dietary ω-3

Individual's characteristics according to sex and age by tercile of total dietary ω-3 intake are demonstrated in Table 2. Young men in the third tercile had higher proportion of individuals performing vigorous physical activity and lower proportion of smokers. Both sexes presented higher strength and dietary intake of all the variables, except for the protein percentage and alcohol.

For older men with higher total dietary ω-3 intake, it was observed a larger proportion of non-Hispanic white, upper annual family income, greater educational level, and dietary intake in all variables, except for the carbohydrate percentage and alcohol. Regarding older women in the third tercile, a higher total ω-3, EPA, DHA, DPA in plasma, as well as higher dietary intake of all variables were observed, except for the protein percentage and alcohol.

Associations between ω-3 and muscle strength in young individuals

Linear regression analyses between plasma ω-3 and muscle strength in young individuals (Table 3) showed an inverse association between total ω-3 and DHA when men and women were analyzed together (Model 1). After the adjustment for covariates, a positive association between plasma DHA and handgrip strength was noted in young men. Crude analyzes (Model 1) between ω-3 intake and muscle strength (Table 3) indicates positive associations of total ω-3, EPA and ALA with muscle strength in men and women. After adjustments (Model 2), no associations were observed. For young women, no significant association was found (Model 2).

Associations between ω-3 and muscle strength in older individuals

Table 4 presents linear regression analyses between plasma and dietary ω-3 with muscle strength in older individuals. No association was observed between plasma ω-3 and muscle strength in crude analyses. After adjustments for confounders, a positive association was observed between plasma total ω-3 and handgrip strength in older men. Regarding ω-3 dietary intake, ALA and EPA were positively associated with strength in men and women (Model 1), but after adjustments, only DHA consumption was positively associated with muscle strength in older men. No significant associations were observed for older women after adjustments for confounders.

Discussion

The present study showed that plasma DHA was positively associated with muscle strength in young men, while total ω-3 in plasma and dietary DHA intake were positively associated with muscle strength in older men. For women, no significant associations were observed, suggesting that the associations between ω-3 and strength were sex-dependent. To the best of our knowledge, this is the first study showing these results when both plasma and dietary ω-3 were evaluated.

In an observational study, Robinson et al. [15] found that fatty fish intake (ω-3 food source) was the largest predictor of handgrip strength. However, Reinders et al. [20] did not observe significant associations between plasma ω-3 and muscle strength. It is important to mention that this study [20] performed the associations evaluating men and women together. Our results are partially in agreement with Reinders et al. study [20], because when we evaluated the total sample, we also did not find significant associations. Therefore, since we observed positive associations between ω-3 and strength only in men (both young and older), we noted that the associations seem to be sex-dependent. Although the mechanisms are still unclear, it can be possible explained due to sex-differences on ω-3 metabolism [35]. Men and women produce different oxylipins derived from ω-3 intake [36], which could act in different ways on strength according to the sex. However, to date, no study evaluated the effects of oxylipins on muscle strength, which shows that this hypothesis is only speculative. In addition, the present study is the first that evaluated the association of plasma and dietary ω-3 with strength in young individuals. We also observed positive associations between plasma DHA and muscle strength in young men, but not in women, which is in agreement with the associations performed in older individuals; showing that this association is independently of the age.

DHA can be found in animal food sources [37], or is metabolized from other ω-3, such as ALA and EPA [25]. We found positive associations between DHA and muscle strength in young and older men, when evaluated by plasma and diet, respectively. In this sense, DHA may have important incorporation into the cells, especially in nervous tissue [38]. One possible explanation for the results could be the incorporation of DHA into neural cells, which can increase the membrane fluidity and acetylcholine sensitivity, a neurotransmitter whose supports muscle contraction [39]. In addition, total plasma ω-3 was associated with strength in older men in the present study.

The present study had limitations. The sum of ALA, EPA and DHA were analyzed as total ω-3, although there were other types of ω-3 available. This occurred because only these three types were the same evaluated by dietary intake and plasma fatty acid methods, besides presenting greater biological effects than others ω-3. However, even when the analyzes were performed involving all ω-3 for biochemical profile or dietary assessment, the results were not different from those showed in the present study (data not shown). Also, important covariates, as diseases or conditions that could affect muscle strength, were not included in the analyzes, since data were not available for all participants. In addition, the study design does not allow to conclude a cause-effect. Moreover, the lipid profile of the cell membrane has not been evaluated. As strengths, we can mention that the dietary evaluation included two days of the week and we evaluated the ω-3 plasma content, which is a method that allows greater reliability of the ω-3 consumption. In addition, the analyzes provided representative data for the U.S. population.

We concluded that, in young men, plasma DHA was positively associated with strength. In older men, total ω-3 in plasma and DHA consumption were positively associated with handgrip strength. No associations were observed in women, suggesting a sex-dependent association.

Conflicts of interest

The authors declare no conflicts of interest.

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Authorship

LTR participated in interpretation of the data, performed statistical analysis, and wrote the manuscript; FMSB participated in analysis and interpretation of the data. CMA and AEMR: participated in the configuration of datasets, organization of the statistical analysis and contributed with the revision of the manuscript. EPO participated in the interpretation of the data, wrote, and contributed with the revision of the manuscript. All authors read and approved the final manuscript.

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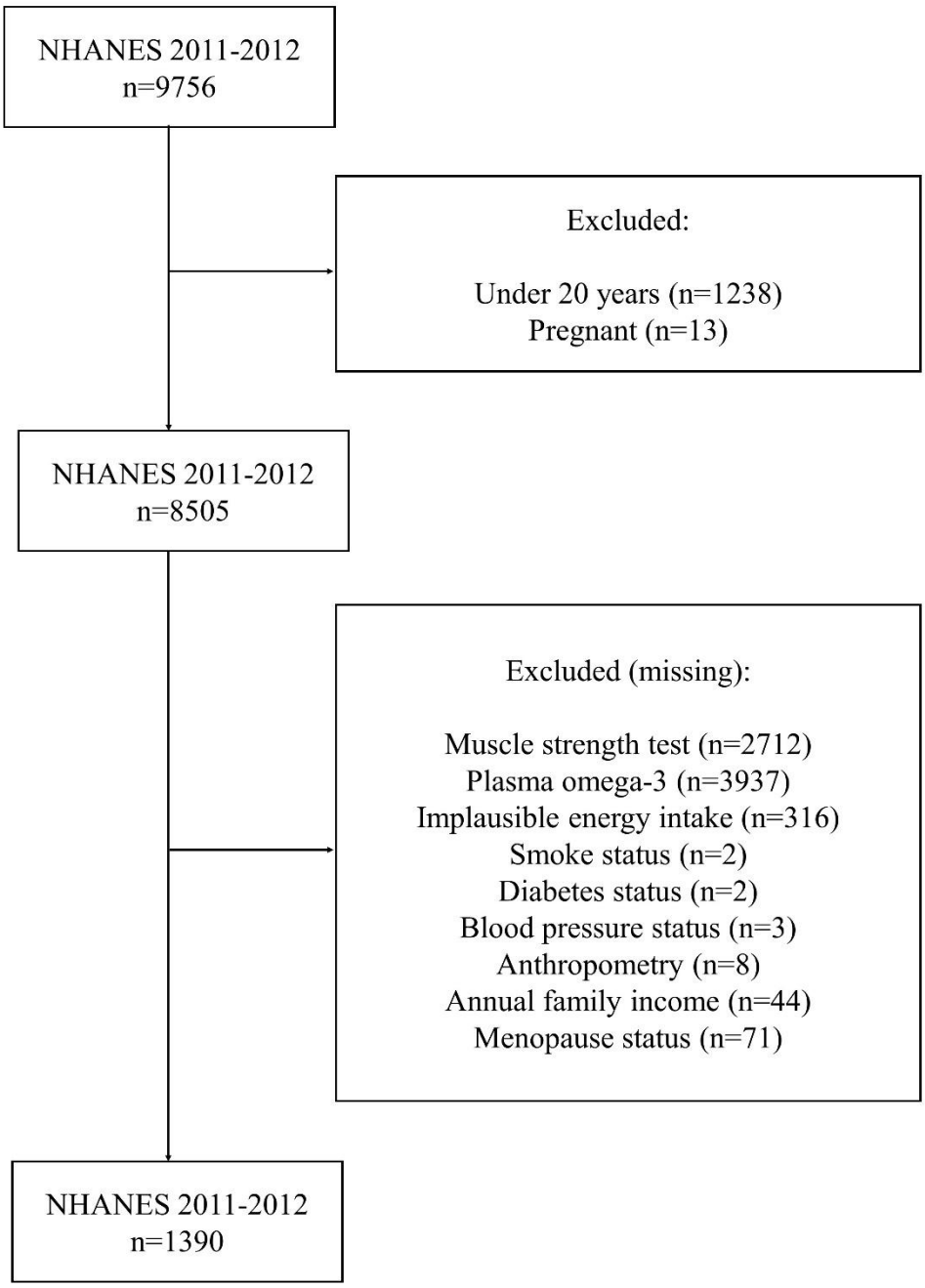

Figure 1 - Flowchart of the sample selection from NHANES 2011-2012.

Table 1. Weighted sociodemographic, healthy conditions and habits, physical activity, anthropometric, strength, plasma fatty acids and dietary habits of young and older adults by plasma omega-3. NHANES, 2011-2012.

Variables		<50 years								≥50 years							
	Total	Men				Women				Men				Women			
		T1	T2	T3	*p*	T1	T2	T3	*p*	T1	T2	T3	*p*-value	T1	T2	T3	*p*-value
Demographic																	
Age, y	48.58 (16.76)	40.04 (12.63)	41.90 (12.47)	47.34 (11.29)	**<0.001**	38.10 (12.73)	44.43 (13.19)	48.47 (13.36)	**<0.001**	71.99 (6.07)	72.04 (4.97)	71.39 (4.89)	0.710	72.56 (5.46)	74.21 (5.05)	72.58 (5.14)	0.722
Race, %					0.256				0.908				0.817				0.452
Non-Hispanic white	71.74 (69.13 – 74.22)	72.45 (65.85 – 78.20)	69.95 (62.19 – 76.71)	66.40 (57.40 – 74.35)		66.68 (58.75 – 74.11)	71.82 (64.47 – 78.17)	66.00 (56.57 – 74.31)		84.45 (71.44 – 92.19)	87.45 (79.64 – 92.54)	83.01 (71.96 – 90.37)		78.98 (63.06 – 89.21)	75.09 (61.39 – 85.11)	82.48 (74.72 – 88.24)	
Marital status, %					0.232				0.376				**0.047**				0.992
Single/ Divorced/ Widowed/ Never Married	35.83 (32.54 – 39.25)	38.18 (30.28 – 46.77)	31.64 (23.23 – 41.45)	30.44 (21.02 – 41.84)		41.82 (32.76 – 51.46)	40.28 (31.08 – 50.22)	35.46 (26.04 – 46.17)		8.15 (2.92 – 20.78)	10.38 (4.32 – 22.91)	25.56 (13.09 – 43.89)		45.89 (26.04 – 67.13)	47.06 (30.66 – 64.12)	46.32 (33.69 – 59.45)	
Married/ Living as married	64.16 (60.74 – 67.45)	61.81 (53.22 – 69.71)	68.35 (58.54 – 76.76)	69.55 (58.15 – 78.97)		58.17 (48.53 – 67.23)	59.71 (49.77 – 68.91)	64.53 (53.82 – 73.95)		91.84 (79.21 – 97.07)	89.61 (77.08 – 95.67)	74.43 (56.10 – 86.90)		54.10 (32.86 – 73.95)	52.93 (35.87 – 69.33)	53.67 (40.54 – 66.30)	
Annual Family Income, %					0.304				**0.002**				0.829				0.721
$0-19999	18.68 (16.34 – 21.27)	18.05 (13.06 – 25.53)	16.11 (10.42 – 24.06)	13.83 (8.72 – 21.23)		25.41 (18.36 – 34.03)	21.82 (15.02 – 30.58)	10.96 (7.35 – 16.04)		13.66 (5.24 – 31.14)	10.14 (4.98 – 19.54)	11.98 (5.72 – 23.40)		35.09 (18.95 – 55.56)	23.98 (13.27 – 39.40)	28.73 (18.79 – 41.25)	
$20000-54999	36.19 (32.86 – 39.65)	36.63 (28.80 – 45.23)	28.83 (20.84 – 38.40)	25.90 (17.99 – 35.77)		33.16 (24.83 – 42.69)	37.13 (28.12 – 47.13)	34.69 (25.07 – 45.75)		59.16 (37.63 – 77.67)	51.64 (34.64 – 68.26)	43.49 (25.45 – 63.44)		51.25 (29.85 – 72.20)	60.99 (43.44 – 76.08)	39.22 (27.41 – 52.44)	
Over $55000	45.12 (41.49 – 48.79)	44.86 (36.21 – 53.83)	55.04 (45.08 – 64.62)	60.26 (49.61 – 70.01)		41.42 (31.89 – 51.64)	41.04 (31.38 – 51.44)	54.34 (43.42 – 64.85)		27.17 (12.05 – 50.40)	38.21 (22.75 – 56.48)	44.51 (25.98 – 64.71)		13.64 (3.78 – 38.83)	15.02 (5.53 – 34.81)	32.04 (20.31 – 46.58)	
Education level					0.079				0.929				0.453				0.168
Under high school graduate	34.81 (31.58 – 38.19)	43.68 (35.36 – 52.39)	34.57 (25.72 – 44.62)	32.32 (23.20 – 43.01)		23.08 (16.73 – 30.95)	29.92 (21.51 – 39.96)	23.36 (66.62 – 84.35)		42.13 (24.09 – 62.54)	34.04 (20.78 – 50.38)	52.41 (32.77 – 71.33)		62.63 (38.44 – 81.81)	59.14 (41.60 – 74.63)	45.90 (33.37 – 58.97)	
Some college or over	65.18 (61.80 – 68.41)	56.31 (47.60 – 64.63)	65.42 (55.37 – 74.27)	67.67 (56.98 – 76.79)		76.91 (69.04 – 83.26)	70.07 (60.03 – 78.48)	76.63 (66.62 – 84.35)		57.86 (37.45 – 75.90)	65.95 (49.61 – 79.21)	47.58 (28.66 – 67.22)		37.36 (18.18 – 61.55)	40.85 (25.36 – 58.69)	54.09 (41.02 – 66.62)	
Health conditions and habits																	
Hypertension, %					0.087				0.258				0.871				0.279
Yes	34.49 (31.19 – 68.80)	24.73 (17.87 – 33.17)	28.54 (20.14 – 38.73)	36.42 (26.39 – 47.80)		21.80 (14.71 – 31.05)	32.51 (23.81 – 42.62)	28.83 (20.19 – 39.34)		32.93 (17.36 – 53.43)	48.81 (32.07 – 65.83)	35.68 (17.82 – 58.66)		38.28 (18.22 – 63.32)	18.50 (9.08 – 34.03)	46.41 (33.51 – 59.80)	
No	65.50 (62.05 – 68.80)	75.26 (66.82 – 33.17)	71.45 (61.26 – 79.85)	63.57 (52.19 – 73.60)		78.19 (68.94 – 85.28)	67.48 (57.37 – 76.18)	71.16 (60.65 – 79.80)		67.06 (46.56 – 82.63)	51.18 (34.16 – 67.92)	64.31 (41.33 – 82.17)		61.71 (36.67 – 81.77)	81.49 (65.96 – 90.91)	53.58 (40.19 – 66.48)	
Diabetes, %					0.902				**0.009**				0.877				**0.022**

Pre-diabetes	1.88 (1.13 – 3.11)	1.23 (0.24 – 6.15)	0.93 (0.29 – 2.94)	0.88 (0.20 – 3.26)		1.71 (0.53 – 5.37)	0.59 (0.17 – 1.95)	5.01 (1.77 – 13.35)		0.64 (0.08 – 4.74)	0.88 (0.20 – 3.68)	10.16 (1.72 – 42.13)		1.44 (0.19 – 10.05)	1.14 (0.15 – 7.97)	3.25 (0.74 – 13.09)	
Yes	9.74 (7.99 – 11.82)	6.54 (3.43 – 12.13)	4.60 (2.46 – 8.44)	6.88 (2.89 – 15.51)		3.63 (1.55 – 8.26)	7.46 (4.07 – 13.30)	11.33 (6.26 – 19.64)		35.08 (17.75 – 57.51)	13.69 (5.37 – 30.71)	22.72 (11.29 – 40.44)		57.66 (36.10 – 76.65)	17.88 (9.35 – 31.48)	15.59 (9.31 – 24.95)	
No	88.36 (86.09 – 90.31)	92.21 (86.24 – 95.71)	94.45 (90.47 – 96.82)	92.29 (83.89 – 96.49)		94.64 (89.63 – 97.31)	91.94 (86.13 – 95.44)	83.65 (74.10 – 90.15)		64.26 (41.96 – 81.72)	85.41 (68.75 – 93.96)	67.10 (45.88 – 83.08)		40.89 (22.31 – 62.50)	80.97 (67.26 – 89.81)	81.15 (70.72 – 88.47)	
Smoke, %					0.096				0.242				0.348				0.459
Yes	18.78 (16.08 – 21.80)	27.45 (20.25 – 36.06)	23.77 (16.30 – 33.28)	17.05 (10.17 – 27.19)		82.95 (74.39 – 89.07)	76.30 (66.17 – 84.12)	89.25 (80.83 – 94.24)		3.46 (1.30 – 8.89)	21.94 (10.97 – 39.07)	11.73 (2.52 – 40.60)		9.15 (3.12 – 23.92)	11.18 (3.86 – 28.31)	6.51 (3.00 – 13.55)	
No	81.21 (78.19 – 83.19)	72.54 (63.93 – 79.74)	76.22 (66.71 – 83.69)	82.94 (72.80 – 89.82)		17.04 (10.92 – 25.60)	23.69 (15.87 – 33.82)	10.74 (5.75 – 19.16)		96.53 (91.11 – 98.69)	78.05 (60.92 – 89.02)	88.26 (59.39 – 97.47)		90.84 (76.07 – 96.87)	88.81 (71.68 – 96.13)	93.48 (86.44 – 96.99)	
Physical activity																	
Moderate PA in past 30 days, %					0.182				0.922				0.975				0.364
Yes	29.82 (36.34 - 43.42)	45.41 (36.91 – 54.20)	47.21 (37.33 – 57.31)	34.84 (25.20 – 45.90)		38.58 (29.39 – 48.66)	39.26 (29.96 – 49.41)	37.81 (27.59 – 49.24)		33.60 (16.60 – 56.25)	39.70 (24.85 – 56.71)	33.34 (18.57 – 52.30)		19.48 (8.16 – 39.73)	41.91 (25.82 – 59.93)	34.44 (23.01 – 48.01)	
No	60.17 (56.57 - 63.65)	54.58 (45.79 – 63.08)	52.78 (42.68 – 62.66)	65.15 (54.09 – 74.79)		61.41 (51.33 – 70.60)	60.73 (50.58 – 70.03)	62.18 (50.75 – 72.40)		66.40 (43. 74 – 83.39)	60.29 (43.28 – 75.14)	66.65 (47.69 – 81.42)		80.51 (60.26 – 91.83)	58.08 (40.06 – 74.17)	65.55 (51.98 – 76.98)	
Vigorous PA in past 30 days, %					**0.008**				0.140				0.237				0.001
Yes	19.84 (17.01 – 23.00)	35.36 (27.42 – 44.20)	36.72 (27.26 – 47.32)	16.70 (9.98 – 26.61)		17.73 (10.95 – 27.40)	10.72 (5.95 – 18.56)	9.54 (4.52 – 19.04)		30.55 (13.57 – 55.20)	6.33 (1.65 – 21.34)	14.88 (5.94 – 32.58)		10.62 (3.23 – 29.71)	17.02 (6.71 – 36.91)	0.68 (0.09 – 4.87)	
No	80.15 (76.99 – 82.98)	64.63 (55.79 – 72.57)	63.27 (52.67 – 72.73)	83.29 (73.38 – 90.01)		82.26 (72.59 – 89.04)	89.27 (81.43 – 94.04)	90.45 (80.95 – 95.47)		69.44 (44.79 – 86.42)	93.66 (78.65 – 98.34)	85.11 (67.41 – 94.05)		89.37 (70.28 – 96.76)	82.97 (63.08 – 93.28)	99.31 (95.12 – 99.90)	
Anthropometric																	
Weight, kg	83.11 (20.06)	89.57 (20.11)	91.16 (16.52)	87.47 (18.41)	0.536	78.56 (21.20)	79.41 (22.40)	74.41 (16.55)	0.162	84.64 (14.25)	87.89 (14.51)	91.09 (17.52)	0.153	75.65 (16.92)	75.60 (17.48)	74.55 (17.38)	0.752
Height, m	1.69 (0.09)	1.76 (0.07)	1.77 (0.06)	1.76 (0.07)	0.650	1.64 (0.06)	1.62 (0.06)	1.61 (0.06)	**0.007**	1.72 (0.06)	1.74 (0.06)	1.73 (0.06)	0.660	1.60 (0.07)	1.60 (0.07)	1.60 (0.05)	0.769
Body mass index, kg/m^2	28.96 (6.34)	28.49 (5.44)	29.04 (5.10)	28.09 (5.50)	0.724	29.18 (7.88)	30.01 (8.00)	28.52 (5.96)	0.571	28.52 (5.25)	28.96 (4.79)	30.33 (5.70)	0.282	29.36 (6.31)	29.15 (5.72)	28.98 (6.21)	0.785
Strength																	
Sum of handgrip strength	72.79 (22.52)	93.66 (15.98)	95.21 (15.86)	90.39 (17.06)	0.240	60.29 (9.91)	56.70 (10.06)	58.27 (9.30)	0.133	67.02 (17.41)	75.52 (13.05)	75.65 (14.75)	0.056	46.86 (8.52)	46.02 (7.56)	46.87 (10.77)	0.903
Plasma fatty acids																	
Total plasma ω-3, µmol/L	328.80 (158.25)	200.25 (31.50)	302.25 (29.89)	489.35 (149.59)	**<0.001**	208.62 (31.67)	294.89 (28.35)	488.16 (191.81)	**<0.001**	200.48 (29.80)	311.71 (26.75)	511.79 (172.89)	**<0.001**	204.80 (32.86)	304.45 (27.33)	554.75 (179.57)	**<0.001**
ALA, µmol/L	93.69 (55.14)	65.96 (19.73)	95.72 (27.84)	145.51 (100.87)	**<0.001**	65.92 (18.52)	84.92 (27.33)	124.27 (73.88)	**<0.001**	53.31 (13.85)	90.61 (26.46)	106.12 (86.32)	**<0.001**	65.12 (19.08)	90.83 (27.82)	124.76 (54.12)	**<0.001**
EPA, µmol/L	73.14 (74.23)	35.52 (14.27)	60.45 (18.82)	118.92 (83.85)	**<0.001**	35.53 (13.88)	57.24 (18.11)	131.18 (140.30)	**<0.001**	39.34 (12.02)	65.45 (19.22)	148.14 (82.72)	**<0.001**	35.34 (10.79)	55.80 (22.23)	145.84 (94.38)	**<0.001**

DHA, µmol/L	161.97 (76.38)	98.76 (23.60)	146.07 (31.96)	224.92 (71.90)	**<0.001**	107.16 (24.78)	152.72 (30.81)	232.70 (77.24)	**<0.001**	107.82 (27.78)	155.64 (25.79)	257.51 (74.94)	**<0.001**	104.33 (30.04)	157.81 (33.34)	284.14 (97.77)	**<0.001**
DPA, µmol/L	54.25 (19.74)	42.45 (9.62)	54.86 (12.79)	72.95 (22.87)	**<0.001**	39.87 (10.74)	51.08 (15.33)	66.20 (22.16)	**<0.001**	43.86 (9.25)	53.17 (10.88)	70.55 (20.81)	**<0.001**	44.67 (11.89)	48.21 (11.28)	75.09 (21.70)	**<0.001**
SDA, µmol/L	4.27 (4.01)	2.47 (1.51)	4.46 (2.87)	6.88 (6.14)	**<0.001**	2.52 (1.42)	3.93 (2.16)	6.44 (6.83)	**<0.001**	2.26 (0.90)	4.12 (2.10)	5.49 (5.49)	**<0.001**	2.31 (1.09)	4.25 (2.11)	5.92 (4.13)	**<0.001**
Total plasma ω-6, µmol/L	4376.02 (1961.42)	3995.90 (1447.92)	4440.03 (1927.43)	5417.37 (2044.67)	**<0.001**	4135.59 (1339.95)	4285.96 (2019.14)	4508.24 (2471.32)	0.230	3150.20 (1903.17)	4262.70 (1654.75)	4151.89 (2283.10)	0.084	3777.00 (1838.02)	4139.54 (2059.62)	4943.60 (2334.36)	**0.019**
Total plasma saturated, µmol/L	3295.25 (1963.93)	2921.13 (1399.03)	3492.74 (1934.40)	3704.10 (2936.65)	**0.012**	2787.22 (1357.72)	3402.52 (1665.73)	3879.46 (2335.96)	**<0.001**	132.04 (1602.88)	2844.08 (1869.00)	3675.60 (2122.52)	**<0.001**	2773.78 (1562.85)	2773.17 (1811.92)	4017.78 (2080.49)	**0.001**
Dietary habits																	
Energy, kcal	2065 (701)	2415 (684)	2428 (631)	2510 (748)	0.374	1833 (522)	1807 (602)	1780 (505)	0.457	2210 (657)	2163 (671)	1777 (511)	**0.005**	1289 (418)	1481 (528)	1678 (508)	**0.003**
Carbohydrate, g	252.49 (91.76)	292.22 (95.30)	288.75 (83.10)	308.05 (102.75)	0.306	234.03 (75.80)	224.33 (77.37)	219.52 (67.63)	0.151	261.05 (90.41)	260.39 (89.54)	200.16 (65.63)	**0.005**	147.51 (46.68)	181.17 (72.46)	212.31 (65.00)	**<0.001**
Carbohydrate, %	49.36 (9.34)	48.56 (8.50)	48.10 (8.89)	49.65 (11.00)	0.508	51.32 (10.37)	50.17 (9.25)	49.77 (9.21)	0.306	47.15 (8.55)	48.11 (7.54)	45.55 (9.40)	0.478	46.44 (8.30)	48.88 (10.29)	51.01 (7.41)	**0.015**
Protein, g	80.77 (31.28)	94.68 (31.77)	95.60 (31.36)	99.56 (36.61)	0.336	67.76 (23.44)	69.98 (25.92)	69.13 (22.37)	0.662	87.32 (32.20)	88.27 (23.24)	74.49 (27.37)	0.097	56.83 (21.07)	58.47 (18.22)	66.77 (21.76)	**0.042**
Protein, %	15.87 (3.97)	15.87 (3.89)	15.84 (3.69)	16.20 (4.55)	0.582	14.96 (4.02)	15.67 (3.90)	15.76 (3.70)	0.178	15.96 (3.83)	17.06 (4.34)	16.79 (4.33)	0.450	17.73 (3.17)	16.18 (3.14)	16.15 (3.59)	0.134
Protein, g/kg	1.00 (0.40)	1.09 (0.40)	1.08 (0.41)	1.16 (0.43)	0.300	0.91 (0.37)	0.93 (0.41)	0.95 (0.33)	0.360	1.06 (0.458)	1.02 (0.28)	0.83 (0.30)	**0.018**	0.79 (0.41)	0.80 (0.27)	0.91 (0.30)	0.100
Lipids, g	77.46 (32.87)	92.49 (32.31)	88.88 (32.73)	89.46 (35.78)	0.477	70.49 (27.33)	68.46 (30.31)	65.67 (26.87)	0.218	86.39 (34.05)	82.62 (32.98)	66.49 (23.41)	**0.014**	53.85 (25.72)	57.02 (30.14)	62.64 (24.52)	0.203
Lipids, %	33.38 (7.05)	34.09 (6.158)	32.64 (7.22)	31.54 (6.83)	**0.006**	34.25 (7.81)	33.39 (7.25)	32.86 (7.10)	0.222	34.55 (6.61)	33.84 (5.64)	33.35 (5.10)	0.441	36.71 (8.58)	34.21 (9.32)	33.08 (5.763)	0.074
Total ω-3, g	1.974 (1.04)	2.127 (1.032)	2.180 (0.988)	2.425 (1.382)	0.108	1.723 (0.793)	1.752 (0.883)	1.875 (0.951)	0.219	2.006 (1.034)	1.991 (0.834)	1.935 (1.160)	0.800	1.300 (0.547)	1.490 (0.763)	2.013 (1.344)	**0.006**
ALA, g	1.727 (0.962)	1.872 (0.948)	1.885 (0.924)	2.064 (1.299)	0.277	1.525 (0.734)	1.566 (0.814)	1.640 (0.887)	0.325	1.752 (0.924)	1.758 (0.794)	1.655 (1.149)	0.717	1.160 (0.483)	1.328 (0.707)	1.743 (1.253)	**0.020**
EPA, g	0.024 (0.061)	0.017 (0.039)	0.025 (0.049)	0.051 (0.119)	**0.002**	0.017 (0.042)	0.012 (0.028)	0.034 (0.069)	**0.029**	0.024 (0.075)	0.012 (0.018)	0.037 (0.068)	0.394	0.004 (0.007)	0.013 (0.020)	0.039 (0.093)	**<0.001**
DHA, g	0.053 (0.107)	0.038 (0.054)	0.063 (0.117)	0.096 (0.199)	**0.001**	0.038 (0.070)	0.035 (0.065)	0.070 (0.121)	**0.022**	0.040 (0.078)	0.035 (0.032)	0.071 (0.102)	0.181	0.019 (0.031)	0.037 (0.047)	0.078 (0.162)	**0.001**
Linoleic acid, g	16.340 (8.067)	18.709 (7.869)	18.891 (8.443)	18.606 (8.767)	0.967	15.420 (6.996)	14.523 (7.765)	14.197 (6.401)	0.190	16.922 (8.537)	17.441 (8.126)	13.617 (8.513)	0.121	10.144 (4.311)	12.458 (6.317)	14.238 (9.053)	**0.047**
Saturated fat, g	24.76 (11.41)	30.03 (11.01)	27.41 (10.79)	29.04 (14.15)	0.451	22.60 (9.65)	22.36 (10.87)	20.42 (9.66)	0.119	29.15 (12.45)	25.17 (10.14)	21.51 (8.39)	**0.009**	18.97 (10.49)	18.01 (10.46)	19.58 (7.20)	0.693
Polyunsaturated fat, g	18.50 (8.96)	21.04 (8.80)	21.38 (9.22)	21.26 (9.76)	0.838	17.32 (7.74)	16.43 (8.59)	16.20 (7.08)	0.275	19.18 (9.52)	19.63 (8.92)	15.74 (6.34)	0.149	11.54 (4.86)	14.03 (7.02)	16.43 (10.32)	**0.034**
Monounsaturated fat, g	27.80 (0.48)	33.57 (12.81)	32.72 (14.37)	31.73 (13.62)	0.320	24.87 (11.17)	24.02 (11.23)	23.56 (11.06)	0.434	31.01 (12.17)	31.29 (13.89)	23.62 (10.09)	**0.011**	18.88 (10.14)	20.47 (12.59)	21.61 (8.29)	0.319
Fiber, g	18.12 (13.10)	18.38 (8.68)	20.50 (11.19)	23.48 (16.77)	**0.009**	15.77 (7.68)	15.72 (8.26)	18.96 (9.13)	**0.014**	16.65 (7.05)	19.94 (7.60)	15.40 (5.62)	0.425	11.15 (5.29)	15.55 (7.46)	15.97 (6.07)	**0.010**
Alcohol, g	9.16 (20.37)	8.96 (1.58)	17.50 (3.07)	15.88 (3.55)	**0.037**	2.62 (8.16)	6.33 (13.07)	9.69 (19.43)	**0.007**	8.93 (13.77)	8.03 (20.44)	14.78 (25.29)	0.325	0.06 (0.41)	5.27 (11.26)	3.54 (8.45)	0.105

Notes: ALA: alpha linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; SDA: stearidonic acid. Data described as mean (standard deviation) or percentage (confidence interval).

Table 2. Weighted sociodemographic, healthy conditions and habits, physical activity, anthropometric, strength, plasma fatty acids and dietary habits of young and older adults by dietary omega-3. NHANES, 2011-2012.

Variables		<50 years								≥50 years							
	Total	Men				Women				Men				Women			
		T1	T2	T3	*p*	T1	T2	T3	p	T1	T2	T3	*p*-value	T1	T2	T3	*p*-value
Demographic																	
Age, y	48.60 (17.03)	43.08 (13.37)	41.97 (13.26)	42.61 (12.48)	0.907	41.95 (14.17)	42.45 (12.65)	45.59 (14.34)	0.131	72.82 (5.12)	72.58 (6.14)	71.21 (4.53)	0.211	72.62 (4.78)	74.94 (5.60)	73.50 (5.31)	0.366
Race, %					0.727				0.799				**0.011**				0.202
Non-Hispanic white	71.72 (68.69 – 74.56)	69.54 (58.77 – 78.53)	72.07 (63.17 – 79.51)	71.97 (64.36 – 78.50)		63.07 (53.51 – 71.70)	74.63 (66.41 – 81.40)	59.41 (47.14 – 70.60)		76.36 (62.89 – 86.03)	81.75 (68.22 – 90.33)	92.17 (84.98 – 96.07)		77.14 (65.67 – 85.62)	78.44 (66.35 – 87.03)	86.96 (75.85 – 93.40)	
Marital status, %					0.216				0.780				0.191				0.467
Single/ Divorced/ Widowed/ Never Married	36.72 (32.94 – 40.66)	42.47 (30.21 – 55.73)	39.76 (28.39 – 52.35)	33.11 (24.74 – 42.69)		43.59 (33.28 – 54.49)	30.01 (21.41 – 40.28)	43.12 (31.04 – 56.08)		17.59 (8.03 – 34.27)	17.05 (8.01 – 32.67)	8.27 (3.38 – 18.84)		42.53 (29.24 – 56.99)	52.33 (35.64 – 68.52)	50.41 (30.68 – 70.01)	
Married/ Living as married	63.27 (59.33 – 67.05)	57.52 (44.26 - 69.78)	60.23 (47.64 – 71.60)	66.88 (57.30 – 75.25)		56.40 (45.50 – 66.71)	69.98 (59.71 – 78.58)	56.87 (43.91 – 68.95)		82.40 (65.72 – 91.96)	82.94 (67.32 – 91.98)	91.73 (81.15 – 96.61)		57.47 (43.00 – 70.75)	47.66 (31.47 – 68.52)	49.58 (29.98 – 69.31)	
Annual Family Income, %					0.093				0.033				**0.001**				0.417
$0-19999	20.04 (17.15 – 23.28)	26.94 (16.20 – 41.28)	18.70 (10.81 – 30.38)	15.63 (10.64 – 22.37)		28.21 (20.17 – 37.93)	19.27 (11.81 – 29.84)	15.83 (9.98 – 24.19)		20.15 (10.30 – 35.67)	10.77 (4.49 – 23.67)	2.64 (0.92 – 7.31)		27.08 (17.28 – 39.77)	27.80 (16.07 – 43.64)	18.66 (8.91 – 34.98)	
$20000-54999	35.91 (32.15 – 39.85)	25.61 (16.34 – 37.77)	36.46 (25.99 – 48.39)	30.83 (22.63 – 40.46)		39.28 (29.28 – 50.27)	30.29 (21.15 – 41.31)	27.01 (17.90 – 38.57)		43.58 (26.37 – 62.49)	60.51 (40.46 – 77.55)	53.13 (32.95 – 72.33)		53.91 (39.06 – 68.10)	56.25 (39.63 – 71.57)	45.88 (26.69 – 66.38)	
Over $55000	44.03 (39.86 – 48.28)	47.44 (34.46 – 60.77)	77.83 (32.97 – 57.31)	53.52 (43.62 – 63.15)		32.50 (22.81 – 43.95)	50.43 (39.10 – 61.71)	57.15 (44.36 – 69.04)		36.26 (19.67 – 56.92)	28.71 (14.53 – 48.81)	44.22 (25.39 – 64.89)		18.99 (8.73 – 36.49)	15.94 (6.84 – 32.85)	35.44 (18.66 – 56.76)	
Education level					0.344				0.094				**0.034**				0.054
Under high school graduate	35.97 (32.19 – 39.93)	38.63 (27.03 – 51.67)	43.52 (31.73 – 56.08)	33.08 (24.82 – 42.54)		33.21 (24.24 – 43.59)	24.37 (15.94 – 35.37)	21.49 (13.24 – 32.92)		49.95 (31.70 – 68.21)	60.34 (39.31 – 78.14)	22.95 (11.91 – 39.63)		63.41 (47.83 – 76.61)	61.82 (44.79 – 76.61)	35.91 (19.10 – 57.07)	
Some college or over	64.02 (60.06 – 67.80)	61.63 (48.32 – 72.96)	56.47 (43.91 – 68.2)	66.91 (57.45 – 75.17)		66.78 (56.40 – 75.75)	75.62 (64.62 – 84.02)	78.50 (67.07 – 86.75)		50.04 (31.78 – 68.29)	39.65 (21.85 – 60.68)	77.04 (60.36 – 88.08)		36.58 (23.38 – 52.16)	38.17 (23.63 – 55.20)	64.08 (42.92 – 80.89)	
Health conditions and habits																	
Hypertension, %					0.181				0.946				0.891				0.500
Yes	35.19 (31.42 - 39.15)	24.90 (15.58 – 37.33)	28.61 (18.61 – 41.25)	34.82 (25.88 – 44.98)		29.43 (20.56 – 40.19)	23.28 (15.30 – 33.76)	30.92 (20.27 – 44.07)		57.77 (38.17 – 75.19)	53.85 (32.85 – 73.56)	55.70 (34.78 – 74.77)		57.95 (42.59 – 71.92)	76.01 (58.54 – 87.67)	63.02 (42.55 – 79.68)	

No	64.80 (60.84 – 68.57)	75.09 (62.66 – 84.41)	71.38 (58.74 – 81.38)	65.17 (55.01 – 74.11)		70.56 (59.80 – 79.43)	76.71 (66.23 – 84.69)	69.07 (55.92 – 79.72)		42.22 (24.80 – 61.82)	46.14 (26.43 – 67.14)	44.30 (25.22 – 65.21)		42.04 (28.07 – 57.40)	23.98 (12.32 – 41.45)	36.97 (20.31 – 57.44)	
Diabetes, %					0.470				0.970				0.329				0.878
Pre-diabetes	1.98 (1.11 – 3.51)	0	0.30 (0.07 – 1.24)	2.98 (0.82 – 10.21)		1.35 (0.32 – 5.52)	2.63 (0.70 – 9.31)	2.43 (0.88 – 6.52)		1.44 (0.28 – 6.94)	14.14 (2.60 – 50.39)	0		0.28 (0.03 – 2.03)	0.29 (0.04 – 2.18)	7.51 (1.50 – 30.23)	
Yes	10.47 (8.53 – 12.78)	7.82 (3.91 – 15.03)	7.10 (2.75 – 17.08)	7.47 (3.86 – 13.98)		9.84 (5.44 – 17.16)	6.05 (3.42 – 10.50)	8.95 (3.96 – 18.96)		21.36 (11.40 – 36.43)	24.76 (11.48 – 45.49)	14.44 (6.59 – 28.78)		22.81 (13.68 – 35.53)	35.40 (20.61 – 53.63)	10.94 (4.93 – 22.52)	
No	87.54 (84.97 – 89.72)	92.17 (84.96 – 96.08)	92.59 (82.78 – 97.01)	89.53 (81.87 – 94.18)		88.79 (81.30 – 93.52)	91.30 (85.16 – 95.05)	88.61 (78.81 – 94.21)		77.19 (62.00 – 87.53)	61.09 (38.09 – 80.02)	85.55 (71.21 – 93.40)		76.90 (64.19 – 86.08)	64.29 (46.12 – 79.11)	81.54 (63.74 – 91.73)	
Smoke, %					0.236				**0.002**				0.205				0.587
Yes	21.82 (18.35 – 25.74)	26.97 (15.99 – 41.73)	35.80 (24.59 – 48.82)	20.96 (13.91 – 30.32)		28.15 (19.04 – 39.49)	23.93 (17.74 – 36.39)	7.89 (3.97 – 15.05)		22.71 (10.06 – 43.55)	16.22 (3.72 – 49.25)	9.30 (2.57 – 28.46)		8.55 (3.73 – 18.40)	7.54 (3.50 – 15.51)	5.00 (0.69 – 28.51)	
No	78.17 (74.25 – 81.64)	73.02 (58.26 – 84.00)	64.19 (51.17 – 75.40)	79.03 (69.67 – 86.08)		71.84 (60.50 – 80.955)	76.07 (63.60 – 85.25)	92.10 (84.94 – 96.02)		72.29 (56.44 – 89.93)	83.77 (50.74 – 96.27)	90.69 (71.53 – 97.42)		91.44 (81.59 – 96.26)	92.45 (84.48 – 96.49)	94.99 (71.48 – 99.30)	
Physical activity																	
Moderate PA in past 30 days, %					0.042				0.452				0.864				0.321
Yes	40.02 (35.99 – 44.19)	34.64 (23.18 – 48.22)	44.80 (33.00 – 57.23)	52.17 (42.19 – 61.98)		36.75 (26.95 – 47.77)	30.89 (21.73 – 41.85)	44.67 (31.78 – 58.30)		42.07 (24.68 – 61.69)	27.32 (14.41 – 45.62)	39.23 (21.37 – 60.53)		27.00 (15.25 – 43.17)	36.21 (21.76 – 53.68)	38.52 (20.77 – 59.95)	
No	59.97 (55.80 – 64.00)	65.35 (51.77 – 76.81)	55.19 (42.76 – 66.99)	47.82 (42.19 – 61.98)		63.24 (52.22 – 73.04)	69.10 (58.14 – 78.26)	55.32 (41.69 – 68.21)		57.92 (38.30)	72.67 (54.37 – 85.58)	60.76 (39.46 – 78.62)		73.00 (56.82 – 84.74)	63.78 (46.31 – 78.23)	61.47 (40.04 – 79.22)	
Vigorous PA in past 30 days, %					**0.037**				0.251				0.522				0.620
Yes	20.67 (17.26 – 24.56)	20.53 (12.08 – 32.69)	32.49 (21.74 – 45.47)	37.72 (28.17 – 48.32)		16.81 (9.67 – 27.26)	12.54 (6.86 – 21.83)	8.86 (2.89 – 24.09)		10.09 (2.43 – 33.57)	13.95 (5.56 – 30.84)	16.68 (6.73 – 35.69)		9.45 (2.77 – 27.62)	4.55 (0.98 – 18.60)	6.55 (1.58 – 23.41)	
No	79.32 (75.43 – 82.73)	79.46 (67.30 – 87.91)	67.50 (54.52 – 78.25)	62.27 (51.67 – 71.82)		83.18 (72.37 – 90.32)	87.45 (78.16 – 93.13)	91.13 (75.90 – 97.10)		89.91 (66.42 – 97.56)	86.04 (69.15 – 94.43)	83.31 (64.30 – 93.26)		90.54 (72.37 – 97.22)	95.44 (81.39 – 99.01)	93.44 (76.58 – 98.41)	
Anthropometric																	
Weight, kg	82.84 (20.29)	86.15 (17.25)	88.37 (18.62)	91.83 (19.56)	0.074	76.68 (23.03)	74.76 (16.82)	80.38 (22.91)	0.382	85.73 (14.31)	90.17 (20.80)	86.59 (12.75)	0.817	74.59 (19.13)	74.50 (17.90)	76.08 (16.59)	0.773
Height, m	1.69 (0.10)	1.75 (0.07)	1.77 (0.07)	1.78 (0.07)	0.054	1.62 (0.07)	1.62 (0.06)	1.63 (0.05)	0.301	1.73 (0.07)	1.71 (0.05)	1.75 (0.05)	0.163	1.58 (0.06)	1.60 (0.06)	1.60 (0.05)	0.278
Body mass index, kg/m^2	28.73 (6.28)	27.94 (5.37)	27.89 (4.97)	28.86 (5.66)	0.265	28.97 (7.36)	28.31 (6.48)	30.14 (8.43)	0.432	28.66 (5.29)	30.43 (6.50)	28.00 (3.79)	0.545	29.38 (6.45)	28.84 (6.56)	29.41 (5.43)	0.953
Strength																	
Sum of handgrip strength	73.28 (23.38)	91.30 (15.57)	92.35 (14.87)	96.60 (17.22)	**0.027**	56.24 (10.79)	58.94 (9.22)	59.49 (9.76)	**0.035**	72.10 (16.72)	70.54 (16.59)	76.86 (14.30)	0.283	45.26 (10.97)	44.27 (9.46)	45.66 (10.09)	0.960
Plasma fatty acids																	
Total plasma ω-3, µmol/L	330.20 (158.83)	309.34 (149.54)	301.64 (111.28)	326.06 (158.34)	0.422	323.35 (174.79)	303.18 (112.16)	331.22 (138.02)	0.821	312.26 (98.05)	365.11 (157.54)	331.88 (149.70)	0.648	396.98 (206.43)	383.59 (185.76)	565.41 (254.86)	**0.011**

ALA, µmol/L	95.60 (61.58)	95.12 (83.87)	97.01 (59.96)	105.91 (78.12)	0.372	88.19 (54.25)	85.23 (36.14)	99.28 (55.84)	0.172	86.61 (43.63)	92.14 (74.55)	82.30 (37.69)	0.619	93.49 (46.08)	103.01 (50.13)	122.95 (62.51)	0.057
EPA, µmol/L	72.61 (68.51)	61.86 (39.45)	62.95 (37.33)	70.97 (59.19)	0.201	70.42 (109.50)	64.09 (41.93)	72.20 (56.48)	0.948	73.86 (46.56)	87.74 (58.55)	78.52 (61.93)	0.811	91.26 (85.88)	88.29 (64.65)	159.42 (141.93)	**0.037**
DHA, µmol/L	161.99 (78.15)	152.36 (72.25)	141.67 (54.02)	149.18 (69.87)	0.934	164.73 (73.92)	153.85 (60.41)	159.74 (73.55)	0.511	151.79 (53.84)	185.22 (77.06)	171.05 (70.87)	0.345	212.23 (110.17)	192.29 (109.06)	283.03 (119.09)	**0.045**
DPA, µmol/L	54.15 (19.35)	55.12 (17.77)	53.27 (18.31)	56.13 (19.16)	0.621	51.24 (20.25)	48.46 (16.03)	53.16 (18.44)	0.615	55.40 (15.02)	57.94 (17.40)	52.12 (15.79)	0.468	58.07 (23.76)	61.90 (21.78)	73.26 (23.68)	**0.019**
SDA, µmol/L	4.32 (3.89)	3.92 (3.50)	4.62 (5.38)	4.61 (3.44)	0.360	4.06 (5.14)	3.75 (2.10)	4.71 (3.45)	0.303	3.78 (2.23)	3.99 (2.89)	3.92 (3.28)	0.809	4.28 (2.82)	4.74 (3.18)	6.37 (6.55)	0.075
Total plasma ω-6, µmol/L	4398.41 (1950.38)	4261.49 (2397.56)	4480.13 (1921.81)	4784.52 (1520.98)	0.132	3887.65 (2321.54)	4279.56 (1634.81)	4788.76 (1872.06)	**0.007**	3495.45 (2222.81)	3743.21 (2048.21)	4429.71 (1327.90)	0.076	4190.37 (2239.00)	4487.87 (2073.43)	5223.14 (1864.98)	0.073
Total plasma saturated, µmol/L	3307.53 (1969.12)	3114.67 (2194.023)	3258.74 (3258.80)	3495.48 (2073.45)	0.307	3229.66 (2131.83)	3406.38 (1506.23)	3334.36 (1832.51)	0.708	2863.81 (2306.93)	3243.94 (1905.97)	2548.82 (1592.02)	0.575	3091.39 (2078.26)	3750.18 (1558.90)	3931.45 (2092.73)	0.090
Dietary habits																	
Energy, kcal	2087 (710)	1811 (501)	2289 (541)	2871 (559)	**<0.001**	1407 (443)	1927 (424)	2249 (561)	**<0.001**	1718 (480)	2011 (525)	2618 (559)	**<0.001**	1328 (332)	1585 (362)	1953 (618)	**<0.001**
Carbohydrate, g	256.42 (94.91)	234.09 (79.42)	284.57 (99.03)	338.57 (81.84)	**<0.001**	182.94 (71.23)	246.41 (63.26)	261.81 (87.19)	**<0.001**	207.84 (63.66)	245.92 (91.50)	305.85 (82.15)	**<0.001**	176.56 (50.64)	195.42 (62.92)	222.55 (82.42)	**0.025**
Carbohydrate, %	49.37 (9.17)	51.81 (10.72)	49.20 (10.08)	47.21 (7.17)	**0.003**	51.61 (11.92)	51.03 (7.26)	46.45 (9.03)	**0.009**	48.83 (9.90)	48.22 (9.25)	46.36 (5.16)	0.169	53.11 (7.09)	48.85 (8.68)	45.16 (7.61)	**<0.001**
Protein, g	80.84 (30.41)	72.23 (23.98)	88.03 (25.95)	111.28 (29.21)	**<0.001**	55.44 (21.14)	71.73 (17.79)	84.08 (27.76)	**<0.001**	71.13 (25.45)	90.56 (28.47)	95.00 (18.54)	**<0.001**	55.00 (16.89)	63.83 (17.21)	76.37 (23.37)	**<0.001**
Protein, %	15.79 (3.99)	16.31 (4.79)	15.72 (4.41)	15.56 (3.01)	0.241	16.20 (5.29)	15.18 (3.25)	15.01 (3.57)	0.138	16.77 (4.38)	18.28 (4.97)	14.83 (2.57)	**0.032**	16.69 (3.69)	16.41 (4.11)	15.95 (3.17)	0.414
Protein, g/kg	1.01 (0.39)	0.87 (0.32)	1.02 (0.32)	1.26 (0.40)	**<0.001**	0.77 (0.36)	1.00 (0.29)	1.11 (0.51)	**<0.001**	0.85 (0.32)	1.02 (0.30)	1.12 (0.28)	**0.001**	0.77 (0.26)	0.90 (0.34)	1.03 (0.34)	**0.001**
Lipids, g	78.41 (33.03)	60.94 (24.14)	80.45 (21.81)	113.85 (28.86)	**<0.001**	48.19 (19.053)	71.50 (18.61)	93.13 (29.58)	**<0.001**	56.87 (17.24)	71.70 (22.23)	110.91 (25.91)	**<0.001**	45.49 (14.26)	62.35 (20.00)	82.55 (28.98)	**<0.001**
Lipids, %	33.47 (6.79)	30.06 (7.90)	31.85 (5.72)	35.68 (5.65)	**<0.001**	31.02 (8.05)	33.57 (5.35)	37.25 (6.66)	**<0.001**	30.21 (6.38)	32.18 (5.09)	38.04 (3.71)	**<0.001**	30.85 (6.01)	35.42 (7.42)	37.87 (5.31)	**<0.001**
Total ω-3, g	1.978 (1.004)	1.087 (0.286)	1.796 (0.247)	3.089 (0.875)	**<0.001**	0.97 (0.334)	1.76 (0.202)	2.89 (0.80)	**<0.001**	1.094 (0.270)	1.769 (0.225)	2.983 (0.624)	**<0.001**	0.943 (0.243)	1.728 (0.250)	3.266 (1.167)	**<0.001**
ALA, g	1.724 (0.925)	0.910 (0.242)	1.543 (0.209)	2.705 (0.864)	**<0.001**	0.823 (0.288)	1.555 (0.212)	2.584 (0.798)	**<0.001**	0.924 (0.239)	1.515 (0.258)	2.647 (0.670)	**<0.001**	0.813 (0.218)	1.515 (0.254)	2.808 (1.166)	**<0.001**
EPA, g	0.025 (0.110)	0.013 (0.020)	0.015 (0.030)	0.048 (0.099)	**<0.001**	0.011 (0.025)	0.018 (0.031)	0.037 (0.080)	**<0.001**	0.008 (0.012)	0.028 (0.046)	0.035 (0.061)	**0.008**	0.007 (0.015)	0.022 (0.055)	0.079 (0.156)	**0.006**
DHA, g	0.055 (0.036)	0.025 (0.036)	0.038 (0.0510)	0.095 (0.162)	**<0.001**	0.029 (0.053)	0.042 (0.056)	0.082 (0.141)	**<0.001**	0.027 (0.035)	0.059 (0.081)	0.066 (0.072)	**0.014**	0.019 (0.026)	0.053 (0.095)	0.160 (0.268)	**0.002**
Linoleic acid, g	16.497 (8.073)	11.535 (5.877)	15.510 (4.638)	24.601 (6.719)	**<0.001**	8.870 (4.118)	15.591 (3.806)	22.585 (8.242)	**<0.001**	9.864 (3.156)	14.052 (4.370)	24.265 (6.107)	**<0.001**	8.470 (2.958)	12.989 (2.985)	21.476 (9.637)	**<0.001**
Saturated fat, g	25.18 (11.65)	20.15 (8.38)	27.03 (8.94)	35.99 (12.10)	**<0.001**	16.67 (7.90)	22.77 (8.01)	27.56 (10.93)	**<0.001**	19.95 (7.22)	23.34 (9.41)	34.01 (9.93)	**<0.001**	15.18 (5.16)	21.17 (9.80)	23.27 (9.49)	**<0.001**
Polyunsaturated fat, g	18.66 (8.94)	12.82 (6.07)	17.53 (4.72)	27.92 (7.26)	**<0.001**	9.95 (4.39)	17.53 (3.99)	25.67 (8.73)	**<0.001**	11.10 (3.33)	15.97 (4.57)	27.54 (6.35)	**<0.001**	9.54 (3.18)	14.91 (3.20)	24.83 (10.69)	**<0.001**
Monounsaturated fat, g	28.08 (13.00)	22.30 (11.27)	29.11 (9.60)	40.78 (12.40)	**<0.001**	17.30 (7.41)	25.19 (8.04)	32.78 (11.96)	**<0.001**	21.04 (7.76)	26.10 (9.94)	40.79 (11.07)	**<0.001**	16.87 (6.08)	21.24 (7.84)	28.18 (11.01)	**<0.001**

Fiber, g	18.01 (9.54)	16.26 (7.95)	17.01 (8.59)	24.58 (12.02)	**<0.001**	12.49 (6.91)	17.62 (6.98)	19.27 (9.91)	**<0.001**	14.07 (5.56)	18.23 (6.66)	21.63 (7.21)	**0.001**	13.18 (5.22)	15.98 (6.37)	18.28 (6.95)	**0.002**
Alcohol, g	8.91 (19.40)	9.00 (21.10)	14.40 (24.19)	12.23 (22.70)	0.515	5.55 (15.35)	6.14 (12.00)	8.80 (22.66)	0.420	15.77 (30.75)	6.21 (13.80)	8.01 (13.)	0.238	1.97 (7.02)	1.96 (6.40)	6.90 (10.33)	0.084

Notes: ALA: alpha linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; SDA: stearidonic acid. Data described as mean (standard deviation) or percentage (confidence interval).

Table 3. Weighted linear regression between plasma and dietary omega-3 and handgrip strength for young individuals (<50 years). NHANES, 2011-2012.

Plasma ω-3								
	Model 1			***p*-trend**	**Model 2**			***p*-trend**
	β (95%CI)				**β (95%CI)**			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
Total ω-3								
Total	1	-4.06 (-8.51; 0.39)	-6.12 (-10.32; -1.92)	**0.004**	1	-0.52 (-2.81; 1.77)	0.46 (-2.14; 3.07)	0.778
Men	1	1.54 (-2.57; 5.67)	-3.26 (-7.86; 1.32)	0.240	1	1.42 (-2.24; 5.08)	0.12 (-3.98; 4.23)	0.851
Women	1	-2.59 (-6.28; -0.90)	-2.02 (-4.75; 0.70)	0.133	1	-2.84 (-5.13; -0.56)	-0.34 (-2.66; 1.97)	0.690
ALA								
Total	1	-1.24 (-5.62; 3.14)	0.81 (-3.61; 5.25)	0.733	1	0.53 (-1.56; 2.63)	-0.74 (-3.09; 1.60)	0.547
Men	1	0.43 (-3.72; 4.60)	-1.50 (-5.93; 2.92)	0.500	1	0.97 (-2.72; 4.67)	-1.42 (-5.17; 2.32)	0.446
Women	1	-0.48 (-3.21; 2.24)	-0.49 (-3.13; 2.13)	0.699	1	0.48 (-1.76; 2.72)	0.10 (-2.25; 2.45)	0.912
EPA								
Total	1	-2.21 (-6.55; 2.12)	-3.40 (-7.81; 1.00)	0.130	1	0.19 (-2.07; 2.45)	0.23 (-2.43; 2.90)	0.864
Men	1	1.68 (-2.62; 5.99)	-0.64 (-5.11; 3.82)	0.800	1	-0.09 (-3.70; 3.51)	0.73 (-3.42; 4.89)	0.739
Women	1	-0.12 (-2.81; 2.56)	-2.11 (-4.88; 0.65)	0.128	1	0.46 (-1.97; 2.90)	-0.60 (-3.12; 1.92)	0.600
DHA								
Total	1	-5.86 (-10.21; -1.51)	-5.98 (-10.36; -1.60)	**0.005**	1	-0.04 (-2.21; 2.13)	2.77 (0.25; 5.29)	**0.042**
Men	1	1.26 (-2.83; 5.36)	-0.65 (-5.26; 3.95)	0.877	1	1.81 (-1.60; 5.23)	4.16 (0.07; 8.25)	**0.043**
Women	1	-2.82 (-5.50; -0.15)	-1.15 (-4.12; 1.81)	0.436	1	-2.23 (-4.52; 0.05)	0.31 (-2.22; 2.85)	0.861
Dietary ω-3								
	Model 1			***p*-trend**	**Model 2**			***p*-trend**
	β (95%CI)				**β (95%CI)**			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
Total ω-3								
Total	1	3.49 (-1.44; 8.43)	13.55 (8.19; 18.90)	**<0.001**	1	0.40 (-2.48; 2.56)	0.75 (-2.21; 3.73)	0.610
Men	1	1.05 (-3.35; 5.45)	5.30 (0.45; 10.16)	**0.027**	1	-1.99 (-6.40; 2.41)	-0.61 (-5.59; 4.36)	0.900
Women	1	2.69 (-0.54; 5.94)	3.25 (0.14; 6.35)	**0.035**	1	1.30 (-1.19; 3.80)	0.26 (-2.69; 3.22)	0.825
ALA								
Total	1	3.84 (-1.07; 8.77)	13.43 (7.95; 18.91)	**<0.001**	1	-0.49 (-3.04; 2.06)	1.33 (-1.65; 4.33)	0.345
Men	1	-0.29 (-4.68; 4.08)	5.45 (0.41; 10.48)	**0.020**	1	-2.16 (-6.69; 2.35)	0.13 (-5.36; 5.62)	0.830
Women	1	2.47 (-0.80; 5.76)	3.27 (0.20; 6.35)	**0.035**	1	0.71 (-1.81; 3.24)	0.44 (-2.62; 3.51)	0.774
EPA								
Total	1	10.63 (5.59; 15.68)	11.24 (6.25; 16.23)	**<0.001**	1	0.47 (-2.12; 3.07)	-0.33 (-3.04; 2.37)	0.793
Men	1	6.03 (1.41; 10.66)	4.64 (-0.29; 9.59)	0.136	1	0.99 (-3.56; 5.54)	-1.82 (-6.56; 2.90)	0.351
Women	1	0.57 (-2.71; 3.86)	2.03 (-1.12; 5.19)	0.220	1	-0.67 (-3.11; 1.77)	0.89 (-1.55; 3.33)	0.561
DHA								
Total	1	4.95 (-0.50; 10.40)	4.44 (-0.90; 9.80)	0.096	1	-0.57 (-3.26; 2.12)	-0.49 (-3.07; 2.09)	0.705

Men	1	1.55 (-3.77; 6.88)	0.98 (-3.96; 5.93)	0.709	1	-1.60 (-6.10; 2.89)	-1.53 (-5.86; 2.80)	0.499
Women	1	1.25 (-2.03; 4.53)	0.08 (-3.16; 3.33)	0.895	1	0.73 (-1.66; 3.14)	0.94 (-1.68; 3.58)	0.471

Notes: ALA: alpha linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid. Model 1: crude analysis; Model 2 was adjusted for age (years), education level, family income, marital status, race/ethnicity, physical activity (yes or no), diabetes (pre, yes or no), hypertension (yes or no), body weight (kg), protein intake (g/day), energy intake (kcal/day), alcohol consumption (g/day), smoke status (yes or no) and total plasma or dietary saturated fat. Women was also adjusted for menopausal status. The analysis for total sample was also adjusted for sex in Model 2.

Table 4. Weighted linear regression between plasma and dietary omega-3 and handgrip strength for older individuals (≥50 years). NHANES, 2011-2012.

Plasma ω-3								
	Model 1			***p*-trend**	**Model 2**			***p*-trend**
	β (95%CI)				**β (95%CI)**			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
Total ω-3								
Total	1	5.65 (-2.02; 13.34)	-2.64 (-9.63; 4.35)	0.193	1	3.10 (-2.03; 8.24)	2.45 (-1.77; 6.69)	0.287
Men	1	8.50 (-1.09; 18.11)	8.63 (-0.46; 17.73)	0.056	1	7.28 (-1.22; 15.79)	9.31 (1.84; 16;79)	**0.014**
Women	1	-0.83 (-4.83; 3.15)	0.01 (-4.48; 4.49)	0.903	1	-1.00 (-5.46; 3.46)	-2.71 (-6.95; 1.51)	0.170
ALA								
Total	1	-8.49 (-14.66; -2.32)	-3.01 (-9.90; 3.87)	0.440	1	1.63 (-1.84; 5.11)	3.19 (-1.35; 7.73)	0.167
Men	1	1.81 (-5.61; 9.24)	6.48 (-1.98; 14.95)	0.138	1	4.85 (-0.86; 10.56)	4.47 (-3.57; 12.52)	0.196
Women	1	-0.01 (-3.50; 3.49)	2.64 (-2.09; 7.38)	0.246	1	-1.23 (-4.40; 1.93)	0.56 (-2.76; 3.89)	0.592
EPA								
Total	1	6.18 (-1.06; 13.43)	-0.06 (-6.00; 5.87)	0.568	1	1.87 (-2.13; 5.89)	-1.72 (-5.61; 2.16)	0.257
Men	1	4.43 (-4.44; 13.31)	3.69 (-3.58; 10.95)	0.430	1	3.53 (-4.19; 11.26)	-0.81 (-9.97; 8.36)	0.697
Women	1	1.15 (-2.21; 4.53)	-1.08 (-5.10; 2.93)	0.488	1	0.70 (-2.90; 4.31)	-2.99 (-6.02; 0.03)	**0.030**
DHA								
Total	1	3.05 (-4.96; 11.08)	-3.92 (-10.96; 3.11)	0.136	1	0.65 (-4.11; 5.42)	0.61 (-3.51; 4.74)	0.778
Men	1	3.19 (-6.50; 12.88)	4.78 (-3.85; 13.42)	0.268	1	0.42 (-7.63; 8.48)	5.44 (-2.97; 13.87)	0.209
Women	1	-0.50 (-4.59; 3.59)	-0.01 (-4.30; 4.28)	0.953	1	-0.36 (-5.09; 4.35)	-2.66 (-7.06; 1.72)	0.152
Dietary ω-3								
	Model 1			***p*-trend**	**Model 2**			***p*-trend**
	β (95%CI)				**β (95%CI)**			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
Total ω-3								
Total	1	-0.18 (-6.75; 6.39)	/	0.058	1	1.11 (-2.83; 5.06)	1.33 (-.290; 5.58)	0.514
Men	1	-1.55 (-10.23; 7.11)	4.75 (-3.97; 13.49)	0.283	1	-2.47 (-11.21; 6.26)	0.92 (-7.45; 9.30)	0.860
Women	1	-0.98 (-5.77; 3.79)	0.40 (-5.49; 6.29)	0.960	1	3.15 (-0.57; 6.87)	0.84 (-3.67; 5.37)	0.541
ALA								
Total	1	2.95 (-3.71; 9.62)	9.78 (1.78; 17.78)	**0.017**	1	2.48 (-1.37; 6.33)	1.93 (-2.38; 6.25)	0.314
Men	1	2.68 (-5.79; 11.17)	6.33 (-2.74; 15.40)	0.170	1	2.15 (-6.49; 10.80)	2.92 (-5.89; 11.74)	0.508
Women	1	-1.12 (-5.79; 3.54)	0.22 (-5.89; 6.34)	0.982	1	3.01 (-08/.84; 6.87)	0.88 (-3.63; 5.41)	0.486
EPA								
Total	1	7.70 (0.39; 15.02)	6.73 (-0.65; 14.12)	**0.045**	1	0.56 (-2.99; 4.13)	1.51 (-2.29; 5.31)	0.435
Men	1	1.30 (-7.84; 10.46)	2.32 (-4.91; 9.55)	0.522	1	-1.92 (-9.49; 5.63)	1.93 (-5.81; 9.68)	0.597
Women	1	5.89 (0.65; 11.13)	3.65 (-1.40; 8.71)	0.080	1	2.23 (-1.15; 5.63)	0.91 (-3.17; 4.99)	0.583
DHA								
Total	1	-0.40 (-7.64; 6.83)	6.09 (-1.35; 13.53)	0.124	1	0.66 (-3.01; 4.35)	4.23 (0.38; 8.09)	**0.033**

Men	1	2.07 (-7.53; 11.69)	4.45; (-2.38; 11.30)	0.200	1	2.43 (-5.23; 10.10)	7.80 (1.44; 14.16)	**0.015**
Women	1	1.47 (-3.37; 6.31)	3.29 (-1.33; 7.92)	0.159	1	-0.03 (-3.70; 3.62)	2.18 (-2.05; 6.41)	0.356

Notes: ALA: alpha linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid. Model 1: crude analysis; Model 2 was adjusted for age (years), education level, family income, marital status, race/ethnicity, physical activity (yes or no), diabetes (pre, yes or no), hypertension (yes or no), body weight (kg), protein intake (g/day), energy intake (kcal/day), alcohol consumption (g/day), smoke status (yes or no) and total plasma or dietary saturated fat. Women was also adjusted for menopausal status. The analysis for total sample was also adjusted for sex in Model 2.

6. CONCLUSÃO

Em conclusão, foram encontradas evidências mistas sobre a influência do ω-3 na massa e na força muscular de adultos e idosos. Ao realizarmos associações entre o consumo ou as concentrações plasmáticas de ω-3, encontramos associações positivas apenas para o grupo masculino, enquanto que para mulheres, não foram encontradas associações significativas, sugerindo associações sexo-dependentes. Assim, sugere-se que os próximos estudos avaliem homens e mulheres separadamente. Além disso, mais estudos são necessários envolvendo esse tema, afim de melhor elucidar a relação entre o ω-3 e a saúde muscular.