Meeting 5

Individuals with Chronic Conditions

Chair: David Buchner

Members: Bill Kraus, Rich Macko, Anne McTiernan, Linda Pescatello, Ken Powell

Experts and Consultants

- Consultants:
  - Virginia Byers Kraus, M.D., Ph.D.
    Duke University
  - Christine M. Friedenreich, Ph.D.
    Alberta Health Services
  - Ronald J. Sigal, M.D., M.P.H.
    University of Calgary

Subcommittee Questions

1. Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary cancer?

2-7. In people with chronic conditions, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

   2) Osteoarthritis: Additional outcomes (4) disease progression & (5) pain
   3) Hypertension: Additional outcome (4) disease progression
   4) Type 2 Diabetes: Additional outcome (4) disease progression
   5) Multiple Sclerosis
   6) Spinal Cord Injury
   7) Intellectual Disability

Question 1

1. Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary cancer?
   - Is there a dose-response relationship? If yes, what is the shape of the relationship?
   - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
   - Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

- Source of evidence to answer question
  - Systematic Review, Meta-Analyses, and Existing Report

Analytical Framework

Systematic Review Question

Among cancer survivors, what is the relationship between physical activity and (1) all cause mortality; (2) cancer specific mortality, and (3) risk of cancer recurrence or second primary cancer?

Target Population

Cancer survivors of all ages

Comparison

Cancer survivors who participate in varying levels of physical activity

Intervention/Exposure

All types and intensities of physical activity

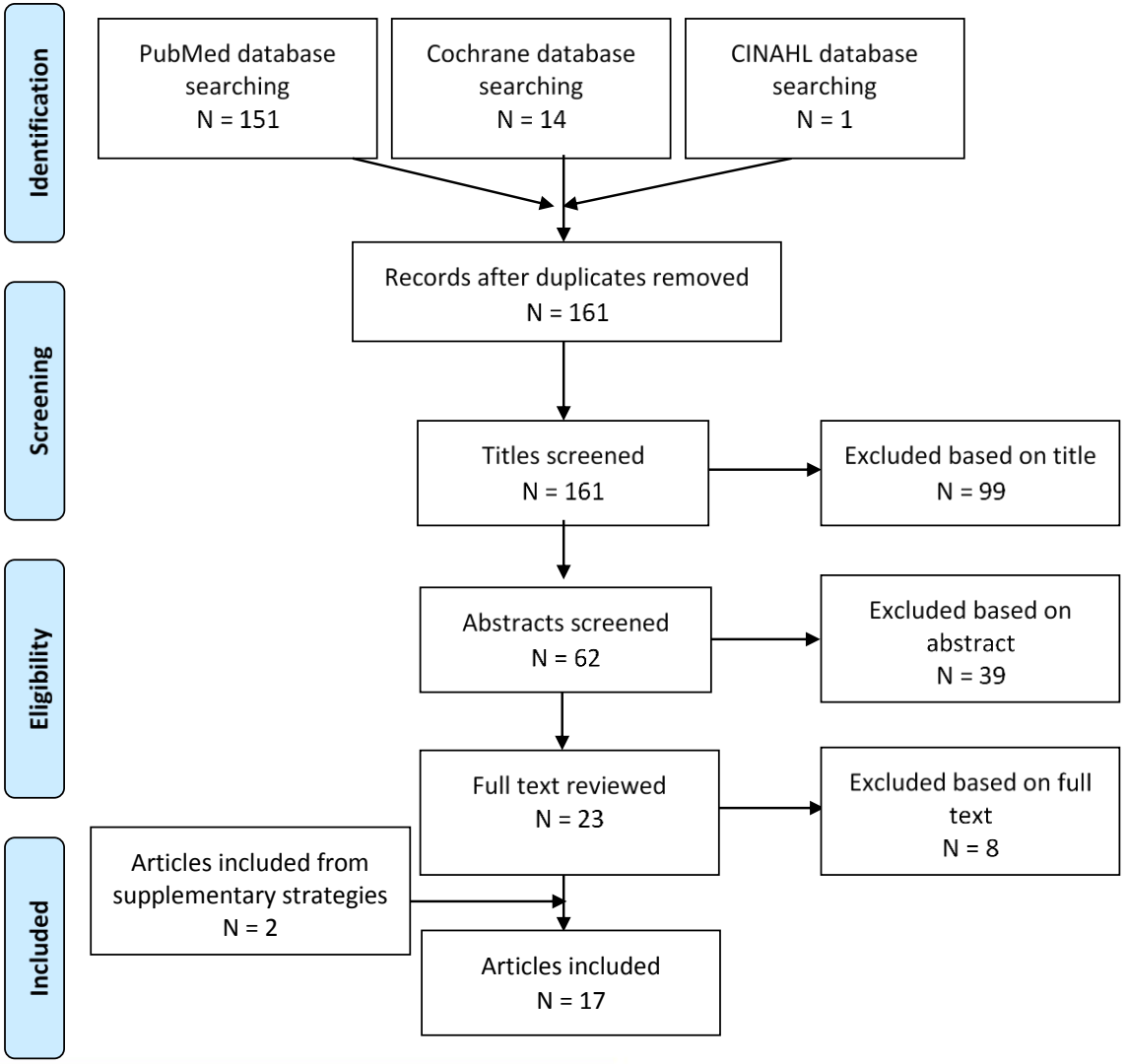
Endpoint Health Outcomes

- All-cause mortality
- Cancer-specific mortality
- Cancer recurrence
- Second primary cancer
- Adverse events related to physical activity

Key Definitions

- Cancer survivor: A person who has been diagnosed with, is undergoing treatment for, or has received treatment for any type of cancer
- Cancer recurrence: Original primary cancer is detected after a remission (when cancer was not detectable)
- Second Primary cancer: A new cancer that occurs sometime after diagnosis of original primary

Q1 Search Results: High-Quality Reviews[1] and Reports



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Draft Conclusion Statements: Breast

Is there a dose-response relationship? If yes, what is the shape of the relationship?

- Moderate evidence indicates that as levels of physical activity increase, risk of breast cancer mortality and all-cause mortality decreases. **PAGAC Grade: Moderate**

Draft Conclusion Statements: Breast

Does the relationship vary by age, race/ethnicity, socio-economic status, or weight status?

- Moderate evidence indicates that physical activity reduces risk for breast cancer specific death in both pre- and postmenopausal women, with menopause as a proxy for age, while high levels of physical activity reduces all-cause mortality in only postmenopausal women.
  - **PAGAC Grade:** Moderate
- Moderate evidence indicates that physical activity reduces risk for all-cause mortality in both normal-weight and overweight/obese women, while it may only reduce breast cancer-specific death risk in overweight/obese survivors.
  - **PAGAC Grade:** Moderate
- There is insufficient evidence to grade whether the relationship between physical activity and breast cancer differs by race/ethnicity or socioeconomic status.
  - **PAGAC Grade – Not assignable**

Draft Conclusion Statements: Breast

Does the relationship vary based on: frequency, duration, intensity, type (mode), and how physical activity is measured?

- There is insufficient evidence to analyze whether the frequency, duration, intensity, or type (mode) of physical activity is related to all-cause or cancer-specific mortality among survivors of breast cancer.
  - PAGAC Grade – Not assignable.

Draft Conclusion Statements: Colorectal

Is there a dose-response relationship? If yes, what is the shape of the relationship?

- There is a dose-response relationship such that higher vs. lower levels of physical activity after the diagnosis of colorectal cancer are associated with a significant HR of 0.68 indicating an ~32% reduction in overall mortality, and a significant HR of 0.56 indicating an ~44% reduction in colorectal cancer specific mortality. The inverse association for physical activity with reduced all-cause mortality and colorectal cancer specific mortality is consistent across meta-analyses including >6,300 patients across follow-up times ranging 3.8 to 11.9 years after the diagnosis. **PAGAC Grade: Moderate**

Draft Conclusion Statements: Colorectal

Does the relationship vary by age, race/ethnicity, socio-economic status, or weight status?

- **Age:** Moderate evidence indicates that the association between PA and colorectal cancer mortality does not vary across age groups from middle to older ages.
  - **PAGAC Grade – Moderate**
- **Gender:** Moderate evidence indicates that the association between PA and colorectal cancer mortality does not vary between genders.
  - **PAGAC Grade – Moderate**
- There is insufficient evidence to grade whether the relationship between physical activity and colorectal cancer mortality differs by race/ethnicity, socioeconomic status, or weight status.
  - **PAGAC Grade – Not assignable**

Draft Conclusion Statements: Colorectal

Does the relationship vary based on: frequency, duration, intensity, type (mode), and how physical activity is measured?

- Moderate evidence indicates that moderate to vigorous PA of at least 17 MET hours per week is associated with reduced mortality in persons with colorectal cancer.
  - **PAGAC Grade – Moderate**
- There is insufficient evidence to grade whether frequency, duration, intensity, type (mode) of PA are associated with mortality in persons with colorectal cancer.
  - **PAGAC Grade – Not assignable**

Draft Conclusion Statements: Prostate

Is there a dose-response relationship? If yes, what is the shape of the relationship?

- Limited evidence suggests that increased frequency, duration, and intensity may be associated with decreased risks for overall mortality and prostate cancer specific mortality. **PAGAC Grade:** Limited

Draft Conclusion Statements: Prostate

Does the relationship vary based on: frequency, duration, intensity, type (mode), and how physical activity is measured?

- Limited evidence suggests that increased frequency, duration, and intensity may be associated with decreased risks for overall mortality and prostate cancer specific mortality.
  - PAGAC Grade – Limited

Committee Discussion

1. Among cancer survivors, what is the relationship between physical activity and (1) all-cause mortality, (2) cancer-specific mortality, or (3) risk of cancer recurrence or second primary cancer?
   - Is there a dose-response relationship? If yes, what is the shape of the relationship?
   - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
   - Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

Question 2: Osteoarthritis

2. In persons with osteoarthritis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, (4) pain, and (5) disease progression?
   - Is there a dose-response relationship? If yes, what is the shape of the relationship?
   - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
   - Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

- Source of evidence to answer question
  - Combination of Systematic Reviews and Meta-Analyses and de novo systematic review of original articles
    - De novo for progression outcome only

Analytical Framework

Systematic Review Question

In people with osteoarthritis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, (4) pain, and (5) disease progression.

Target Population

Individuals of all ages with osteoarthritis

Comparison

Individuals with osteoarthritis who participate in varying levels or no physical activity

Intervention/Exposure

All types and intensities of physical activity

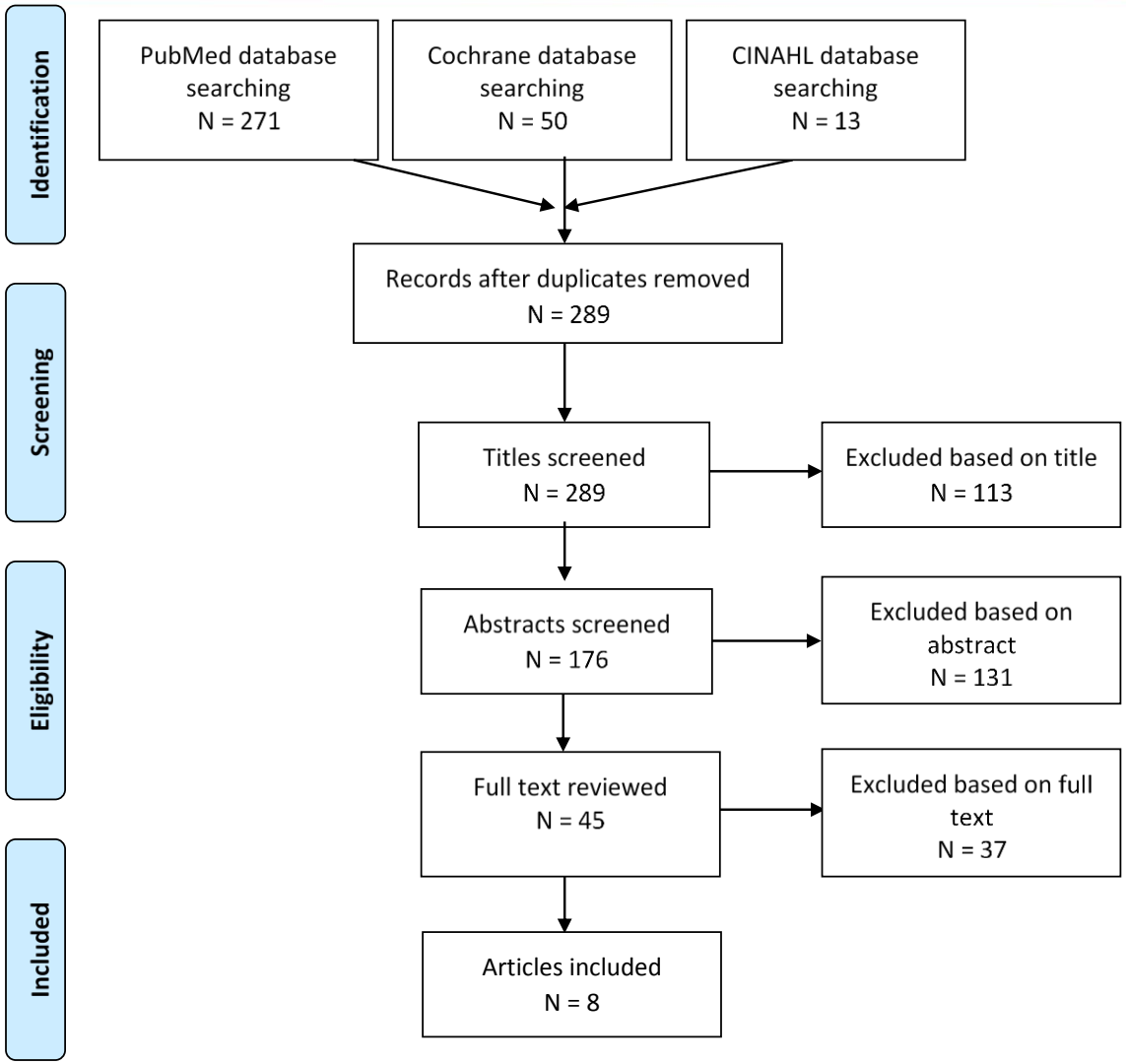
Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Pain
- Health-related quality of life
- Disease progression

Key Definitions

- Risk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being
- Pain
- Disease progression: A change or worsening of a disease over time.

Q2 Search Results: High-Quality Reviews[1]



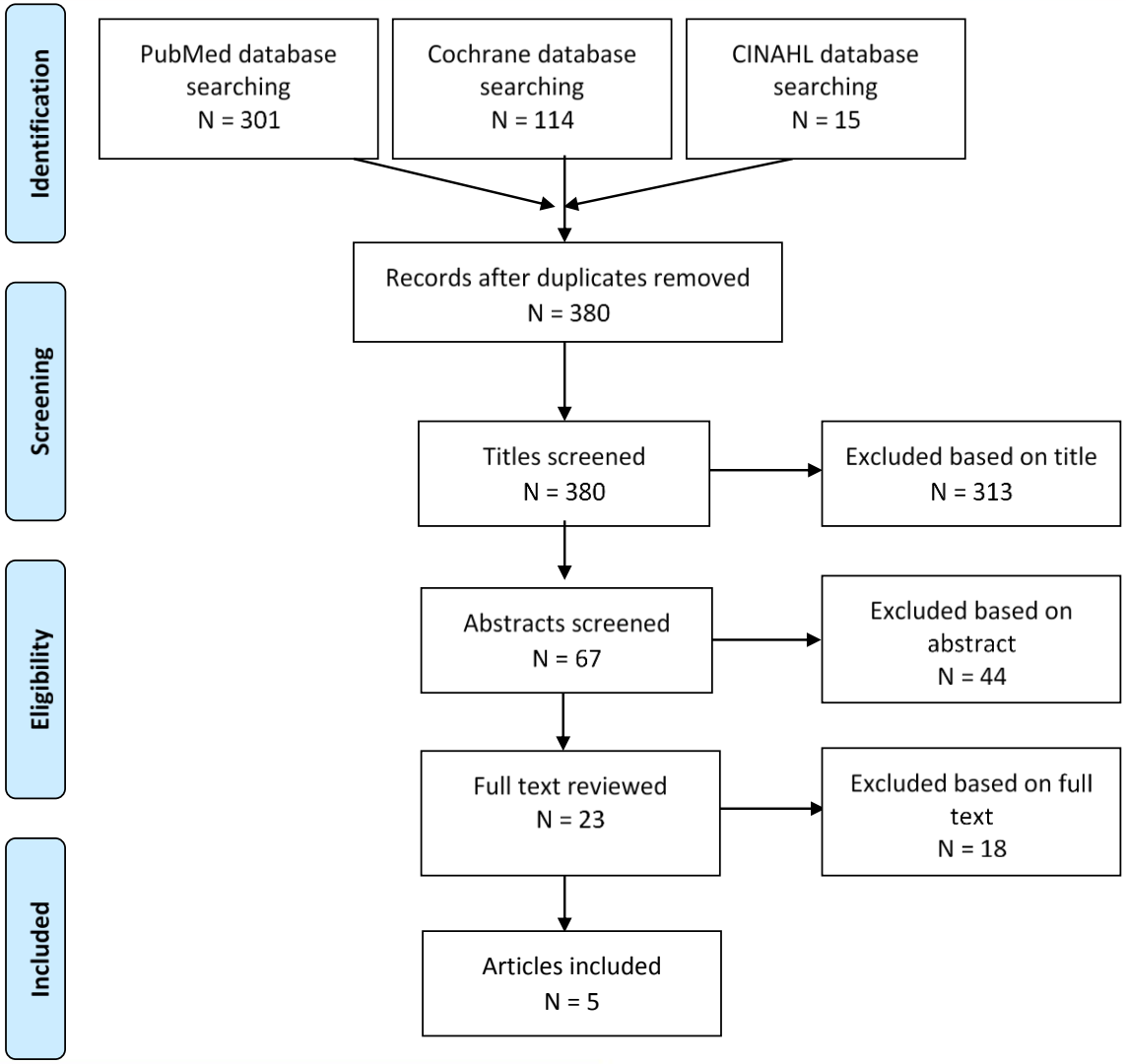
[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Draft Conclusion Statement

- There is insufficient evidence available to determine whether there is a relationship between greater amounts of physical activity and comorbidities in individuals with osteoarthritis.
  - PAGAC Grade: Not assignable

Effects on Pain, Physical Function and Quality of Life

Q2 Search Results: Original Research
(Progression Only)



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Description of the Evidence: OA and Pain, Physical Function and Quality of Life

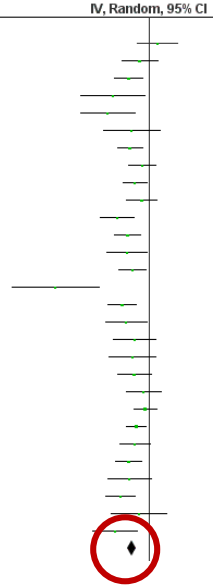
- 14 meta-analyses & systematic reviews
  - Of these 7 chosen for analysis based upon unique, non-overlapping populations and outcomes.
- Of the 7 studies
  - 131 individual studies dealing with knee OA alone
    - 10,948 individuals with pain as an outcome
    - 9,798 with physical function as an outcome
    - 2,771 with QoL as an outcome

Description of the Evidence: OA and Pain, Physical Function and Quality of Life

- Of the 7 studies
  - 13 individual studies dealing with hip OA alone
    - 1,320 individuals with pain as an outcome
    - 3,021 with physical function as an outcome
    - 1,190 with QoL as an outcome
  - 13 individual studies dealing with knee and hip OA together
  - One of the MA with 10 individual studies examining running and OA outcomes, including joint surgery, included 6962 individuals

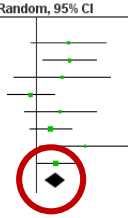
Pain

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.1.1 Change scores									
Minor 1989	-0.6	1.9	26	-1.1	1.9	20	1.8%	0.26 [-0.33, 0.84]	1989
Minor 1989	-0.76	1.7	49	-0.31	1.6	19	2.1%	-0.27 [-0.80, 0.27]	1989
Kovar 1992	-1.38	1.99	47	-0.1	2.31	45	2.7%	-0.59 [-1.01, -0.17]	1992
Schilke 1996	-6.1	4.9	10	0.4	6.7	10	0.9%	-1.06 [-2.01, -0.11]	1996
Bautch 1997	-1.4	2.32	15	1.03	1.55	15	1.2%	-1.20 [-1.98, -0.41]	1997
Rogind 1998	-3	3.9	11	-0.1	6.7	12	1.1%	-0.50 [-1.34, 0.33]	1998
van Baar 1998	-27.4	28.7	54	-11.7	28.5	59	2.9%	-0.55 [-0.92, -0.17]	1998
Maurer 1999	-43.54	80.3	49	-28.49	80.3	49	2.8%	-0.19 [-0.58, 0.21]	1999
Peloquin 1999	-1.44	2	59	-0.59	2.2	65	3.1%	-0.40 [-0.76, -0.04]	1999
Hopman-Rock 2000	-0.7	24.1	45	4	21.2	37	2.6%	-0.20 [-0.64, 0.23]	2000
Deyle 2000	-129.63	91	33	-33.83	111.5	36	2.2%	-0.93 [-1.43, -0.43]	2000
Fransen 2001	-10.6	19.5	83	1.5	19.4	43	2.9%	-0.62 [-0.99, -0.24]	2001
Baker 2001	-79	88	22	-20	93	22	1.8%	-0.64 [-1.25, -0.03]	2001
Topp 2002	-1.53	3.2	67	0.02	3.2	35	2.7%	-0.48 [-0.90, -0.07]	2002
Gur 2002	-20.9	8.3	17	0.7	4.6	6	0.5%	-2.74 [-4.02, -1.47]	2002
Huang 2003	-1.6	1.5	99	-0.4	1.6	33	2.8%	-0.78 [-1.19, -0.38]	2003
Song 2003	-2.45	3.9	22	0.61	5.1	21	1.7%	-0.66 [-1.28, -0.05]	2003
Foley 2003	-1.19	2.94	21	-0.05	2.55	20	1.7%	-0.41 [-1.02, 0.21]	2003
Keefe 2004	-0.7	1.69	16	0.03	1.27	18	1.5%	-0.48 [-1.17, 0.20]	2004
Huang 2005	-1.2	1.6	30	-0.5	1.7	32	2.2%	-0.42 [-0.92, 0.09]	2005
Thorstensson 2005	-1.8	14	30	0.3	15	31	2.2%	-0.14 [-0.65, 0.36]	2005
Bennell 2005	-2.2	1.7	73	-2	2.1	67	3.3%	-0.10 [-0.44, 0.23]	2005
Hay 2006	-1.56	3.4	93	-0.41	2.8	89	3.5%	-0.37 [-0.66, -0.07]	2006
Fransen 2007	-1.67	3.28	41	-0.5	2.37	36	2.5%	-0.40 [-0.85, 0.05]	2007
Lim 2008	-9	12	53	-1.75	12.8	54	2.9%	-0.58 [-0.97, -0.19]	2008
Lee 2009	-2.2	4.1	29	-0.2	1.8	15	1.7%	-0.56 [-1.20, 0.07]	2009
Bennell 2010	-2.6	2.6	45	-0.4	2.7	44	2.6%	-0.82 [-1.26, -0.39]	2010
Simao 2012	-62.5	296	11	0	35	12	1.1%	-0.29 [-1.12, 0.53]	2012
Chang 2012	-2.3	1.3	24	-0.9	1.5	17	1.6%	-0.99 [-1.65, -0.33]	2012
Subtotal (95% CI)			**1174**			**962**	**62.7%**	**-0.50 [-0.62, -0.38]**	



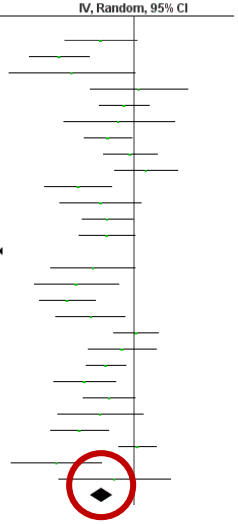
QOL

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.3.1 Change scores									
Minor 1989	-1.7	1.3	28	-2.4	1.7	28	5.3%	0.46 [-0.07, 0.99]	1989
Fransen 2001	2	6.4	83	-0.7	3.7	43	10.7%	0.48 [0.10, 0.85]	2001
Keefe 2004	0.38	1.22	16	0.05	0.33	18	3.2%	0.37 [-0.31, 1.05]	2004
Bennell 2005	0.5	0.13	73	0.51	0.17	67	13.5%	-0.07 [-0.40, 0.27]	2005
Thorstensson 2005	4	13	30	-0.7	14	31	5.8%	0.34 [-0.16, 0.85]	2005
Hay 2006	0.14	2	93	-0.28	2	89	17.5%	0.21 [-0.08, 0.50]	2006
Lee 2009	19.2	15.9	29	9.1	10.3	15	3.6%	0.69 [0.05, 1.34]	2009
Kao 2012	2.1	9.3	114	-0.33	7.9	91	19.4%	0.28 [0.00, 0.55]	2012
Subtotal (95% CI)			**466**			**382**	**78.8%**	**0.27 [0.13, 0.42]**	



Function

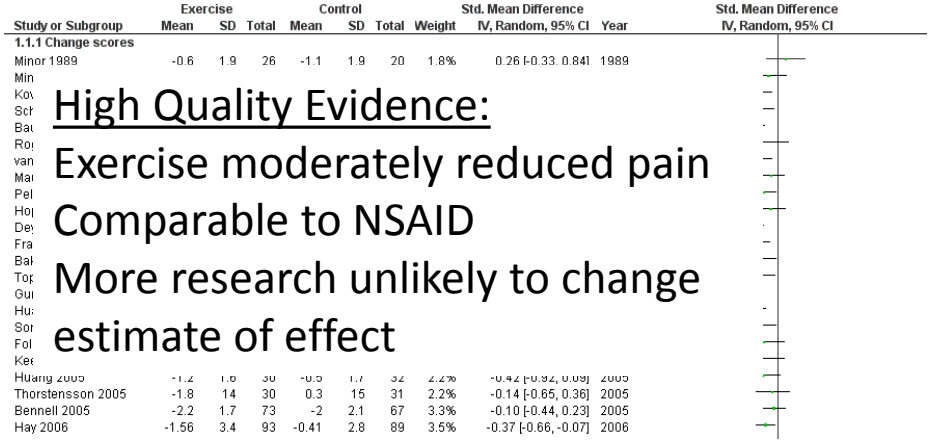
Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.2.1 Change scores									
Minor 1989	-0.89	2.5	49	0.33	2.5	19	2.2%	-0.48 [-1.02, 0.05]	1989
Kovar 1992	-2.4	2.27	47	0.24	2.49	45	2.5%	-1.10 [-1.54, -0.66]	1992
Schilke 1996	-3.66	3.3	10	-0.42	3.5	10	1.2%	-0.91 [-1.84, 0.02]	1996
Bautch 1997	-2.82	7.78	15	-3.49	8.17	15	1.6%	0.08 [-0.63, 0.80]	1997
van Baar 1998	-1.3	5.7	54	-0.5	5.6	59	2.7%	-0.14 [-0.51, 0.23]	1998
Rogind 1998	-3	3.3	11	-2	5.3	12	1.4%	-0.22 [-1.04, 0.60]	1998
Peloquin 1999	-1.5	2.4	59	-0.54	2.6	65	2.8%	-0.38 [-0.74, -0.02]	1999
Maurer 1999	-106.9	390.1	49	-88.3	390.1	49	2.6%	-0.05 [-0.44, 0.35]	1999
Hopman-Rock 2000	-0.8	4.6	37	-1.7	5.2	34	2.4%	0.18 [-0.28, 0.65]	2000
Deyle 2000	-402.51	339.56	33	-98.17	393.9	36	2.3%	-0.82 [-1.31, -0.32]	2000
Baker 2001	-272	295	22	-119	323	22	1.9%	-0.49 [-1.09, 0.11]	2001
Fransen 2001	-7.7	19.9	83	0.1	20.5	43	2.7%	-0.39 [-0.76, -0.01]	2001
Topp 2002	-4.16	10.9	67	0.17	10.9	35	2.6%	-0.39 [-0.81, 0.02]	2002
Gur 2002	-13.8	4.1	17	1	2.5	6	0.6%	-3.77 [-5.29, -2.26]	2002
Foley 2003	-2.81	7.89	21	2.1	8.1	20	1.9%	-0.60 [-1.23, 0.03]	2003
Song 2003	-11.09	12	22	-1.33	10.6	21	1.9%	-0.84 [-1.47, -0.22]	2003
Huang 2003	-2	1.6	99	-0.4	1.7	33	2.6%	-0.98 [-1.39, -0.57]	2003
Huang 2005	-1.5	1.4	30	-0.5	1.7	32	2.2%	-0.63 [-1.14, -0.12]	2005
Bennell 2005	-7.8	8.7	73	-8.2	10	67	2.9%	0.04 [-0.29, 0.37]	2005
Thorstensson 2005	-2	12	30	0.6	18	31	2.3%	-0.17 [-0.67, 0.34]	2005
Hay 2006	-4.79	10.8	95	-0.8	8.5	90	3.0%	-0.41 [-0.70, -0.12]	2006
Fransen 2007	-5.04	10.25	41	2.07	9.06	36	2.4%	-0.72 [-1.19, -0.26]	2007
Lim 2008	-6.5	10.6	53	-2.6	10.9	54	2.7%	-0.36 [-0.74, 0.02]	2008
Lee 2009	-9.4	14.4	29	-2.7	10.8	15	1.9%	-0.49 [-1.13, 0.14]	2009
Bennell 2010	-8.07	7.7	45	-1.9	7.6	44	2.5%	-0.80 [-1.23, -0.37]	2010
Kao 2012	3.2	34	114	1.5	20.3	91	3.1%	0.06 [-0.22, 0.33]	2012
Chang 2012	-10.7	5.9	24	-4.5	4.4	17	1.7%	-1.14 [-1.81, -0.47]	2012
Simao 2012	-100	740	11	75	463	12	1.4%	-0.28 [-1.10, 0.55]	2012
Subtotal (95% CI)			**1240**			**1013**	**62.0%**	**-0.47 [-0.63, -0.31]**	



Moderate Quality Evidence:
Unlikely to change

Fransen M, McConnell M, Harmer S, Van der Esch AR, Simic M, Bennell M, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015. 49(24):1554-7. Land-based. Knee.

Pain; 3537 (44 studies)



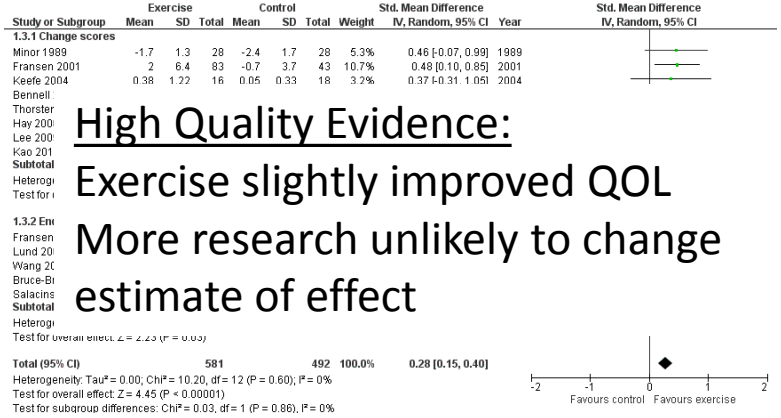
High Quality Evidence:

Exercise moderately reduced pain

Comparable to NSAID

More research unlikely to change estimate of effect

QOL; 1073 (13 studies)

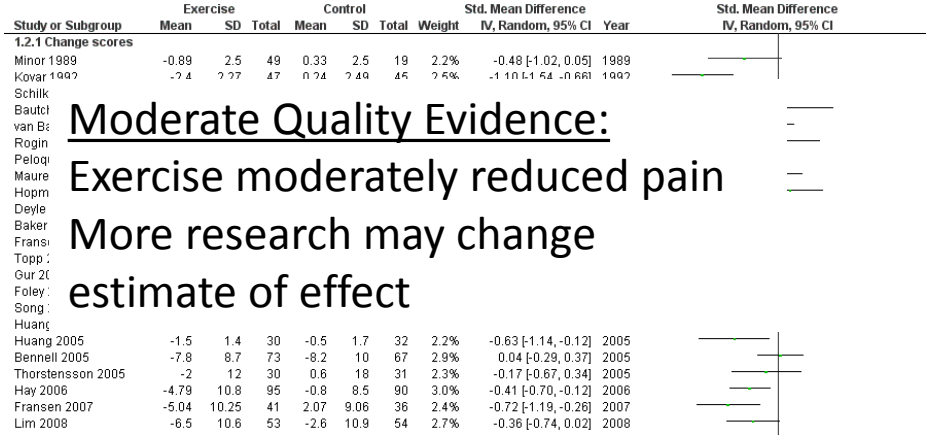


High Quality Evidence:

Exercise slightly improved QOL

More research unlikely to change estimate of effect

Function; 3913 (44 studies)



Moderate Quality Evidence:

Exercise moderately reduced pain

More research may change estimate of effect

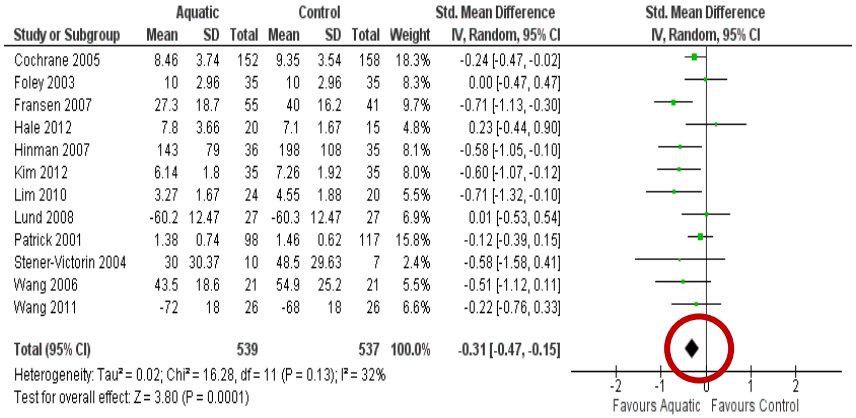
No evidence of increased dropout

4607 (44 studies)

No evidence for increased injuries

Fransen M, McConnell M, Harmer S, Van der Esch AR, Simic M, Bennell M, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015. 49(24):1554-7. Land-based. Knee.

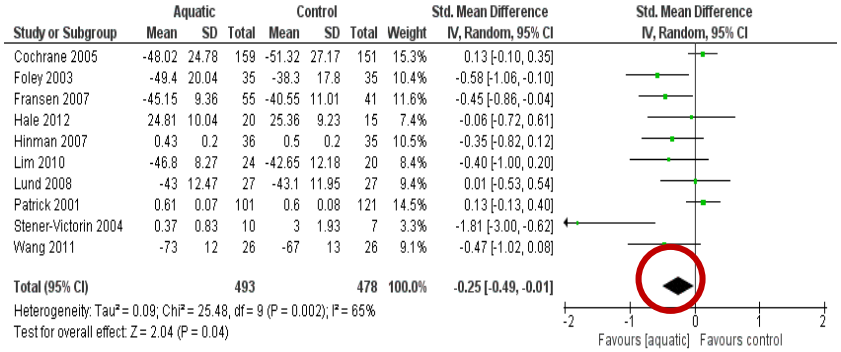
Pain



Study or Subgroup	Aquatic Mean	Aquatic SD	Aquatic Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cochrane 2005	8.46	3.74	152	9.35	3.54	158	18.3%	-0.24 [-0.47, -0.02]
Foley 2003	10	2.96	35	10	2.96	35	8.3%	0.00 [-0.47, 0.47]
Fransen 2007	27.3	18.7	55	40	16.2	41	9.7%	-0.71 [-1.13, -0.30]
Hale 2012	7.8	3.66	20	7.1	1.67	15	4.8%	0.23 [-0.44, 0.90]
Hinman 2007	143	79	36	198	108	35	8.1%	-0.58 [-1.05, -0.10]
Kim 2012	6.14	1.8	35	7.26	1.92	35	8.0%	-0.60 [-1.07, -0.12]
Lim 2010	3.27	1.67	24	4.55	1.88	20	5.5%	-0.71 [-1.32, -0.10]
Lund 2008	-60.2	12.47	27	-60.3	12.47	27	6.9%	0.01 [-0.53, 0.54]
Patrick 2001	1.38	0.74	98	1.46	0.62	117	15.8%	-0.12 [-0.39, 0.15]
Stener-Victorin 2004	30	30.37	10	48.5	29.63	7	2.4%	-0.58 [-1.58, 0.41]
Wang 2006	43.5	18.6	21	54.9	25.2	21	5.5%	-0.51 [-1.12, 0.11]
Wang 2011	-72	18	26	-68	18	26	6.6%	-0.22 [-0.76, 0.33]
Total (95% CI)			**539**			**537**	**100.0%**	**-0.31 [-0.47, -0.15]**

Heterogeneity: Tau² = 0.02; Chi² = 16.28, df = 11 (P = 0.13); I² = 32%
Test for overall effect: Z = 3.80 (P = 0.0001)

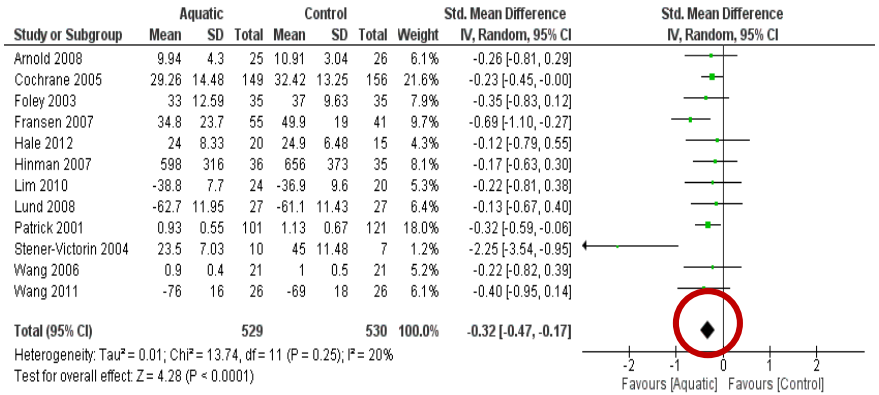
QOL



Study or Subgroup	Aquatic Mean	Aquatic SD	Aquatic Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cochrane 2005	-48.02	24.78	159	-51.32	27.17	151	15.3%	0.13 [-0.10, 0.35]
Foley 2003	-49.4	20.04	35	-38.3	17.8	35	10.4%	-0.58 [-1.06, -0.10]
Fransen 2007	-45.15	9.36	55	-40.55	11.01	41	11.6%	-0.45 [-0.86, -0.04]
Hale 2012	24.81	10.04	20	25.36	9.23	15	7.4%	-0.06 [-0.72, 0.61]
Hinman 2007	0.43	0.2	36	0.5	0.2	35	10.5%	-0.35 [-0.82, 0.12]
Lim 2010	-46.8	8.27	24	-42.65	12.18	20	8.4%	-0.40 [-1.00, 0.20]
Lund 2008	-43	12.47	27	-43.1	11.95	27	9.4%	0.01 [-0.53, 0.54]
Patrick 2001	0.61	0.07	101	0.6	0.08	121	14.5%	0.13 [-0.13, 0.40]
Stener-Victorin 2004	0.37	0.83	10	3	1.93	7	3.3%	-1.81 [-3.00, -0.62]
Wang 2011	-73	12	26	-67	13	26	9.1%	-0.47 [-1.02, 0.08]
Total (95% CI)			**493**			**478**	**100.0%**	**-0.25 [-0.49, -0.01]**

Heterogeneity: Tau² = 0.09; Chi² = 25.48, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 2.04 (P = 0.04)

Function



Study or Subgroup	Aquatic Mean	Aquatic SD	Aquatic Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arnold 2008	9.94	4.3	25	10.91	3.04	26	6.1%	-0.26 [-0.81, 0.29]
Cochrane 2005	29.26	14.48	149	32.42	13.25	156	21.6%	-0.23 [-0.45, -0.00]
Foley 2003	33	12.59	35	37	9.63	35	7.9%	-0.35 [-0.83, 0.12]
Fransen 2007	34.8	23.7	55	49.9	19	41	9.7%	-0.69 [-1.10, -0.27]
Hale 2012	24	8.33	20	24.9	6.48	15	4.3%	-0.12 [-0.79, 0.55]
Hinman 2007	598	316	36	656	373	35	8.1%	-0.17 [-0.63, 0.30]
Lim 2010	-38.8	7.7	24	-36.9	9.6	20	5.3%	-0.22 [-0.81, 0.38]
Lund 2008	-62.7	11.95	27	-61.1	11.43	27	6.4%	-0.13 [-0.67, 0.40]
Patrick 2001	0.93	0.55	101	1.13	0.67	121	18.0%	-0.32 [-0.59, -0.06]
Stener-Victorin 2004	23.5	7.03	10	45	11.48	7	1.2%	-2.25 [-3.54, -0.95]
Wang 2006	0.9	0.4	21	1	0.5	21	5.2%	-0.22 [-0.82, 0.39]
Wang 2011	-76	16	26	-69	18	26	6.1%	-0.40 [-0.95, 0.14]
Total (95% CI)			**529**			**530**	**100.0%**	**-0.32 [-0.47, -0.17]**

Heterogeneity: Tau² = 0.01; Chi² = 13.74, df = 11 (P = 0.25); I² = 20%
Test for overall effect: Z = 4.28 (P < 0.0001)

Aquatic Exercise

Bartels EM, Juhl EM, Christensen CB, Hagen R, Danneskiold-Samsoe KB, Dagfinrud B, *et al.* Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev. 2016. Aquatic, Knee.

Draft Conclusion Statement

- **Conclusion Statement:**
  - Strong evidence demonstrates a significant relationship between greater amounts of physical activity and decreased pain and improved physical function in persons with osteoarthritis of the knee and hip.
  - PAGAC Grade: Strong
  - The strength of the evidence is unlikely to be modified by more studies for these outcomes.

Draft Conclusion Statement

- **Conclusion Statement:**
  - Moderate evidence indicates a significant relationship between greater amounts of physical activity and improved quality of life in persons with osteoarthritis of the knee and hip.
  - PAGAC Grade: Moderate

Subquestions

- Limited evidence suggests that the mode, intensity or duration of physical activity is related to improvement in pain and functional capacity in individuals with osteoarthritis of the knee and hip.
  - PAGAC Grade: Limited
  - Differences in exercise frequency and duration appear to influence pain relief in knee OA.

Subquestions

- There is insufficient evidence available to determine whether any of these relationships vary by age, gender, race, ethnicity, SES, or BMI.
  - PAGAC Grade: Not assignable
  - Note: although a relationship between BMI and female sex with osteoarthritis is generally recognized, no one has investigated whether these translate to effect modifications of these factors in the PA-OA relationship.

Draft Other Key Findings

- Studied effects can be sustained up to 6 months, after cessation of intervention.
- Land-based exercise appears to be as efficacious as water-based exercise.
- The relationships with pain relief, physical function and quality of life appear to be applicable for aerobic exercise, resistance exercise and alternative Chinese-based exercises.
- Most studies on pain, function and quality of life are randomized controlled trials—of one mode, intensity or duration. Therefore limited information on dose-response.
- Due to exposure heterogeneity, cannot estimate an energy expenditure exposure for aerobic exercise.

OA Disease Progression

Effects on OA Disease Progression

Description of the Evidence: OA Progression

- 1 Meta-analysis: knee OA only
  - Low impact exercise
  - 47 longitudinal cohort studies with 78 PA intervention groups and 1 CS study
  - 8,920 subjects
  - Progression defined as structural OA imaging or total knee replacement (TKR)
- 5 Primary literature studies

Description of the Evidence: OA Progression

- 1 Meta-analysis: knee OA only
  - There was no evidence of serious adverse events, increases in pain, decreases in physical function, progression of structural OA on imaging or increased TKR at group level.
  - Summing the four RCTs, there was no evidence of more TKRs within physical activity groups compared to nonphysical activity groups (n = 8 and n = 10 respectively).

Quicke JG, Foster NE, Thomas MJ, Holden MA. Is long-term physical activity safe for older adults with knee pain?: a systematic review. Osteoarthritis Cartilage. 2015. 23(9):1445-56

Description of the Evidence: OA Progression

- 5 Primary Literature studies
  - Knee, PASE, MRI in 100 subjects (OAI) — No progression
  - Knee, accelerometry (steps), radiographic cartilage loss (MOST) in 1179 subjects — No progression
  - Knee, PASE, MRI in 205 asymptomatic OA (OAI) — High and low PASE scores (15%) associated with OA progression (cartilage quality MRI).
  - Knee, PASE, MRI in 2,073 asymptomatic OA subjects; 3,542 knees (OAI and MOST) — Greatest quartile no progression
  - Knee, pedometer counts, MRI with four MRI structural measures, 405 individuals — those less than 10,000 no progression; those over 10,000 steps per day with progression; effect modification by baseline state.

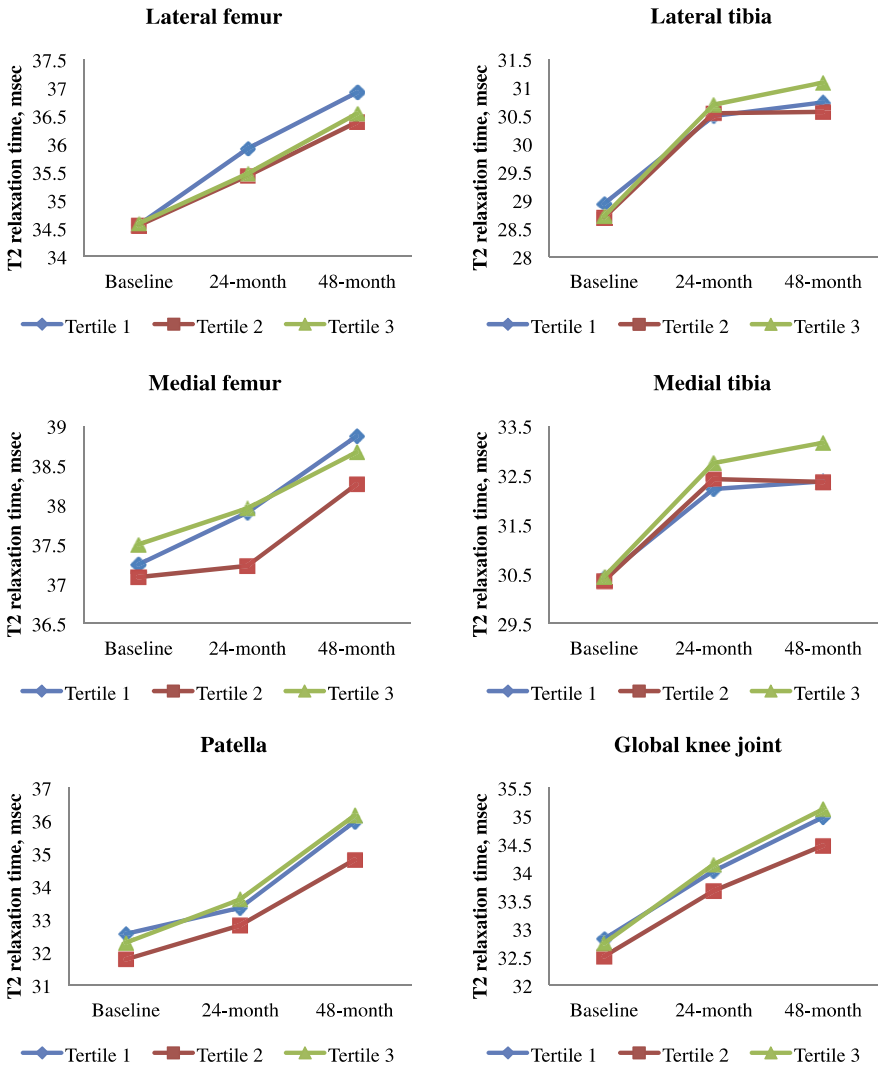


Fig. 2. Longitudinal T2 values over 48 months by compartment. Subjects in the moderate physical activity group overall show the lowest progression of T2 relaxation time over the 48-month time period. Tertiles are based on PASE scores.

Lin W, Alizai H, Joseph GB, Srikhum W, Nevitt MC Lynch JA, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2013. 21(10):1558-66

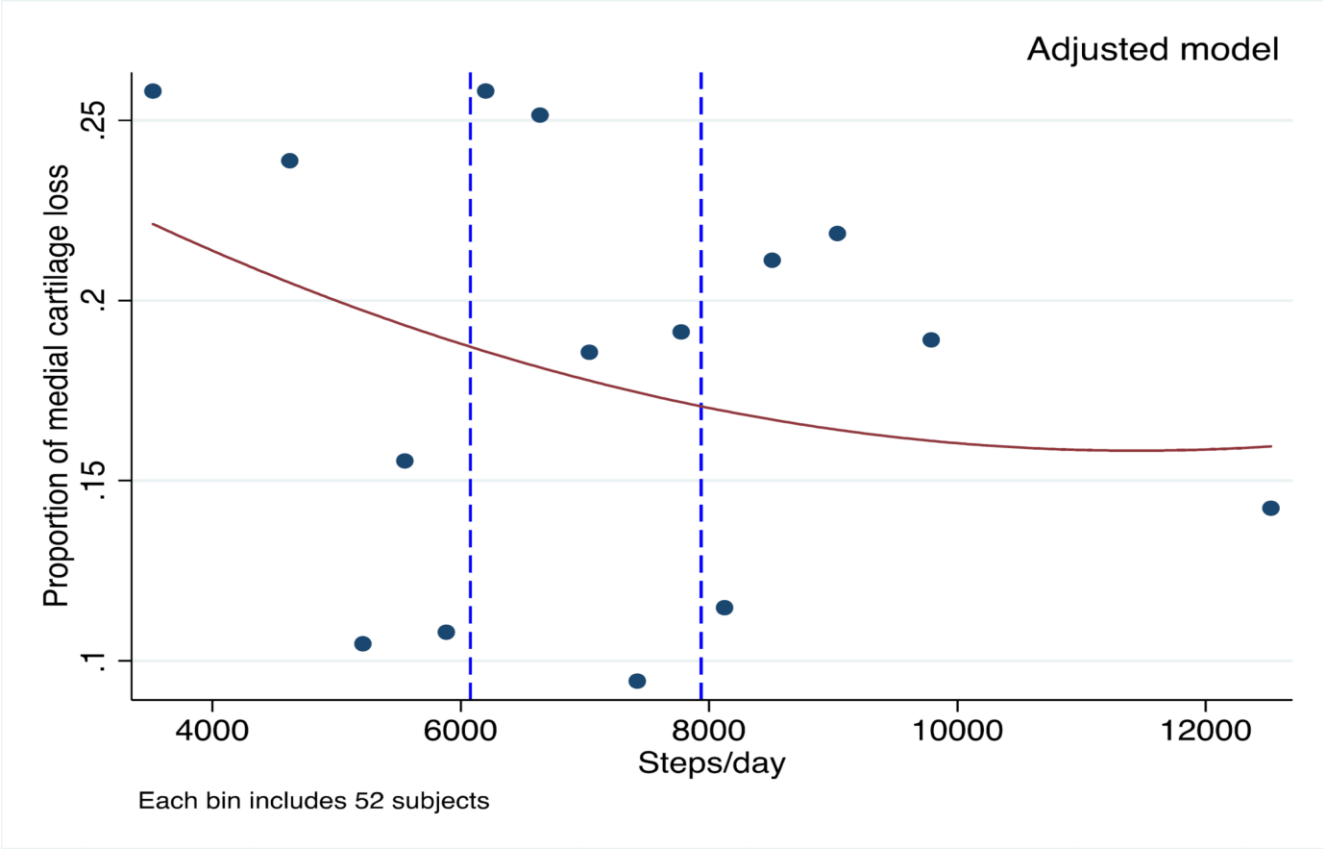


Figure 2.
The binscatter shows proportion of medial cartilage loss for tertiles of steps/day (dashed lines) adjusted for 60-month age, sex, BMI, knee injury, pain, radiographic grade, and alignment. Medial cartilage loss includes any change in the five medial subregions femur central and posterior, and tibia anterior, central, and posterior.

Oiestad BE, Quinn E, White D, Roemer F Guermazi A, Nevitt M, et al. No Association between Daily Walking and Knee Structural Changes in People at Risk of or with Mild Knee Osteoarthritis. Prospective Data from the Multicenter Osteoarthritis Study. J Rheumatol. 2015. 42(9):1685-93

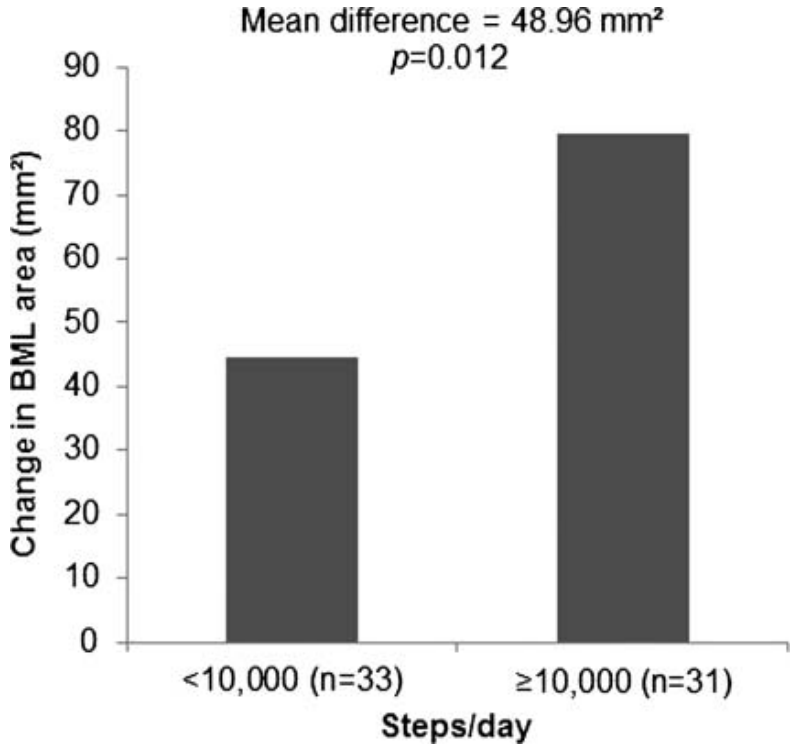
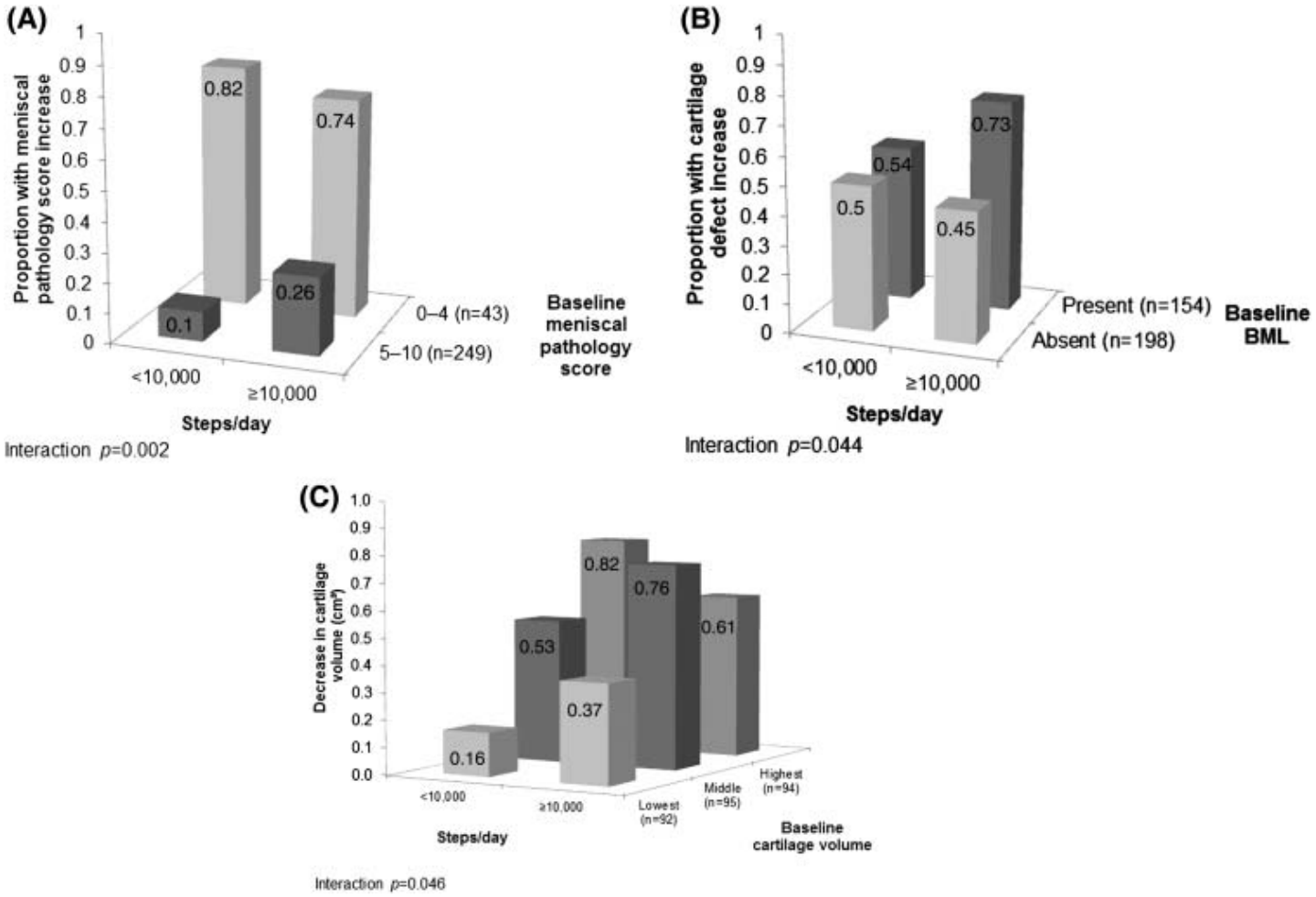


Figure 1 Bone marrow lesion (BML) change for participants with a deleterious increase (>25 mm^2) in BML area against steps/day, after adjustment for age, sex, body mass index, radiographic osteoarthritis, history of knee injury or surgery, and baseline BML.

Dore DA, Winzenberg TM, Ding C, Otahal P, Pelletier JP, Martel-Pelletier J, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis. 2013. 72(7):1170-5



Dore DA, Winzenberg TM, Ding C, Otahal P, Pelletier JP, Martel-Pelletier J, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis. 2013. 72(7):1170-5

Draft Conclusion Statement

- **Conclusion Statements:**
  - Moderate evidence indicates that up to the range of 10,000 steps per day, ambulatory physical activity does not accelerate osteoarthritis of the knee.
    - PAGAC Grade: Moderate
  - Moderate evidence indicates a U-shaped relation between PA amount and progression of OA, particularly in those with advanced OA pathology at baseline.
    - PAGAC Grade: Moderate

Draft Conclusion Statement

- **Conclusion Statements: Did not address**
  - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?

Draft Research Recommendations

- More research is needed to determine the optimal dose, mode, intensity and sustainability for different types and severity of OA.
- More directed research is needed on disease progression: especially prospective cohort studies with molecular and imaging disease status markers.
- Need to determine capacity of individuals with OA to perform PA at a level that modifies comorbidities.
- Need to develop predictors of exercise responsiveness.
- Need direct comparisons of the relative effectiveness of PA and analgesics.

Committee Discussion

Q2. In people with osteoarthritis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, (4) disease progression, and (5) pain?

- Is there a dose-response relationship? If yes, what is the shape of the relationship?
- Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
- Does the relationship based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

Question 3

3. In people with the cardiovascular condition of **hypertension**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) cardiovascular disease progression and mortality?

   – Is there a dose-response relationship? If yes, what is the shape of the relationship?
   – Does the relationship vary by age, sex, race/ethnicity, socio-economic status, weight status, or resting blood pressure level?
   – Does the relationship based on: frequency, intensity, time, duration, type (mode), or how physical activity is measured?

- Source of evidence to answer question
  – Systematic Reviews and Meta-Analyses

Analytical Framework

Systematic Review Question

In people with hypertension, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression, as determined from existing systematic reviews, meta-analyses, pooled analyses, and/or high-quality existing reports?

Target Population

Individuals of all ages with hypertension

Comparison

Individuals with hypertension who participate in varying levels of physical activity

Intervention/Exposure

All types and intensities of physical activity

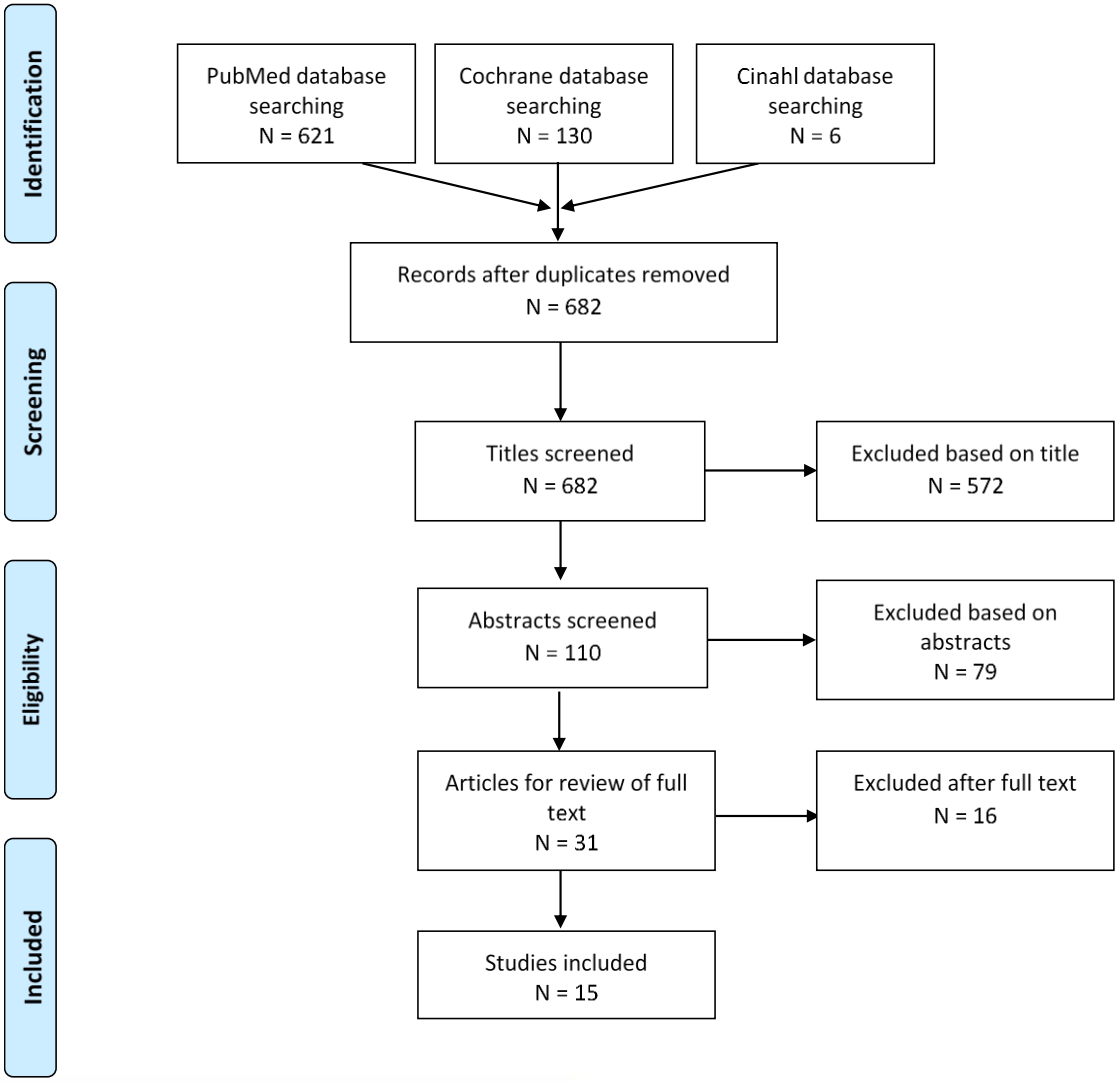
Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Health-related quality of life
- Disease progression

Key Definitions

- Hypertension or high blood pressure is defined as having blood pressure higher than 140/90 mmHg or being on antihypertensive medications regardless of the BP level.
- Risk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being
- Disease progression: A change or worsening of a disease over time.

Search Results: High-Quality Reviews[1]



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Draft Conclusion Statement

- For the outcomes of cardiovascular disease (CVD) progression and mortality:

- Because blood pressure is considered a proxy measure of the risk of CVD, the committee regarded the blood pressure response to physical activity as an indicator of CVD disease progression and the outcome of CVD mortality as an indicator of longstanding hypertension.

Description of the Evidence

- 14 meta-analyses * of RCTs examined the blood pressure response to PA in sedentary adults with hypertension.
  - All qualifying studies included adults with hypertension or subgroup analyses in people with hypertension*
  - Studies published through 2016.
  - Number of included studies varied: 4 to 93.
  - Total sample size: 125,986; sample ranged from 216-96,073.

* [Carlson, 2014; Casonatto, 2016; Conceicao, 2016; Cornelissen, 2011, 2013b; Corso, 2016; Dickinson, 2006; Fagard 2007; MacDonald, 2016; Park, 2017; Wang, 2013; Wen, 2017; Xiong, 2015a,b]

Draft Key Findings: Cardiovascular Disease Progression

- Of these, 13 reported a statistically significant reduction in systolic blood pressure and 14 reported a statistically significant reduction in diastolic blood pressure.
- The magnitude of the reductions ranged from 4.6 to 17.4 mmHg for systolic blood pressure and 2.4 to 10.6 mmHg for diastolic blood pressure.
- The magnitude of these blood pressure reductions may be sufficient to reduce the:
  - Resting blood pressure of some samples with hypertension into prehypertensive and normotensive ranges.
  - Risk of coronary heart disease 4 percent to 22 percent and stroke by 6 percent to 41 percent among adults with hypertension

Draft Conclusion Statement: Cardiovascular Disease Progression

- For the outcome of cardiovascular disease progression and mortality:

- Strong evidence demonstrates that physical activity reduces the risk of progression of cardiovascular disease among adults with hypertension.
  - **PAGAC Grade: Strong.**
- Strong evidence demonstrates that, among adults with hypertension, physical activity reduces the disease progression indicator of blood pressure.
  - **PAGAC Grade: Strong.**
- Moderate evidence indicates an inverse, dose-response relationship between physical activity and the disease progression indicator of cardiovascular disease mortality among adults with hypertension.
  - **PAGAC Grade: Moderate.**

Draft Key Findings: Cardiovascular Disease Progression

- Four meta-analyses examined complementary and alternative types (modes, i.e., Baduanjin, Qigong, Tai Chi, Yoga). Of these, all reported statistically significant reductions in systolic and diastolic blood pressure.
- The magnitude of the reductions ranged from 12.4 to 17.4 mmHg for systolic blood pressure and 2.4 to 10.6 mmHg for diastolic blood pressure.
- The magnitude of these blood pressure reductions may be sufficient to reduce the:
  - Resting blood pressure of some samples with hypertension into prehypertensive and normotensive ranges.
  - Risk of coronary heart disease 4 percent to 22 percent and stroke by 6 percent to 41 percent among adults with hypertension

Draft Conclusion Statement : Cardiovascular Disease Progression

- For the outcome of cardiovascular disease progression and mortality:

- Moderate evidence indicates the relationship between physical activity and the disease progression indicator of blood pressure does not vary by traditional type (mode, i.e., aerobic, dynamic resistance, combined) of physical activity.
  - **PAGAC Grade: Moderate**.
- Limited, but poor-quality, evidence suggests that the relationship between physical activity and the disease progression indicator of blood pressure does not vary by complementary and alternative type (mode, i.e., Baduanjin, Qigong, Tai Chi, Yoga).
  - **PAGAC Grade: Limited.**

Question 4

4. In people with **type 2 diabetes**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression?
   - Is there a dose-response relationship? If yes, what is the shape of the relationship?
   - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
   - Does the relationship based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

- Source of evidence to answer question
  - Systematic Reviews and Meta-Analyses

Analytical Framework

Systematic Review Question

In people with type 2 diabetes, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression, as determined from existing systematic reviews, meta-analyses, pooled analyses, and/or high-quality existing reports?

Target Population

Individuals of all ages with type 2 diabetes

Comparison

Individuals with type 2 diabetes who participate in varying levels of physical activity

Intervention/Exposure

All types and intensities of physical activity, including sedentary behavior

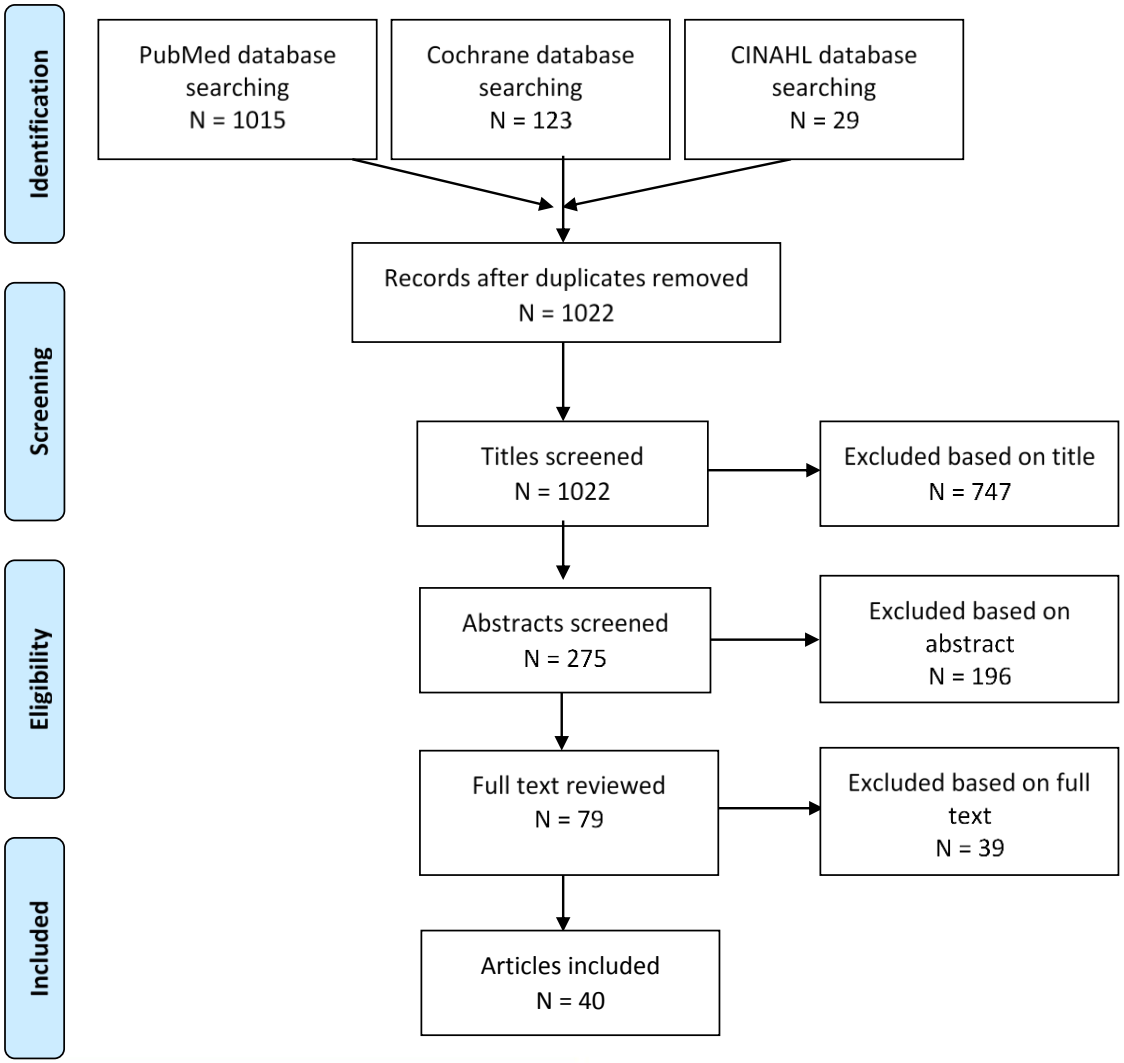
Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Health-related quality of life
- Disease progression

Key Definitions

- Type 2 Diabetes is a condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. (Source: American Diabetes Association: http://www.diabetes.org/diabetes-basics/common-terms/common-terms-s-z.html#sthash.ezhRSF7M.dpuf)
- Risk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being
- Disease progression: A change or worsening of a disease over time.

Q4 Search Results: High-Quality Reviews[1]



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

T2DM: Overview of Main conclusions

- Co-morbidity: Strong evidence for CVD mortality
- Physical function: Grade not assignable
- Quality of life: Grade not Assignable
- Progression: Grade not assignable for retinopathy, nephropathy, neuropathy, foot disorders
- Progression: Strong evidence for risk factors for progression (A1C, BP, BMI, Lipids)

Overview of Evidence – applies to all outcomes

- Reviews published 2011-2017.
- Sufficient evidence located for conclusions for adults (but not children).
- Main focus was on controlled trials comparing physical activity/exercise interventions to no-exercise control groups.

Description of the Evidence: T2DM Co-morbid conditions

- 2 meta-analyses & 1 pooled analysis
  - Cardiovascular mortality is only co-morbid condition with evidence
  - 14 total studies in the 2 MA, 5 in both
    - Various types, measurement, categories of PA, mostly leisure-time MVPA
  - 3000+ subjects in pooled analysis
    - Common questionnaire: LTMVPA, transport, household; with frequency, duration, relative effort

Kodama, 2013; Sadarangani, 2014; Sluik 2012;

Draft Key Findings: T2D comorbid conditions

- Meta-analyses:
  - RR = 0.71 (0.60, 0.84) Kodoma 2013
  - HR= 0.63 (0.48, 0.83) Sluik 2012
- Pooled analysis:
  - Sadarangani 2014

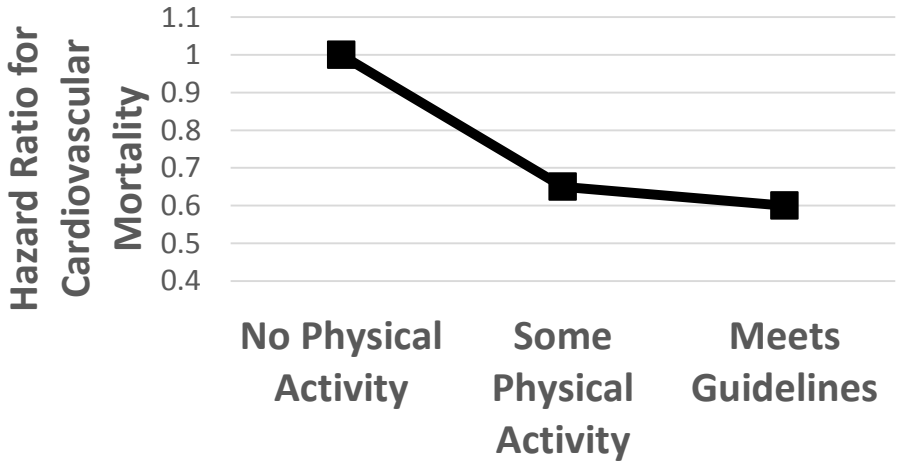


Figure created from data from Sadarangani, 2014

Draft Conclusion Statement: Overall statement for Co-morbidity outcome

- Conclusion Statement:
  - Strong evidence demonstrates an inverse association between volume of physical activity and risk of cardiovascular mortality among adults with T2DM.

- **PAGAC Grade: Strong.**

Draft Conclusion Statement: Co-morbidity: dose-response

- Conclusion Statement:
  - Moderate evidence indicates an inverse, curvilinear dose response relationship between physical activity and cardiovascular mortality among adults with T2DM.

- **PAGAC Grade: Moderate.**

Draft Conclusion Statement
Comorbidity: variation by individual characteristics

- Conclusion Statement:
  - Insufficient evidence was available to determine whether the relationship between physical activity and cardiovascular mortality among adults with T2DM varies with age, sex, race/ethnicity, SES, or weight status.

- **PAGAC Grade: Not assignable.**

Draft Conclusion Statement
Comorbidity: variation by PA exposure

- Conclusion Statement:
  - Insufficient evidence was available to determine whether the relationship between physical activity and cardiovascular mortality among adults with T2DM varies with frequency, duration, intensity, or type (mode) of physical activity or how physical activity is measured among people with type 2 diabetes mellitus.

- **PAGAC Grade: Not assignable.**

Description of the Evidence - QOL

- 6 systematic reviews
  - Two large reviews: 37 total studies, 13 in both
    - QOL most commonly measured with SF36 scales.
    - Various exercise types (e.g. walking, strength training, video game, Tai Chi, Yoga)
    - Mostly small, short-term studies. Of 30 studies in one review, 21 were < 3months exercise and/or <50 participants.
    - Some effect sizes provided by one review.
  - One review of Tai Chi updated an older review:
    - 3 RCTs with QOL measures; total N=157 participants.
    - Did not specify the QOL measures; no effect sizes in tables
  - One review of Yoga
    - 3 RCTs and 1 non-rCT with QOL measures; total N=420 participants
    - Outcome types reported (e.g. “well-being”) but measures not named
    - No effect sizes in tables
  - One review with only 1 relevant study.

(Innes, 2016; Lee, 2011; Lee, 2015; Plotnikoff, 2013; Cai, 2017; van der Heijden, 2013)

Draft Key Findings – QOL (1)

- Conflicting conclusions in the two large SRs:
  - N=16 studies: "Between group comparisons showed no significant results for aerobic training with the exception of 1 study, and mixed results for resistance and combined training." Abstract characterized overall results as "conflicting." (van der Heijden et al, 2013).
  - N=20 studies: 15 studies "reported a significant effect of aerobic exercise on quality of life….". Abstract characterized aerobic exercise as "effective;" effects of resistance and combined exercise as "mixed," and yoga "need more research." (Cai et al, 2017)
  - One issue =heterogeneity. E.g.
    - 13 of 20 studies of aerobic training in one review (Cai et al, 2017) used SF-36, but no two studies had same pattern of significant changes in subscales (except for negative trials)
    - One of the larger trials reported QOL improved significantly more in control group.

Draft Key Findings – QOL (2)

- Tai Chi [1]:
  - 3 RCT's report positive effects on QOL.
  - On 7 point scale, study quality: 2, 2, 3.
  - Abstract: "the existing trial evidence is not convincing enough to suggest that Tai Chi is effective…."

- Yoga [2]:
  - 3 of 4 controlled trials report positive effects on QOL
  - On 10 point scale, study quality was: 1, 3, 4, 4.
  - Abstract: " given the methodological limitations of existing studies, additional high quality investigations are required to confirm...the potential benefits of yoga programs…."

1. Lee, 2015; 2. Innes, 2016

Draft Conclusion Statement- QOL

- Conclusion Statement:
  - Insufficient evidence was available to determine the relationship between physical activity and health-related quality of life in adults with T2DM.

- **PAGAC Grade: Grade not assignable.**

Description of the Evidence – Physical Function

- One systematic review:
  - Adults with diabetic peripheral neuropathy.
  - Multicomponent fall prevention exercise.
  - 4 of the 10 studies had a no-exercise control group.
    - The quality ratings for 2 of these 4 trials were low (3/10 & 4/10).
  - The remaining 2 RCTs.
    - Exercise of 10-12 weeks duration; N=71 & N=101

Gu & Dennis, 2017

Draft Key Findings—Physical Function

- In a high quality RCT: significant benefit of PA on all 4 physical function measures.
- In a 3-arm RCT, significant benefit of PA on 1 of 6 comparisons of PA versus control
- The authors characterized evidence reviewed as “preliminary evidence.”

Draft Conclusion Statement – Physical Function

- Conclusion Statement:
  - Insufficient evidence was available to determine the relationship between physical activity and physical function in adults with T2DM.
- **PAGAC Grade: Grade not assignable.**

Indicators of Progression

- Two sets of progression indicators:
  - Retinopathy, nephropathy, neuropathy, diabetes-related foot conditions.
  - Risk factors for progression: A1C, blood pressure, obesity/adiposity, lipids.

Description of the Evidence - Progression Conditions re: eye, kidney, nerve, and foot

- No reviews were located of the relationship of physical activity to progression of neuropathy, retinopathy, nephropathy, or foot disorders in adults with T2DM.

Draft Conclusion Statement – Progression Conditions re: eye, kidney, nerve, and foot

- Conclusion Statement:
  - Insufficient evidence was available to determine the relationship between physical activity and indicators of progression of neuropathy, nephropathy, retinopathy, and foot disorders.
- **PAGAC Grade: Grade not assignable**

Description of the Evidence – Progression: A1C, BP, BMI, Lipids

- For PA types: aerobic, resistance, or both:
  - Primary sources were meta-analyses of RCTs of exercise versus control -- aerobic/resistance/combined PA
    - Hemoglobin A1C (A1C) N=12
    - Blood pressure (BP) N= 6
    - Adiposity /BMI (BMI) N= 6
    - Lipids N= 5
  - Secondary sources
    - Meta-analyses comparing PA types: N= 3
    - Meta-analyses not requiring RCT's: N= 3
    - Systematic reviews without MAs: N= 6

Draft Key Findings—Progression A1C – aerobic or resistance

- For A1C, there were consistent effects-typically moderate size, with fewer studies and slightly smaller effects for resistance training;

- Aerobic activity & A1C:
  - 5 large MAs (19-26 comparisons of Ex vs Con) reported similar significant effects (one MA of walking) (-0.50% to -0.73%) [1]

  - An MA of 10 studies of device-based walking interventions found no effect on A1C (ES=0.02), with the lack of effect essentially attributed to intervention implementation [2]

1. Umpierre,2013; Umpierre,2011; Grace, 2017; Qui, 2014a, Chudky, 2011; 2. Qiu, 2014b]

Draft Key Findings—Progression A1C – aerobic+resistance

- Resistance training & A1C
  - 2 overlapping MAs (4 & 5 comparisons) of supervised exercise reported significant effects: -0.62% & -0.37% [1]
  - An MA of 7 studies of resistance bands, and a MA with 1 of 8 studies with bands found NS trends: -0.18% & -0.33% [2]
- Combined training & A1C
  - 4 MAs (7 to 14 comparisons) reported similar significant effects : -0.47% to -0.74%) [3]

1. Umpierre,2013; Umpierre,2011]
2. [McGinley, 2015; Chudky, 2011] 3.) [Hayashino,2012; Umpierre,2011; Umpierre,2013; Chudky,2011].

Draft Key Findings—Progression BMI

- Physical Activity and BMI
  - Large MAs of 10+ studies report small but significant effects of PA on BMI units for:
    - "Free living exercise:" -0.77 (at 6 months) [1]
    - Aerobic: -0.53 [2]
    - Aerobic: -1.56 [3]
    - Walking: -0.91 [4]
    - Aerobic + resistance: -0.50 [2]
  - Results of smaller MAs generally a non-significant trend favoring PA

1.Avery 2012; 2. Hayashino,2012; 3. Grace,2017; 4. Qiu,2014

Draft Key Findings—Progression Blood pressure Meta-analyses

For blood pressure, consistent evidence of small to moderate effect of PA

- Systolic blood pressure
  - Aerobic
    - WMD = -5.47 [1]
    - WMD = -3.20 * [2]
    - WMD = -6.08 [3]
  - Resistance
    - WMD = -4.44 [1]
    - WMD = -4.36 [2]
  - Combined
    - WMD = -2.42 [4]
    - WMD = -3.59 [3]
  - Any
    - WMD = -7.98 [5]
- Diastolic blood pressure
  - Aerobic
    - WMD = -2.06 [1]
    - WMD = -1.97 [2]
  - Resistance
    - WMD = -2.84 [1]
  - Combined
    - WMD = -2.23 [4]
  - Any
    - WMD = -2.70 [5]

N= 6 to 21 comparisons per MA; all analyses significant except one

1. Figueira,2014; 2. Qui,2014; 3.Chudyk,2011; 4. Hayashino,2012 5. Zou,2016 * Outlier study removed

Draft Key Findings—Progression Lipids

- Effects of PA on lipids appeared to be small and required large meta-analyses to detect.
  - A meta-analysis which pooled effects of aerobic, resistance, and combined (N=35 studies) reported significant effects of HDL-C (WMD=0.4) and LDL-C (WMD = -0.16), but no effect on triglycerides (N=32 studies) [3]
  - Generally non-significant effects on Total-C, HDL-C, and LDL-C in 3 other reviews (5 to 9 comparisons per MA) [1,2,4]
- A meta-regression in the largest MA reported:
  - Effects of PA on lipids did not differ by type (aerobic, resistance, combined)
  - Longer exercise programs had significantly stronger effects on LDL-C ($p<.03$)
  - Indeed, another MA which analyzed only 2 studies at 12 months found significant effects of PA on HDL and triglycerides (no data for LDL-C) [4]

1. Qui,2014; 2.Chudyk,2011; 3. Hayashino,2012 4. Zou,2016

5 to 9 comparisons per MA

Draft Key Findings—Progression Comparison on Aerobic and resistance

- 2 meta-analyses comparing exercise types:
  - MA with 14 RCTs compared aerobic, resistance, and combined [1]
  - MA with 12 RCTs compared aerobic and resistance [2]
- Both reported no difference aerobic vs resistance for BP &, lipids.
- Inconsistent results on BMI (1 favored aerobic; 1 no difference)
- Combined aerobic + resistance produced larger effect on A1C (MD=-0.17) than aerobic alone, even though both MAs reported aerobic had stronger effect on A1C than resistance.
- In both MAs, no significant differences among the exercise types when removed lower quality trials from analysis.

1. Schwingshackl, 2014; 2. Yang,2014

Draft Overall Conclusion Statement

- Conclusion Statement:
  - Strong evidence demonstrates an inverse association between aerobic activity, muscle strengthening activity, and aerobic + muscle strengthening activity and risk of progression among adults with T2DM, as assessed by overall effects of physical activity on four indicators of risk of progression: body mass index (BMI), lipids, blood pressure, and glycated hemoglobin (A1C).

- **PAGAC Grade: Strong**

Description of the Evidence – Progression: A1C, BP, BMI, Lipids

- For PA types: Yoga, Tai Chi, Qigong:
  - Primary sources were meta-analyses of RCTs of exercise versus control:
    - Hemoglobin A1C (A1C) N= 6
    - Blood pressure (BP) N= 0
    - Adiposity /BMI (BMI) N= 0
    - Lipids N= 1
  - Secondary sources
    - Meta-analyses comparing PA types: N= 1
    - Meta-analyses not requiring RCT's: N= 0
    - Systematic reviews without MAs: N= 3

Draft Key Findings—Progression
A1C, BP, BMI, Lipids – Tai Chi & Qigong

- Tai Chi – A1C [1]
  - 3 meta-analyses involving 2 or 3 of a total of 5 RCTs;
  - 1 of 3 statistically significant effect)
  - Results heterogeneous with MDs: -1.58, -0.75, -0.19.

- Qigong – A1C [2]
  - 1 meta-analysis of 3 RCTs: MD= -0.04 (not statistically significant)

1. Pai, 2016; Lee,2015;Yan,2013; 2. Pai, 2016

Draft Key Findings—Progression A1C, BP, BMI, Lipids - Yoga

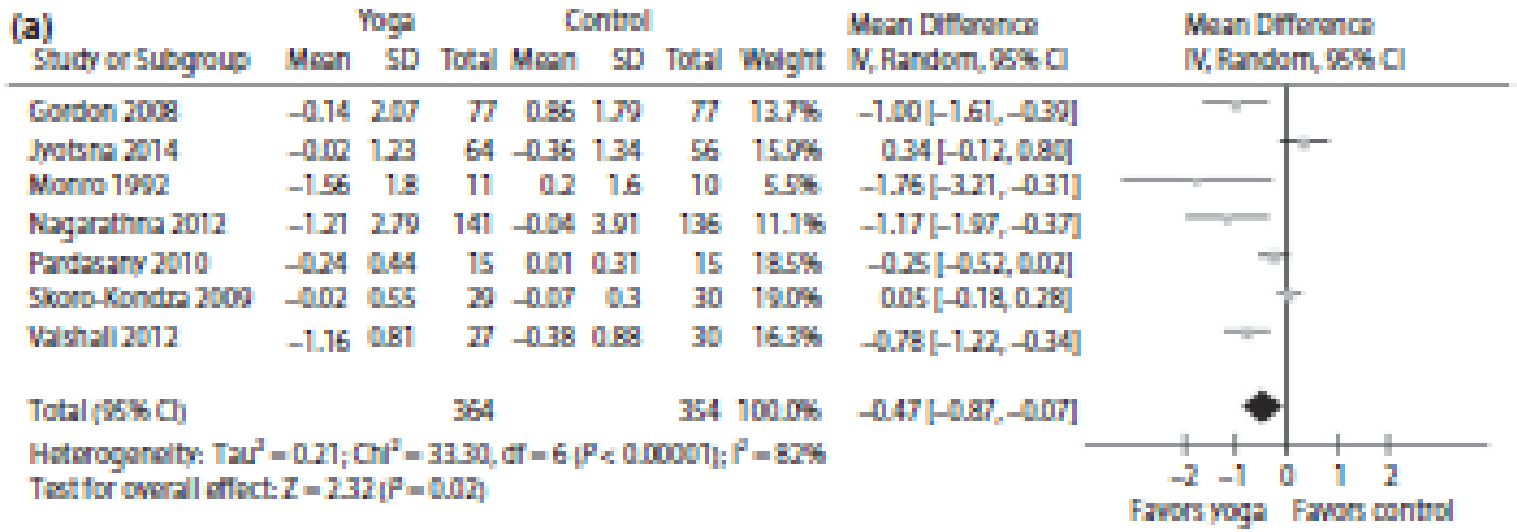
- Yoga – A1C [1]
  - 3 meta-analysis involving 12 RCTs; 5-8 studies in each MA; total N=220 – 392:
    - One non-significant trend: MD =-0.53 (-1.19, 0.13) with I^2=97%.
    - Two significant: MD = -0.47 (-1.22, -0.34) with I^2=82% and MD = -0.81 (-122, -0.39) with I^2=97%
  - One MA not useful (active treatment some control groups).

- Yoga – lipids [2]
  - 1 meta-analysis of 5 RCTS showed MD =-18.50 (-18.84,-7.06) for Total-C, and MD=-12.95 (-18.84,-7.06) for LDL-C I^2=75% and I^2=37%

1. Cui,2017;Vizcaino,2016; Pai,2016; 2. Cui,2016

Draft Key Findings—Progression A1C, BP, BMI, Lipids - Yoga

- Closer look at heterogeneity in yoga studies (data from effect of yoga on A1C in Cui *et al*, 2017):
  - Intervention components: Large variety in types & forms of yoga studied. Authors stated: "the optimal exercise form and appropriate exercise parameters [for T2DM] patients are unknown" [p.205]
  - Effect sizes: I^2 = 82% (effects range from .34 to -1.76)



Cui et al. Effects of Yoga…. J Diabetes Invest 2017;8:201-209

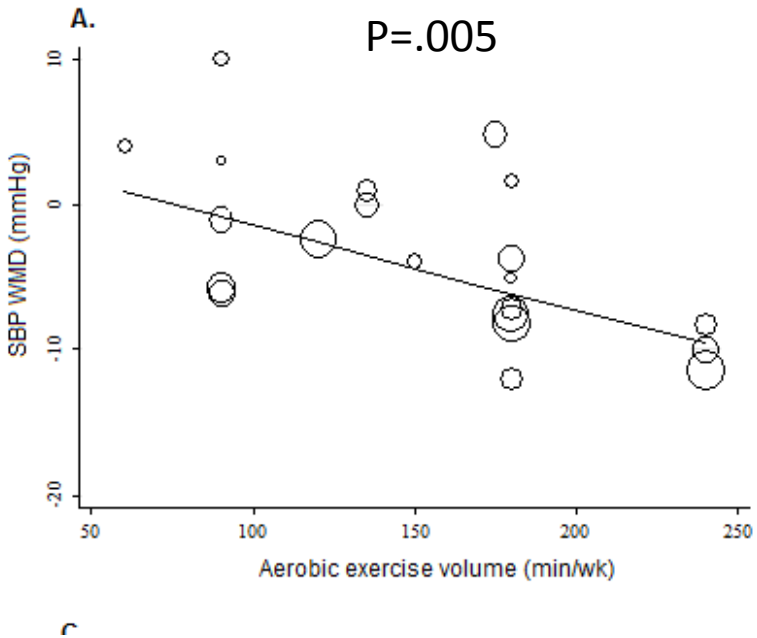
Draft Conclusion Statement Individual characteristics

- Conclusion Statement:
  - Insufficient evidence was available to determine the relationship between Tai Chi, Qigong, and Yoga exercise with risk factors for progression.

- **PAGAC Grade: Grade not assignable**

Draft Key Findings—Progression Dose-response Blood pressure

- Blood pressure and weekly exercise volume [1]:
  - >150 min week aerobic PA had greater effect of SPB (WMD=-6.17) than less than 150 min (WMD= -2.80); dose response effect (p<.003) for min/week of aerobic PA in meta-regression



Aerobic

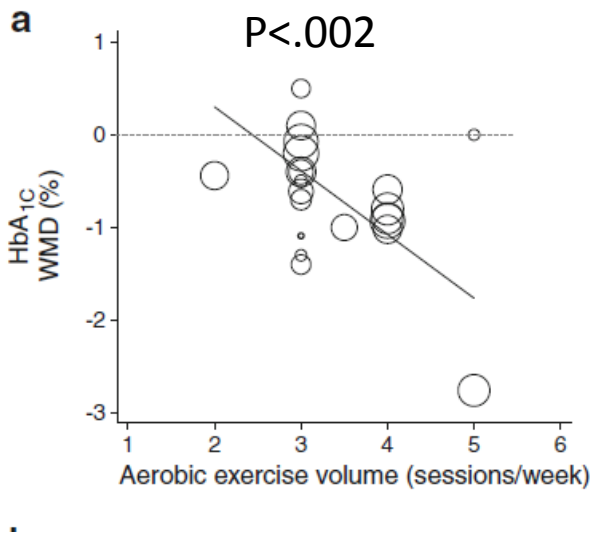
1. Figueira et al. Sports Med 2014;44:1557-1572

Draft Key Findings—Progression Dose-response A1C

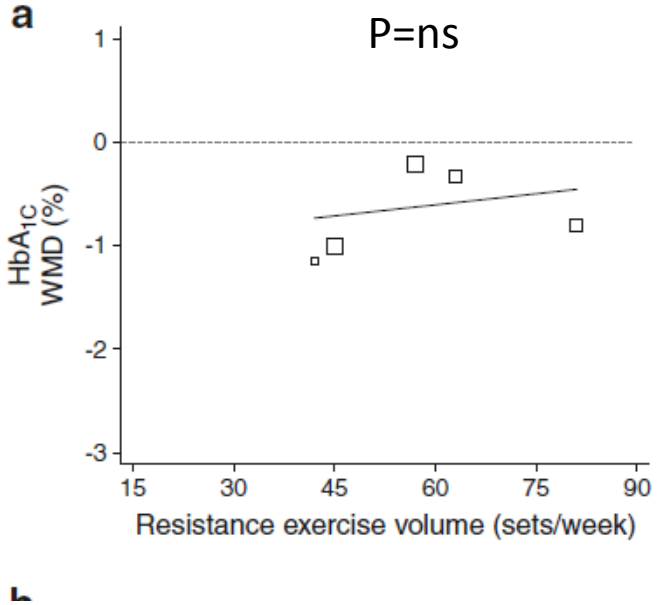
- A1C and weekly exercise volume [1]

Alone

Aerobic



Resistance



1. Umpierre et al. Diabetologica 2013;56:242-251

Draft Key findings: Dose-response A1C

- 150+ minutes/week of PA had a stronger effect on A1C (.89%) than less than 150 min/week (.36%) [1]
- >21 sets resistance training per bout of exercise had greater effect on A1C (.65%) compared to <21 sets (.16%) p<.03 [2]

1. Umpierre,2011; 2. Ishiguo, 2016;

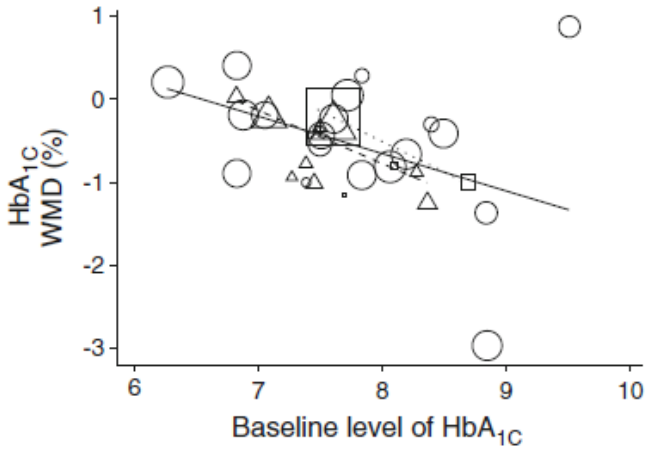
Draft Conclusion Statement: Dose response

- Conclusion Statements:
  - Moderate evidence indicates an inverse dose-response relationship between volume of aerobic activity and risk factors (blood pressure, A1C) for progression among adults with T2DM.
  - **PAGAC Grade: Moderate**
  - Limited evidence indicates an inverse dose-response relationship between volume of resistance training and a risk factors for progression (A1C) among adults with T2DM.
  - **PAGAC Grade: Limited**

Draft Key Findings—Progression Characteristics of adults

- Effects of aerobic and resistance training on blood pressure were larger (p<.001) in studies in hypertensive patients compared to normotensive (hypertensive studies defined as >70% participants have BP>140/90). [1]

- The effect of PA on A1C depends upon the baseline level of A1C [2].



r= -0.52
P=.001

Figure from Umpierre et al. Diabetologica 2013;56:242-251

1. Figueira,2014; 2. Umpierre,2013

Draft Conclusion Statement Individual characteristics

- **Conclusion Statements:**
  - Moderate evidence indicates that effects of physical activity on blood pressure are stronger in hypertensive individuals, and effects of physical activity on A1C are stronger in individuals with higher levels of A1C.
  - **PAGAC Grade: Moderate**

  - Insufficient evidence was available to determine whether the effects of physical activity on risk factors for progression in adults of T2DM vary by age, sex, race/ethnicity, socio-economic status, or weight status.
  - **PAGAC Grade: Not assignable**

Draft Key Findings—Progression Duration of exercise

- MA's addressing effect of PA duration generally found stronger effects on A1C, BMI, and lipids with longer durations:
  - Effect sizes for "free-living" PA on **A1C and BMI** increased over f/u intervals of: <6, 6, 12, and 24 months [1]
    - A1C: -0.18, -0.33, -0.33, -0.56
    - BMI: -0.75, -0.77, -1.32, -1.52
  - "For every additional week of [aerobic] exercise **HbA1C** reduces between 0.009 & 0.04%" [2]
  - Longer exercise programs had significantly stronger effects on **LDL-C** ($p<.03$) [3]
  - Long-term trials of $\geq$ 6 months significantly stronger effects on **A1C** [4]
  - However, another MA did not find a significant effect of duration of aerobic exercise on BMI [2]

1. avery,2012 2.Grace 2017; 3.Hayashino,2012; 4Schwingshackl, 2014

Draft Conclusion Statement Duration of exercise

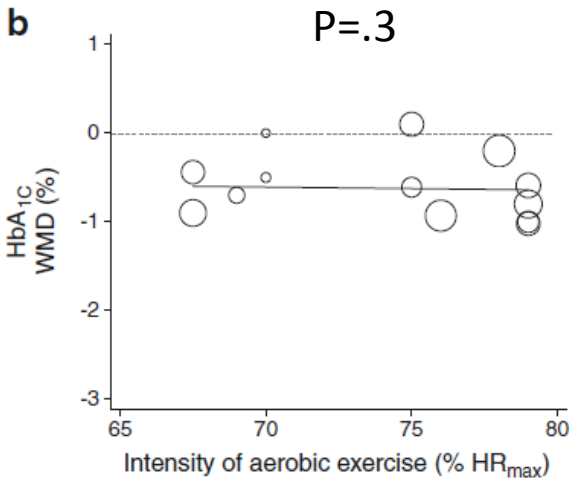
- Conclusion Statement:
  - Limited evidence indicates longer periods of exercise have a larger effect on risk factors (A1C, lipids, BMI) for progression among adults with T2DM.

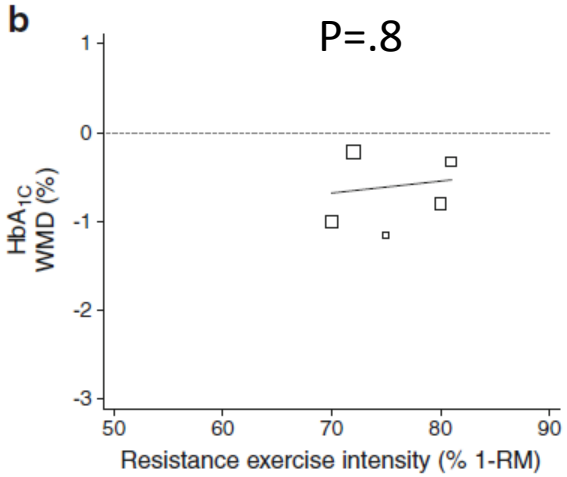
- PAGAC Grade: Limited

Draft Key Findings—Progression Intensity of aerobic exercise

- Blood pressure: No effect of aerobic or resistance training intensity on systolic blood pressure [1]

- A1C: No effect of aerobic intensity on A1C in two meta-regressions [2,3]; no effect of resistance training intensity in 1 meta-regression [3]; However, intensity range was limited.





Figures from Umpierre et al. *Diabetologica* 2013;56:242-251

1.Figueira, 2014; 2. Grace, 2017; 3. Umpierre,2013

Draft Key Findings—Progression Intensity of Aerobic Exercise

- However, MA of 8 RCTs reported higher intensity aerobic PA has stronger effect on A1C: WMD = -0.22% [1].
  - N=235 participants, training for 3 – 6 months, some continuous high-intensity, some interval high intensity.
  - Six studies in adults had total weight in MA of 94.2%
    - compared moderate to vigorous intensity & matched volume
    - Most studies had moderate-intensity training of 150-300 min/week.

1. Liubaoerjijin, 2016

Draft Conclusion Statement: PA exposure

- **Conclusion Statements:**
  - In comparisons of equal volumes of moderate vs vigorous-intensity aerobic training, limited evidence suggests vigorous intensity activity is somewhat more efficient in reducing one risk factor (A1C) for progression in adults with T2DM.
  - **PAGAC Grade: Limited**

  - Insufficient evidence was available to determine the effects of frequency, bout duration, and method of measuring PA on risk factors for progression in adults with T2DM
  - **PAGAC Grade: Not assignable**

Draft Research Recommendations – T2DM: All 4 outcomes (1)

- 1) Cohort studies in adults with T2DM which assess relationship between PA (measured by both devices and self-report) and:
  - Incidence of comorbid conditions
  - Incidence of neuropathy, nephropathy, retinopathy, and foot disorders
  - Incidence of limitations in physical function

- 2) RCTs of fall prevention exercise in adults with T2DM at increased risk of falls and fall injuries.
  - Comment: Fall risk factor profile of adults with T2DM can differ from that of general population of older adults, due to prevalence of neuropathy, impaired vision, foot disorders, myopathy, autonomic neuropathy & orthostatic hypotension, etc.

Draft Research Recommendations – T2DM: All 4 outcomes (2)

- 3) RCTs addressing the effects of different types of PA (including aerobic, muscle strengthening, yoga, Tai Chi) on physical function in adults with T2DM, particularly in adults with limitations in physical function.
  - Comment: RCTs should include a standardized set of physical function measures, so as to facilitate integrating evidence across studies.

- 4) RCTs and meta-analyses addressing the effects of different types of PA (including aerobic, muscle strengthening, yoga, Tai Chi) on summary measures of health related quality of life.
  - Comment: Examples of summary measures: SF-36 PCS and MCS, total depressive symptom score, total well-being score: It is challenging to interpret results of studies reporting multiple subscales of a QOL measure.

Draft Research Recommendations – T2DM: All 4 outcomes (3)

- 5) RCTs of Tai Chi, Qigong, and yoga which identify a) which types/forms are effective in opposing progression of T2DM and b) the minimal volume of PA which is effective.

- 6) RCTs of effects of low vs moderate-intensity PA (aerobic and resistance) on risk of progression of T2DM.
  - Comment: Will inform relative benefit of reducing sedentary behavior by shifting time to low vs moderate-high intensity PA

- 7) In general, additional analyses and studies are needed to assess whether characteristics of individuals and frequency/duration/intensity of PA influence the effects of PA in adults with T2DM

Committee Discussion

4. In people with **type 2 diabetes**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, (3) health-related quality of life, and (4) disease progression?
   - Is there a dose-response relationship? If yes, what is the shape of the relationship?
   - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
   - Does the relationship based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

Question 5

5. In people with **multiple sclerosis**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

- Source of evidence to answer question
  - Systematic Reviews and Meta-Analyses

Analytical Framework

Systematic Review Questions

In people with multiple sclerosis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Population

Individuals of all ages with multiple sclerosis

Exposure

All types and intensities of physical activity, including sedentary behavior

Comparison

Individuals with multiple sclerosis who participate in varying levels of physical activity

Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Health-related quality of life

Key Definitions

- Multiple sclerosis refers to an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system (CNS), which consists of the brain, spinal cord, and optic nerves. It is marked by symptoms such as fatigue, gait disturbances, and spasticity and is typically characterized by evidence of damage in at least two separate areas of the CNS that occurred at least one month apart. http://www.nationalmssociety.org/What-is-MS
- Risk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
  - For example, measures of physical function include measures of ability to walk (e.g., usually gait speed), run, climb stairs, carry groceries, sweep the floor, stand up, and bathe oneself.
  - As measures of behavioral abilities, physical function measures do not include:
    - Physiologic measures, including measures of physiologic capacity (e.g., maximal lung capacities, maximal aerobic capacity, maximal muscle strength, bone density).
    - Measures of the environment or of the host-environmental interaction (e.g., disability accommodation).
    - Measures of what a person usually does (e.g., physical activity level) (as opposed to what a person is capable of doing).
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being

Common Inclusion/ Exclusion Criteria

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  - Exclude: Grey literature
- Study Subjects
  - Exclude: Studies of animals only

Inclusion/Exclusion Criteria

- Date of Publication
  - Original Research: Not applicable
  - Existing Sources: Include 2011 - Present
- Study Subjects
  - Include: Human subjects
- Study Design
  - Include: Systematic reviews, Meta-analyses, Pooled analyses, PAGAC-Approved reports
  - Exclude: Randomized controlled trials, Prospective cohort studies, Narrative reviews, Commentaries, Editorials, Non-randomized controlled trials, Retrospective cohort studies, Case-control studies, Cross-sectional studies, Before-and-after studies
- Exposure/Intervention
  - Include: All types and intensities of physical activity, including sedentary behavior, Studies with single, acute bouts of exercise as the exposure
  - Exclude: Missing physical activity, Single, acute session of exercise, Therapeutic exercise, Physical fitness as the exposure, Only used as confounding variable, Multimodal interventions
- Outcome
  - Include: Risk of co-morbid conditions, Physical function, Health-related quality of life

Search Terms: Physical Activity

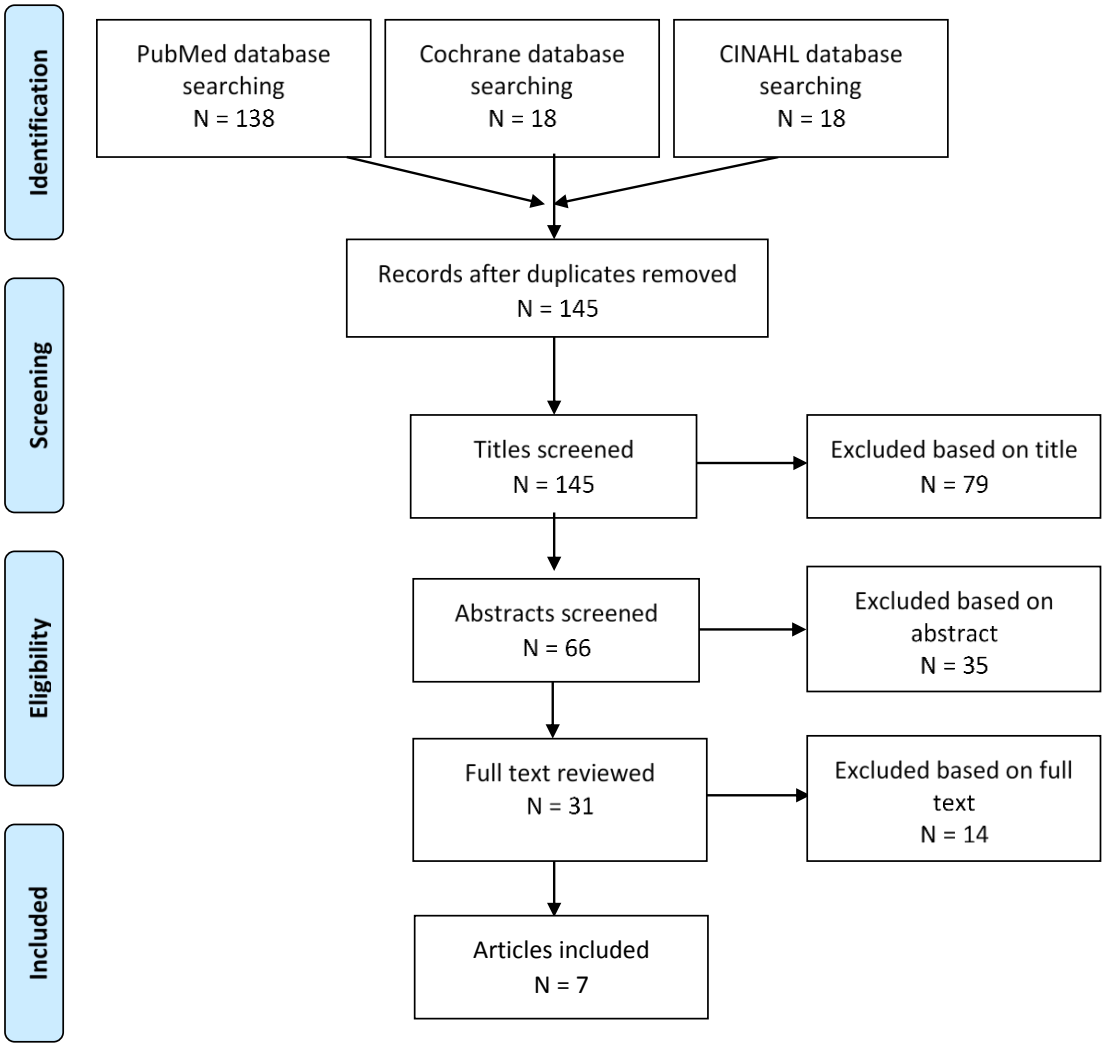
- Aerobic activity(ies)
- Aerobic endurance
- Bicycl*
- Cardiovascular activity(ies)
- Endurance activity(ies)
- Endurance training
- Exercise(s)
- Free living activity(ies)
- Functional training
- Leisure-time physical activity
- Lifestyle activity(ies)
- Muscle stretching exercises
- Physical activity(ies)
- Physical conditioning
- Qi gong
- Recreational activity(ies)
- Resistance training
- Running
- Sedentary lifestyle
- Sedentary
- Speed training
- Strength training
- Tai chi
- Tai ji
- Training duration
- Training frequency
- Training intensity
- Treadmill
- Walking
- Weight lifting
- Weight training
- Yoga

Search Terms: Condition

- Multiple sclerosis

[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Search Results: High-Quality Reviews[1]



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Draft Conclusion Statement: Multiple Sclerosis – Comorbid Conditions

- Conclusion Statement:
  - There is insufficient data to examine the relationship between PA and risk of comorbid conditions for persons with MS.
- PAGAC Grade: Grade not assignable
- **Evidence: Lack of systematic reviews on comorbid conditions.**

Draft Key Findings:
Multiple Sclerosis – Physical Function

Walking: Source-13 RCTs, N=657 persons with mild-moderate disability.

- Evidence- Small-moderate effect sizes for velocity and endurance that are clinically significant.

Fitness and Strength: Source- 20 RCTs, similar demographics.

- Evidence for Fitness: Moderate positive effect size (0.47, 95% CI, .30-0.65).
- Evidence for Strength: Small-moderate effect size (0.27, 95% CI. 0.17-0.38).

Disease Modification, Balance: Source- ~12 studies, various designs.

- Insufficient data, conflicting results.

Draft Conclusion Statement: Multiple Sclerosis – Physical Function

- Conclusion Statement:
  - Strong evidence indicates an association between greater amounts of moderate – vigorous physical activity and small to moderate improvements in physical function including walking velocity and endurance, strength and aerobic fitness.

- Grade: **PAGAC Grade Strong**

Draft Key Findings:
Multiple Sclerosis – Health-Related Quality of Life

Depressed Mood: Sources-12 RCTs, 437 persons

- Evidence- Small effect size, reduced depressive symptoms (-0.37, 95% CI, -0.56 – - 0.17); yoga short-term effects 0.55, 95% CI. -0.96 – -0.13

Fatigue: Source- 7 RCTs, 670 persons

- Evidence- Moderate positive effect size, reduced fatigue (0.52, 95% CI, -1.02 – 0.02, P<0.04).

HRQOL Sources	Evidence on QOL
13 RCTs, men and women	Conflicting results
13 RCTs, mostly (90% women), All studies in Iran.	positive effects (1.021 95% 0.71 – 1.3).
Yoga 7 studies, 670 persons	No effects on HRQoL
Tai Chi 8 studies, 193 persons	Mixed results

Draft Conclusion Statement: Multiple Sclerosis – Health-Related Quality of Life

- Conclusion Statement:
  - Limited evidence shows mixed findings for an association between greater physical activity and HRQOL.
  - Limited evidence supports a relationship for small-moderate reductions in depressive symptoms and fatigue, which are both related to QOL in adults with MS.

- PAGAC Grade: Limited.

Draft Research Recommendations: Multiple Sclerosis

- Randomized studies are needed to determine the effects of physical activity on clinical depression and anxiety disorders in persons with MS.
- Longitudinal studies are needed to better understand the potential for physical activity to function as a moderator of disease progression, brain health and biomarkers for brain health in persons with MS
- Randomized studies are needed to investigate the effects of physical activity on bone health for persons with MS, and value for preventing osteoporosis and fractures.

Draft - Research Recommendations: Multiple Sclerosis

- Randomized studies are needed to determine effects of PA on ADL mobility, instrumental ADL's, free-living physical/ambulatory activity and social participation for persons with MS.
- Controlled studies are needed to investigate the dose and modalities of PA to improve balance function and to prevent injurious falls and fractures across the disability and age spectrum for persons with MS.

Committee Discussion

5. In people with **multiple sclerosis**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Question 6

6. In people with a **spinal cord injury**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

- Source of evidence to answer question
  - Systematic Reviews and Meta-Analyses

Analytical Framework

Systematic Review Questions

In people with a spinal cord injury, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Population

Individuals of all ages with a spinal cord injury

Exposure

All types and intensities of physical activity, including sedentary behavior

Comparison

Individuals with a spinal cord injury who participate in varying levels of physical activity

Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Health-related quality of life

Key Definitions

- Spinal cord injury refers collectively to damage incurred by the spinal cord resulting from trauma, disease, or degeneration and is marked by symptoms that vary according to the level (location) and severity of the injury. http://www.who.int/mediacentre/factsheets/fs384/enRisk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
  - For example, measures of physical function include measures of ability to walk (e.g., usually gait speed), run, climb stairs, carry groceries, sweep the floor, stand up, and bathe oneself.
  - As measures of behavioral abilities, physical function measures do not include:
    - Physiologic measures, including measures of physiologic capacity (e.g., maximal lung capacities, maximal aerobic capacity, maximal muscle strength, bone density).
    - Measures of the environment or of the host-environmental interaction (e.g., disability accommodation).
    - Measures of what a person usually does (e.g., physical activity level) (as opposed to what a person is capable of doing).
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being

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- Study Design
  - Include: Systematic reviews, Meta-analyses, Pooled analyses, PAGAC-Approved reports
  - Exclude: Randomized controlled trials, Prospective cohort studies, Narrative reviews, Commentaries, Editorials, Non-randomized controlled trials, Retrospective cohort studies, Case-control studies, Cross-sectional studies, Before-and-after studies
- Exposure/Intervention
  - Include: All types and intensities of physical activity, including sedentary behavior, Studies with single, acute bouts of exercise as the exposure
  - Exclude: Missing physical activity, Therapeutic exercise, Physical fitness as the exposure, Physical activity only used as confounding variable, Do not present data on physical activity alone
- Outcome
  - Include: Risk of co-morbid conditions, Physical function, Health-related quality of life

Search Terms: Physical Activity

- Aerobic activity(ies)
- Aerobic endurance
- Bicycl*
- Cardiovascular activity(ies)
- Endurance activity(ies)
- Endurance training
- Exercise(s)
- Free living activity(ies)
- Functional training
- Leisure-time physical activity
- Lifestyle activity(ies)
- Muscle stretching exercises
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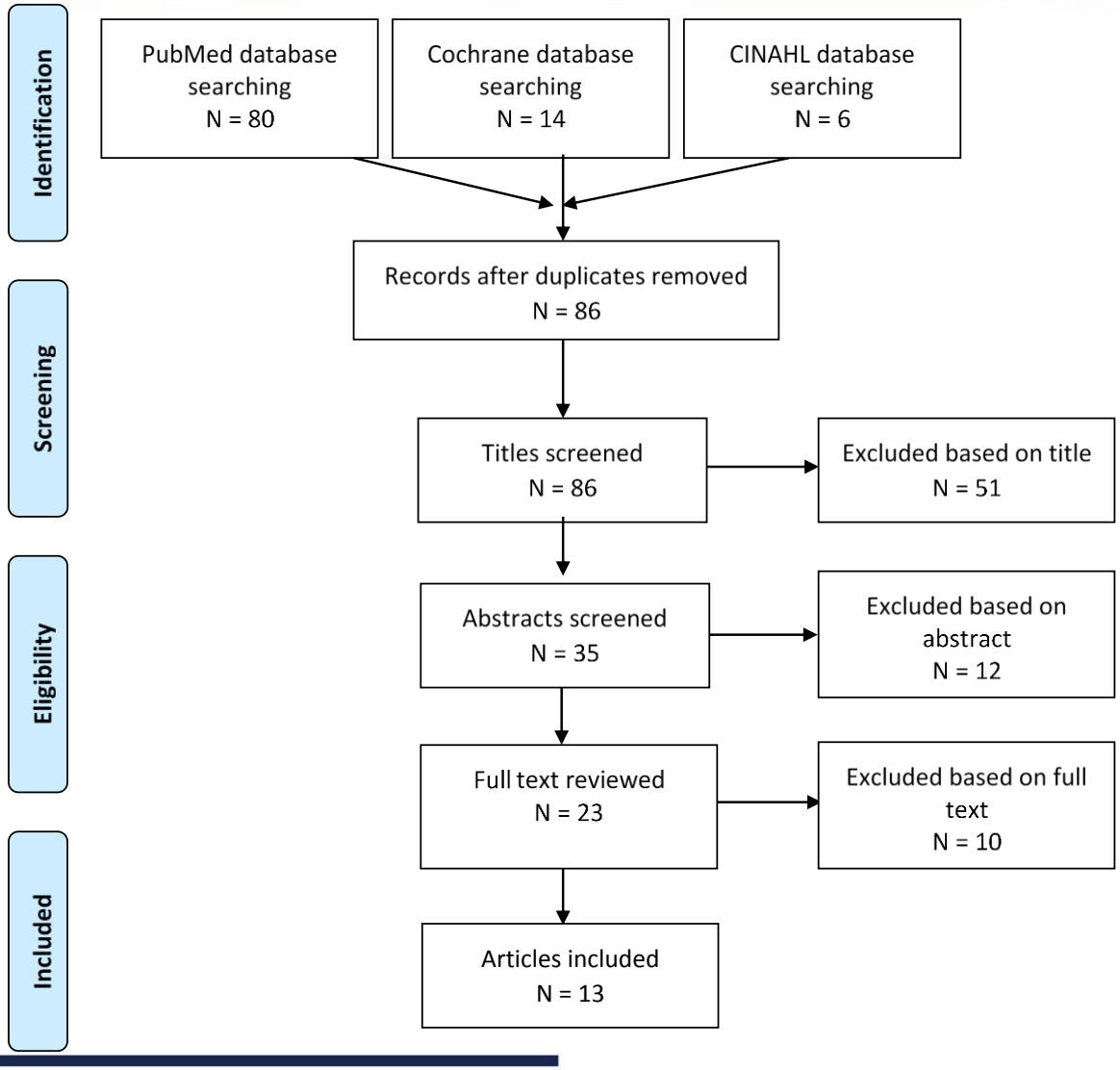
- Speed training
- Strength training
- Tai chi
- Tai ji
- Training duration
- Training frequency
- Training intensity
- Treadmill
- Walking
- Weight lifting
- Weight training
- Yoga

Search Terms: Condition

- Paraparesis
- Paraplegia
- Paraplegic(s)
- Post-traumatic myelopathy(ies)
- Quadriparesis
- Quadriplegia
- Quadriplegic(s)
- Spinal cord contusion(s)
- Spinal cord injury(ies)
- Spinal cord laceration(s)
- Spinal cord trauma(s)
- Traumatic myelopathy(ies)

Search Results: High-Quality Reviews[1]



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Draft Key Findings:
Spinal Cord Injury – Comorbid Conditions

Reduced Shoulder Pain

- Source - 3 RCTs, 4 cohort studies, N=199
- Evidence- 7/7 clinically significant reductions in shoulder pain.

Vascular Function in Paralyzed Limbs

- Source- 15 studies, various designs; N=175
- Evidence- vascular function consistently improves with acute bout and regular exercise.

Draft Conclusion Statement: Spinal Cord Injury – Comorbid Conditions

- Conclusion Statement:
  - There is limited but consistent evidence that increased physical activity is related to clinically significant reductions in shoulder pain, and improved vascular function in paralyzed limbs in persons with SCI.

- Grade: **PAGAC Grade – Limited**

Draft Key Findings*:*
Spinal Cord Injury – Physical Function

Walking: Sources- Locomotor training 13 RCTs, N=586. Adaptive training, various modalities, N=20 Studies, mixed designs.

- Evidence- Small effect sizes for improved velocity and endurance.

Strength: 11 RT studies; 9 combined AT+RT

- Evidence- Consistent small-moderate effect sizes for strength & power.

Upper Extremity Function Source- 6 RCTs

- Evidence - small positive effects for upper extremity, hand function, and wheel chair propulsion.

Balance/Postural Control- 19 studies,

- Evidence - negligible effects.

Draft Conclusion Statement: Spinal Cord Injury – Physical Function

- Conclusion Statement:
  - There is moderate strength evidence for a relationship between greater physical activity and small to moderate positive effect sizes on walking function, muscular strength, and upper extremity function for persons with SCI.

- **PAGAC Grade: Moderate**

Draft Key Findings:
Spinal Cord Injury – Health-Related Quality of Life

Sources: 11 studies, N=634 persons with SCI

- Small positive effect on Life Satisfaction, and QoL.
- Limited evidence that weekly volume of PA is related to QoL:
  - ≥4 hours most positive;
  - 45 min. 2x/week limited effects
  - 30 minutes 2x/week not sufficient

Draft Conclusion Statement: Spinal Cord Injury – Health-Related Quality of Life

- Conclusion Statement:
  - There is limited evidence for a positive relationship between PA and HRQOL for persons with SCI.

- **PAGAC Grade: Limited**

Draft Research Recommendations: Spinal Cord Injury

- Studies are needed to determine effects of PA on comorbid and secondary health conditions, physical function, and quality of life in children and adolescents with SCI. (age gap)
- Randomized studies needed to determine effects of PA on body composition, vascular function and CVD risk factors, pulmonary function, and cardiopulmonary outcomes.

Draft Research Recommendations: Spinal Cord Injury

- Randomized studies needed to examine effects of PA on pain including muscular and neurogenic pain.

- Studies needed to examine effects of PA on secondary health conditions including constipation, skin integrity, and autonomic dysfunctions (effects bladder, renal, bowel, sexual, cardiovascular, and thermoregulatory function).

- Randomized studies needed to examine effects of PA to reduce immobilization hypercalcemia and improve bone health across the phases of care (acute and chronic).

Draft Research Recommendations: Spinal Cord Injury

- Randomized studies needed to examine the dose and modality of PA to improve balance function, and reduce injurious falls and fractures across the spectrum of deficit severity.

- Randomized studies needed to determine effects of PA on ADL mobility, instrumental ADL's, free-living physical/ambulatory activity and social participation for persons with SCI.

- Systematic analyses of relationships between age, race-ethnicity, socioeconomic status, and weight status needs built into these recommended studies.

Committee Discussion

6. In people with a **spinal cord injury**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Question 7

7. In people with **intellectual disabilities**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

- Source of evidence to answer question
  - Systematic Reviews and Meta-Analyses

Analytical Framework

Systematic Review Questions

In people with intellectual disabilities, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Population

Individuals of all ages with intellectual disabilities

Exposure

All types and intensities of physical activity, including sedentary behavior

Comparison

Individuals with intellectual disabilities who participate in varying levels of physical activity

Endpoint Health Outcomes

- Risk of co-morbid conditions
- Physical function
- Health-related quality of life

Key Definitions

- Intellectual disability is characterized by significant limitation in both intellectual function and adaptive behavior, defined as the collection of conceptual, social, and practical skills that are learned and performed within everyday life, that manifests before the age of 18. http://aaidd.org/intellectual-disability/definition#.WbE4XMiGNPY
- Risk of co-morbid conditions: The chance of having one or more additional conditions
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
  - For example, measures of physical function include measures of ability to walk (e.g., usually gait speed), run, climb stairs, carry groceries, sweep the floor, stand up, and bathe oneself.
  - As measures of behavioral abilities, physical function measures do not include:
    - Physiologic measures, including measures of physiologic capacity (e.g., maximal lung capacities, maximal aerobic capacity, maximal muscle strength, bone density).
    - Measures of the environment or of the host-environmental interaction (e.g., disability accommodation).
    - Measures of what a person usually does (e.g., physical activity level) (as opposed to what a person is capable of doing).
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: HealthyPeople.gov https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being

Common Inclusion/ Exclusion Criteria

- Language
  - Exclude: Studies that do not have full text in English
- Publication Status
  - Include: Studies published in peer-reviewed journals, PAGAC-approved reports
  - Exclude: Grey literature
- Study Subjects
  - Exclude: Studies of animals only

Inclusion/Exclusion Criteria

- Date of Publication
  - Original Research: Not applicable
  - Existing Sources: Include 2011 - Present
- Study Subjects
  - Include: Human subjects
- Study Design
  - Include: Systematic reviews, Meta-analyses, Pooled analyses, PAGAC-Approved reports
  - Exclude: Randomized controlled trials, Prospective cohort studies, Narrative reviews, Commentaries, Editorials, Non-randomized controlled trials, Retrospective cohort studies, Case-control studies, Cross-sectional studies, Before-and-after studies
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- Walking
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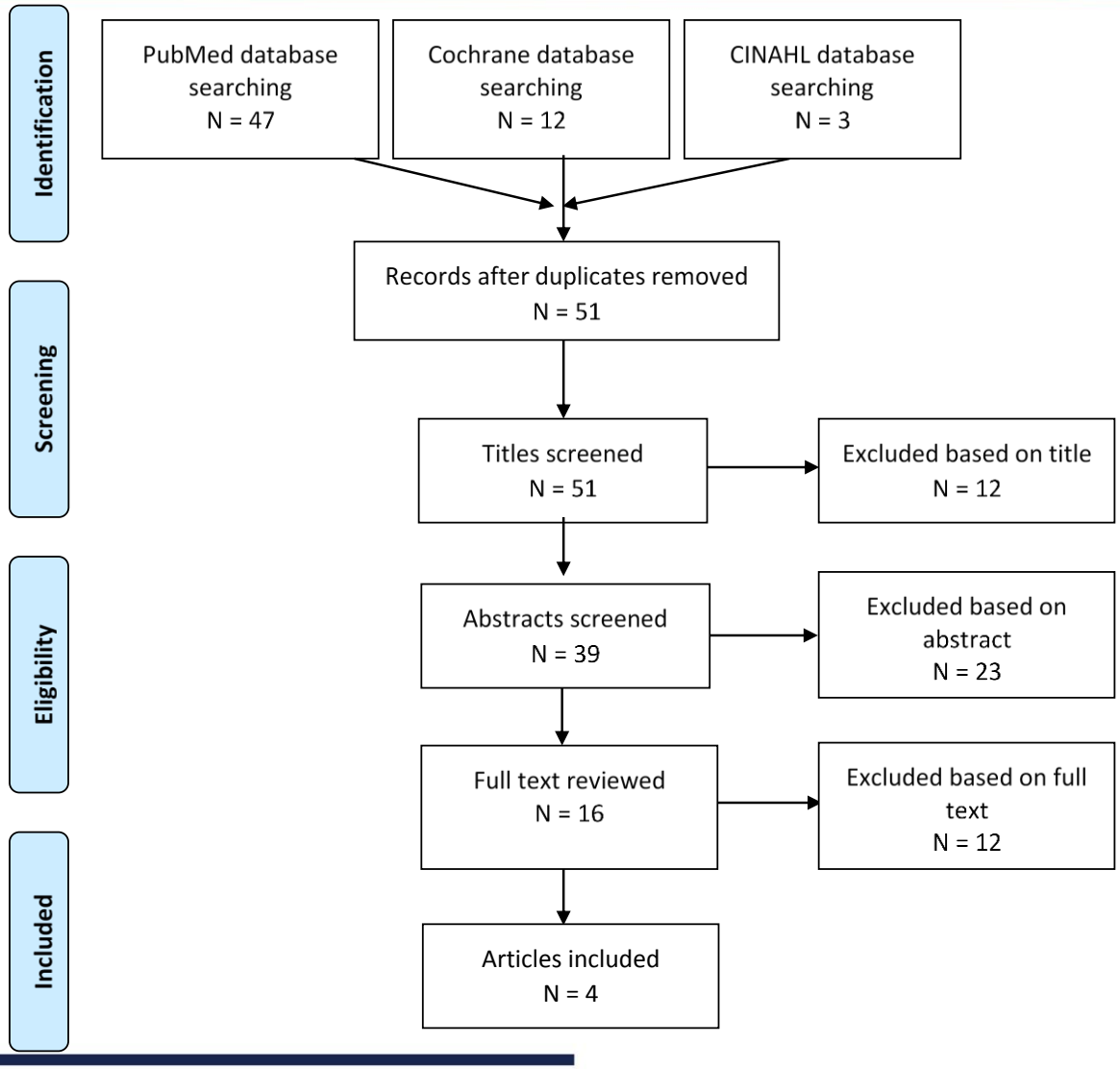
Search Terms: Condition

- Down(s) syndrome
- Down's syndrome
- Intellectual development disorder(s)
- Intellectual disability(ies)
- Langdon Down Disease
- Mental deficiency(ies)
- Mongolism
- Mongoloidism
- (Partial) Trisomy 21
- Translocation 15 21 22
- Trisomy G
- 47,XX,+21
- 47,XY,+21

Search Results: High-Quality Reviews[1]



[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

PA and Challenging Behaviors:

Source- 20 studies of various designs.

Evidence- Beneficial effect of PA to reduce challenging behaviors (30.9% (52.0, 36.8).

Limitation:

Only 2 studies had a control group, 5 are case reports involving N=5 total persons with ID, and remaining 13 studies comprised N= 53 participants.

Draft Key Findings*:*
Intellectual Disabilities – Comorbid Conditions

- Conclusion Statement:
  - There is insufficient evidence to analyze the relationship between physical activity and risk of comorbid conditions for persons with intellectual disabilities.

- **PAGAC Grade: Grade Not Assignable**

Draft Key Findings*:*
Intellectual Disabilities – Physical Function

Sources:

- **19 studies various design, 428 children &adults, aged 3-66 YOA.**
- 9 studies, ~310 adults 21-64 YOA.
- 7 RCTs, 175 children <6 YOA with Down Syndrome, developmental delay, or at moderate risk for developmental

Evidence

- Adults, diverse PA modalities- small improvements in gross motor function and basic mobility.
- Children, diverse PA modalities, small effect size, balance, jumping, gross motor skills.
- Children <6 YOA treadmill locomotor training, greater gait velocity (MD =0.23 MD=0.23,95% CI, 0.08, 0.37); earlier age of independent walking onset MD = -4.00 (-6.96, -1.04).

Draft Conclusion Statement*:* Intellectual Disabilities – Physical Function

- Conclusion Statement:
  - There is limited evidence for a relationship between physical activity and small effect size improvements on selected physical function outcomes in adults and children with intellectual disabilities.

- **PAGAC Grade: Limited**

Draft Key Findings:
Intellectual Disabilities – Health-Related Quality of Life

Sources- 2 studies in adults

Evidence

- Combined aerobic and resistive training, 4% improvement in “Life Satisfaction.
- Aerobic training, 50% improvement in QOL ($p<.05$)

Draft Conclusion Statement:
Intellectual Disabilities – Health-Related Quality of Life

- Conclusion Statement:
  - There is insufficient data to analyze the relationship between physical activity and health related quality of life for persons with intellectual disabilities.

- **PAGAC Grade: Grade Not Assignable**

Draft Research Recommendations: Intellectual Disabilities

- Studies are needed to investigate effects of PA on adaptive functioning including conceptual, social, and practical areas of living for individuals with intellectual disability across the age- and severity spectrum.

- Studies needed to investigate effects of PA on comorbid and secondary health conditions including mental health conditions with increased prevalence in this population, including challenging behaviors, anxiety disorders, depression, schizophrenia/psychosis.

- Studies are needed to determine whether PA modifies the risk or age of onset for early onset dementia of an Alzheimer's type in adults with Downs Syndrome,

Draft Research Recommendations: Intellectual Disability

- Randomized studies needed to determine effects of PA on ADL mobility, instrumental ADL's, free-living physical/ambulatory activity and social participation for persons with ID.

- Systematic analyses of relationships between age, race-ethnicity, socioeconomic status, and weight status needs built into these recommended studies.

- Studies are needed to determine whether PA modifies the risk, age of onset, and biomarkers for early onset dementia of an Alzheimer's type in adults with Downs Syndrome, and to examine modulating effects of genetics and environmental risk factors on this relationship.

Committee Discussion

7. In people with **intellectual disabilities**, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?