

# Shared and distinct changes in the molecular cargo of extracellular vesicles in different neurodegenerative diseases.

Cellular and Molecular Life Sciences

Anna F. Wiersema<sup>1</sup>, Alyssa Rennenberg<sup>1</sup>, Grace Smith<sup>1</sup>, Suzy Varderidou-Minasian<sup>1</sup>, and R. Jeroen Pasterkamp<sup>1</sup>

<sup>1</sup> Department of Translational Neuroscience, University Medical Center Brain Center, Utrecht University, Utrecht, The Netherlands

R. Jeroen Pasterkamp. Email: r.j.pasterkamp@umcutrecht.nl.

**Supplementary Table 1. Overview of studies on EV cargo in AD.**

| Model           | EV origin | Cell type                                                | EV isolation method                                                     | Literature | Method used to determine EV content                              | Major findings                                                                                                                                                                                                           |
|-----------------|-----------|----------------------------------------------------------|-------------------------------------------------------------------------|------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i>  | Human     | Cortical gray matter                                     | Ultracentrifugation                                                     | [10]       | ELISA and mass spectrometry                                      | AD-EVs contained elevated levels of pathogenic markers A $\beta$ 1-42, p-tau S396, APOE and SNCA. ANXA5 and GPM6A were increased whereas VGF and ACTR1A were decreased in AD-EVs.                                        |
| <i>In vivo</i>  | Human     | Plasma                                                   | Size-exclusion chromatography (SEC)                                     | [23]       | Next-generation sequencing and qPCR                              | AD-EVS showed increased levels of miR-451a, miR-21-5p, miR-23a-3p, miR-126-3p, let-7i-5p, and miR-151a-3p.                                                                                                               |
| <i>In vivo</i>  | Human     | Plasma                                                   | Ultracentrifugation and L1CAM-based immunoaffinity                      | [27]       | miRNA qPCR                                                       | AD neural exosomes revealed decreased levels of miR-132 and miR-212.                                                                                                                                                     |
| <i>In vivo</i>  | Human     | Microglia-enriched EVs from parietal cortex              | Filter purification, ultracentrifugation and CD11b-based immunoaffinity | [42]       | Mass spectrometry, western blotting and miRNA expression panels  | In microglial AD-EVs homeostatic microglial markers P2RY12 and TMEM119 levels were lower and activated microglial markers FTH1 and TREM2 higher. miR-28-5p, miR-381-3p, miR-651-5p and miR-188-5p levels were increased. |
| <i>In vivo</i>  | Human     | CSF                                                      | Commercial exosome isolation kit                                        | [60]       | Mass spectrometry                                                | AD-EVs showed increased levels of HSPA1A, NPEPPS and PTGFRN compared to EVs isolated from patients with MCI.                                                                                                             |
| <i>In vitro</i> | Human     | Astrocyte-enriched EVs from frontal cortical grey matter | Ultracentrifugation and size exclusion chromatography                   | [65]       | Label-free quantitative LC-MS/MS proteomics and western blotting | ITGB1 was increased and LRP1 decreased in astrocyte AD-EVs.                                                                                                                                                              |
| <i>In vivo</i>  | Human     | Plasma-derived neural EVs                                | Commercial exosome isolation kit and L1CAM-based immunoaffinity         | [140]      | LC-MS/MS and ELISA                                               | HB levels are elevated in AD exosomes.                                                                                                                                                                                   |
| <i>In vivo</i>  | Human     | Brodmann areas                                           | Ultracentrifugation and size exclusion chromatography                   | [141]      | Mass spectrometry                                                | Antioxidant enzymes PRDX1 and PRDX6 were increased in AD-EVs.                                                                                                                                                            |
| <i>In vivo</i>  | Human     | Plasma                                                   | Commercial exosome isolation kit                                        | [40]       | RNA sequencing and RT-qPCR                                       | MT-ND1-6 mRNAs, MT-ATP6 and -8, MT-CYTB and MT-CO1-3 were increased in AD-EVs.                                                                                                                                           |
| <i>In vivo</i>  | Human     | Plasma                                                   | Commercial exosome isolation kit and L1CAM-based immunoaffinity         | [26]       | RNA sequencing and RT-qPCR.                                      | let-7e-5p, miR-96-5p and miR-484 levels were increased and miR-99b-5p, miR-100-5p, miR-30e-5p, miR-378i, miR-145-5p, miR-378c and miR-451a were decreased in AD-EVs.                                                     |

|                |                        |                                         |                                                                              |       |                                         |                                                                                                                                                                                       |
|----------------|------------------------|-----------------------------------------|------------------------------------------------------------------------------|-------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit                                       | [39]  | RT-qPCR                                 | lncRNA BACE1-AS was increased in AD-EVs.                                                                                                                                              |
| <i>In vivo</i> | Human                  | CSF                                     | Ultracentrifugation<br>and Vn96-based<br>immunoaffinity                      | [64]  | Mass<br>spectrometry<br>and ELISA       | Complement protein C1q was<br>increased in AD-EVs.                                                                                                                                    |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit and L1CAM-<br>based<br>immunoaffinity | [142] | qPCR                                    | miR-23a-3p, miR-223-3p, and miR-<br>190a-5p levels were increased and<br>miR-100-3p levels decreased in AD-<br>EVs.                                                                   |
| <i>In vivo</i> | Human                  | Plasma                                  | Ultracentrifugation                                                          | [46]  | LC-MS/MS                                | FXIII A1, FXIII B, ORM2 and RBP4 were<br>increased and HYDIN decreased in AD-<br>EVs.                                                                                                 |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit and L1CAM-<br>based<br>immunoaffinity | [56]  | ELISA                                   | Inflammatory biomarker MMP-9 was<br>increased in AD-EVs.                                                                                                                              |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit and NCAM-<br>based<br>immunoaffinity  | [51]  | ELISA                                   | GAP43, NRG1, SNAP25, and SYT1<br>levels were lower in AD-EVs.                                                                                                                         |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit and L1CAM-<br>based<br>immunoaffinity | [30]  | qPCR                                    | miR-125b-5p, miR-132-5, miR-9-5p<br>and miR-106b-5p levels were<br>increased and miR-29a-5p decreased<br>in AD-EVs.                                                                   |
| <i>In vivo</i> | Human                  | Hippocampus<br>and prefrontal<br>cortex | Ultracentrifugation                                                          | [143] | Mass<br>spectrometry                    | EPB41L1, BASP1, DPYSL2, PGAM1<br>levels were higher and SPTAN1,<br>HIST1H4A, EPB41L3, ATP6V1D, ATL1,<br>SLC6A1, GNG3, MAPK lower in AD-<br>EVs.                                       |
| <i>In vivo</i> | APP/PSE<br>N1<br>Mouse | Brain tissue                            | Ultracentrifugation                                                          | [69]  | Tandem mass<br>tag-mass<br>spectrometry | PSEN1, APP, and ITGAX levels were<br>increased and WDR61, PMPCA,<br>ALDH1A2, CALU, ANP32B, ACTN4, and<br>NDUFV2 decreased in AD-EVs.                                                  |
| <i>In vivo</i> | Human                  | Plasma                                  | Ultracentrifugation                                                          | [144] | RNA sequencing                          | Small nucleolar RNAs SNORD113,<br>SNORD114, SNORD115 and<br>SNORD116 levels were higher in AD-<br>EVs.                                                                                |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit and L1CAM-<br>based<br>immunoaffinity | [52]  | ELISA                                   | AD-EVs showed lower levels of<br>mitochondrial complexes SOD1,<br>NDUFS1, NDUFS6, UQCRC1, COX1 and<br>ATP5.                                                                           |
| <i>In vivo</i> | Human                  | Plasma                                  | Ultracentrifugation                                                          | [53]  | Mass<br>spectrometry                    | A0A0G2JRQ6, C1QC, CO9, GP1BB,<br>RSU1 levels were increased and<br>ADAM10 was decreased in AD-EVs.                                                                                    |
| <i>In vivo</i> | Human                  | Frontal cortex                          | Size exclusion<br>chromatography                                             | [43]  | RNA sequencing<br>and RT-qPCR           | NCOR2, ERBB3 and NOTCH1 levels<br>were decreased, lncRNAs NEAT1,<br>KCNQ1OT1 and FGD5-AS1 were<br>decreased and circRNAs 0087493,<br>0102923 and 0089902 were increased<br>in AD-EVs. |
| <i>In vivo</i> | Human                  | Plasma                                  | Commercial<br>exosome isolation<br>kit                                       | [37]  | qPCR                                    | miR-93-5p, miR-424-5p and miR-3065-<br>5p were increased and miR-1306-5p<br>decreased in AD-EVs.                                                                                      |
| <i>In vivo</i> | Human                  | Serum                                   | Commercial<br>exosome isolation<br>kits                                      | [57]  | Mass<br>spectrometry,<br>ELISA and WB   | AACT was increased and C4BPα<br>decreased in AD-EVs.                                                                                                                                  |
| <i>In vivo</i> | APP/PSE<br>N1<br>mouse | Choroid<br>plexus                       | Size exclusion<br>chromatography                                             | [68]  | Mass<br>spectrometry                    | Pro-inflammatory complement<br>protein C3 was increased in AD-EVs.                                                                                                                    |
| <i>In vivo</i> | Human                  | Brodman<br>area 9                       | Protein Organic<br>Solvent<br>Precipitation<br>(PROSPR)                      | [145] | LC-MS/MS                                | EFEMP1, OGFRL1, RNF114, RNF181,<br>UBE2E2 and VPS37C levels were<br>increased in early AD-EVs.                                                                                        |

|                 |       |                                  |                                                                              |       |                            |                                                                                                             |
|-----------------|-------|----------------------------------|------------------------------------------------------------------------------|-------|----------------------------|-------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i>  | Human | Serum                            | Commercial<br>exosome isolation<br>kit and L1CAM-<br>based<br>immunoaffinity | [32]  | qPCR                       | miR-204 and miR-373 were decreased<br>in AD-EVs.                                                            |
| <i>In vitro</i> | Human | mTau iPSC-<br>derived<br>neurons | Commercial<br>exosome isolation<br>kit                                       | [70]  | LC-MS/MS                   | NCAN, OLFM1, ALDH2, ATP1A1,<br>GNAO1 and GSN were decreased and<br>NES and COL3A1 increased in mTau<br>EVs. |
| <i>In vitro</i> | Human | Plasma                           | Ultracentrifugation<br>and NCAM (and<br>ABCA1)-based<br>immunoaffinity       | [146] | qPCR                       | miR-384 levels were higher in NCAM-<br>and NCAM/ABCA1-labeled AD<br>exosomes.                               |
| <i>In vivo</i>  | Human | Serum                            | Commercial<br>exosome isolation<br>kit                                       | [35]  | RNA sequencing<br>and qPCR | miR-30b-5p was decreased and miR-<br>22-3p and miR-378a-3p were<br>increased in AD-EVs.                     |
| <i>In vivo</i>  | Human | Plasma                           | Commercial<br>exosome isolation<br>kit                                       | [147] | ELISA                      | LAMP-2 was increased in AD-EVs.                                                                             |

**Supplementary Table 2. Overview of studies on EV cargo in ALS.**

| Model           | EV origin       | Cell type                              | EV isolation method                                                       | Literature | Method used to determine EV content                     | Major findings                                                                                                                                                                                                                      |
|-----------------|-----------------|----------------------------------------|---------------------------------------------------------------------------|------------|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i>  | Human           | CSF                                    | Ultrafiltration liquid chromatography                                     | [148]      | Liquid chromatography-tandem mass spectrometry          | ALS-EVs showed decreased levels of bleomycin hydrolase enzyme and proteasome core complex proteins. C9-ALS EVs specifically showed increased levels of UBA1.                                                                        |
| <i>In vivo</i>  | Human           | Plasma                                 | Exoquick precipitation kit, centrifugation and L1CAM-based immunoaffinity | [76]       | Next-generation sequencing                              | ALS-EVs showed increased levels of miR-146a-5p, miR-199a-3p, miR-151a-3p, miR-151a-5p, miR-199a-5p and decreased levels of miR-4454, miR-10b-5p, miRNA-29b-3p levels.                                                               |
| <i>In vivo</i>  | Human           | Plasma                                 | Polymer based precipitation and L1CAM-based immunoaffinity                | [77]       | qPCR                                                    | Sporadic ALS-EVs showed decreased levels of miRNA-4454, miRNA-10b-5p and miRNA-29b-3p and increased levels of miRNA-151a-5p and miRNA-146a-5p.                                                                                      |
| <i>In vivo</i>  | Human           | Plasma                                 | Polyethylene glycol, centrifugation and L1CAM-based immunoaffinity        | [149]      | ELISA                                                   | The levels of HERV-K in neural EVs of advanced-phase ALS patients were higher when compared to early-phase ALS patients. However, no significant difference was found in HERV-K EV levels between healthy control and ALS patients. |
| <i>In vivo</i>  | Human           | Plasma                                 | VN96-precipitation and centrifugation                                     | [150]      | Next-generation sequencing and droplet digital PCR      | miR-15a-5p and miR-185-5p levels were increased in ALS-EVs.                                                                                                                                                                         |
| <i>In vitro</i> | Mouse           | Spinal and cortical astrocytes         | Ultracentrifugation and filtering                                         | [86]       | qPCR                                                    | miR-155, miR-21 and miR-146a were decreased in ALS-EVs.                                                                                                                                                                             |
| <i>In vitro</i> | Human           | Astrocytes                             | Ultracentrifugation and filtration                                        | [89]       | Microarray analysis                                     | miR-494-3p was decreased in C9ALS-EVs.                                                                                                                                                                                              |
| <i>In vivo</i>  | Human           | Plasma                                 | Differential ultracentrifugation and filtration                           | [11]       | Western Blot                                            | ALS-MVs contained higher SOD1, TDP-43, phospho-TDP-43, and FUS levels.                                                                                                                                                              |
| <i>In vivo</i>  | Human and mouse | Plasma                                 | Ultracentrifugation in parallel with NBI (nickel-based isolation)         | [93]       | Western blot and mass spectrometry                      | Decreased levels of HSP90 were found in ALS-EVs.                                                                                                                                                                                    |
| <i>In vitro</i> | Human           | Muscle cells                           | Differential ultracentrifugation and filtration                           | [97]       | Mass spectrometry and western blot                      | ALS-EVs were enriched in FUS protein and its binding partner RPL5 and ALS muscle cells produced more EVs than control EVs.                                                                                                          |
| <i>In vivo</i>  | Human and mouse | Primary neural cell culture            | Centrifugation                                                            | [98]       | Quantitative proteomics, immuno-precipitation and ELISA | Both EVs from brain and spinal cord of SOD1-mice and human SOD1 patients contained misfolded and nonnative disulfide-cross-linked aggregated SOD1.                                                                                  |
| <i>In vivo</i>  | Human           | Plasma                                 | Exoquick precipitation kit and ACSA-1 immunoprecipitation                 | [90]       | ELISA                                                   | IL-6 levels of astrocyte-derived ALS-EVs were increased.                                                                                                                                                                            |
| <i>In vivo</i>  | Human           | Plasma                                 | Exosome isolation kit                                                     | [91]       | Mass spectrometry and western blot                      | CORO1A levels were increased in ALS-EVs.                                                                                                                                                                                            |
| <i>In vivo</i>  | Human           | Plasma, spinal cord and frontal cortex | Immuno-based affinity (exochip)                                           | [83]       | NanoString miRNA profiling                              | In all 3 sources of tissue miR-342-3p was increased and miR-1254 was decreased in ALS-EVs.                                                                                                                                          |
| <i>In vitro</i> | Human           | Motor neurons                          | Ultracentrifugation                                                       | [151]      | TaqMan® Low Density Arrays and qPCR                     | miR-625 -3p was decreased in C9-ALS-EVs but increased in TARDBP-ALS-EVs.                                                                                                                                                            |
| <i>In vivo</i>  | Human           | Plasma                                 | Exoquick and exoEasy Maxi Kit                                             | [152]      | qPCR                                                    | Decreased levels of miR-27a-3p in ALS-EVs.                                                                                                                                                                                          |
| <i>In vivo</i>  | Human           | CSF                                    | Gel filtration chromatography                                             | [153]      | Liquid chromatography-tandem mass spectrometry          | Nucleolar complex protein 2 homolog (NIR) was enhanced in ALS-EVs.                                                                                                                                                                  |

|                 |       |                     |                     |      |                                                      |                                                                           |
|-----------------|-------|---------------------|---------------------|------|------------------------------------------------------|---------------------------------------------------------------------------|
| <i>In vivo</i>  | Human | Plasma              | ExoEasy Maxi Kit    | [81] | Small RNA sequencing and digital droplet PCR (ddPCR) | miR-23c levels were increased and miR-192-5p decreased in ALS-EVs.        |
| <i>In vivo</i>  | Human | Plasma              | ExoEasy Maxi Kit    | [82] | Small RNA sequencing and qPCR                        | miR-93-5p, miR-16-5p, miR-23a-3p and miR-22-3p were increased in ALS-EVs. |
| <i>In vitro</i> | Rat   | Cortical astrocytes | Ultracentrifugation | [85] | qPCR                                                 | miR-155-5p levels were increased and miR-582-3p decreased in ALS-EVs.     |

**Supplementary Table 3. Overview of studies on EV cargo in PD.**

| Model          | EV origin | Cell type                   | EV isolation method                                | Literature | Method used to determine EV content                           | Major findings                                                                                                                                                                                                                                                       |
|----------------|-----------|-----------------------------|----------------------------------------------------|------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i> | Human     | Plasma                      | ExoQuick kit                                       | [127]      | ELISA, western blot                                           | PD-EV prion protein concentration was increased.                                                                                                                                                                                                                     |
| <i>In vivo</i> | Human     | Plasma                      | Centrifugation and size exclusion chromatography   | [154]      | 2D differential gel electrophoresis                           | CLU, C1R and APOA1 were decreased in PD-EVs.                                                                                                                                                                                                                         |
| <i>In vivo</i> | Human     | Urine                       | Centrifugation                                     | [155]      | Mass spectrometry and quantitative immunoblots                | Calbindin and SNAP23 were increased in PD-EVs.                                                                                                                                                                                                                       |
| <i>In vivo</i> | Human     | Urine                       | Centrifugation and filtration                      | [156]      | Western blot                                                  | DJ-1 levels were increased in PD-EVs and increased in an age-dependent manner in male PD patients.                                                                                                                                                                   |
| <i>In vivo</i> | Human     | Urine and CSF               | Centrifugation                                     | [135]      | Mass spectroscopy                                             | Urinary pS1292- LRRK2 levels were increased in PD-EVs of male patients carrying a LRRK2 mutation.                                                                                                                                                                    |
| <i>In vivo</i> | Human     | CSF                         | Nanoparticle tracking analysis                     | [118]      | Next-generation small-RNA sequencing                          | Signature of increased miR-126-5p and decreased miR-99a-5p and miR-501-3p in EVs can differentiate PD from control samples.                                                                                                                                          |
| <i>In vivo</i> | Human     | Plasma-derived erythrocytes | Centrifugation and filtration                      | [157]      | NanoLC/MSMS                                                   | AIDA, ABHD14B, NADSYN1, QDPR and CNRIP1 were decreased in PD-EVs. AKR1A1, ATP5A1 and USP24 were increased in PD-EVs.                                                                                                                                                 |
| <i>In vivo</i> | Rat       | Midbrain and plasma         | Ultracentrifugation, SEC and ultrafiltration       | [158]      | Next-generation sequencing                                    | miR-103-3p, miR-107-3p, miR-219a-3p and miR-379-5p were increased in PD-EVs.                                                                                                                                                                                         |
| <i>In vivo</i> | Human     | Plasma                      | Centrifugation and ExoEasy Maxi kit                | [130]      | Western Blot                                                  | pro-IL- 1 $\beta$ and TNF- $\alpha$ in were increased in PD-EVs. EVs isolated from PD patients with cognitive deficits also showed higher pro-IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-10, and lower TGF- $\beta$ 1 levels compared to PD without cognitive deficits. |
| <i>In vivo</i> | Human     | Plasma                      | Centrifugation, exoEasy Maxi Kit                   | [131]      | Western blot                                                  | IL-1 $\beta$ and TGF- $\beta$ 1 levels were increased in PD-EVs.                                                                                                                                                                                                     |
| <i>In vivo</i> | Human     | Plasma                      | ExoQuick Kit and L1CAM-based immunoaffinity        | [125]      | ELISA                                                         | Ratio of p-Ser/p- Tyr IRS-1 was higher in PD-EVs.                                                                                                                                                                                                                    |
| <i>In vivo</i> | Human     | Plasma                      | ExoEasy Maxi Kit                                   | [159]      | qPCR                                                          | miR-30c-2-3p was higher and miR-15b-5p, miR-138-5p, miR-338-3p, miR-106b-3p and miR-431- 5p lower in PD-EVs.                                                                                                                                                         |
| <i>In vivo</i> | Human     | Serum                       | Ultracentrifugation                                | [111]      | qPCR                                                          | miR-374a-5p and miR-374b- 5p levels were increased in PD-EVs. Decreased miR-199a-3p levels in PD-EVs distinguished stage II, increased miR-28-5p distinguished stage III and miR-22-5p and miR-151a-5p distinguished stage IV.                                       |
| <i>In vivo</i> | Human     | Plasma                      | Immunoprecipitation                                | [160]      | Western blot                                                  | p-IRS-1 <sup>S312</sup> was increased in PD-EVs.                                                                                                                                                                                                                     |
| <i>In vivo</i> | Human     | Urine                       | Ultracentrifugation                                | [134]      | Western blot                                                  | pS1292-LRRK2 levels were increased in humans with LRRK2 G2019S mutation. Rab8 was higher and pS910-LKKR2 and S935-LRRK2 lower in PD-EVs.                                                                                                                             |
| <i>In vivo</i> | Human     | Urine                       | Chemical affinity, EV trap and ultracentrifugation | [161]      | LC-MS, qPCR, parallel reaction monitoring (PRM), western blot | PRDX3, KLK6, TRIM17, TPT1, VCAM1, LILRB1, PCSK1N, HNRNPA1, LTB4R, PLA2G4A, PRR15, PPFA1, HNF4A, FN1, APP, APOM, STK11, CD9, CD63 and CD81 levels were increased in PD-EVs.                                                                                           |
| <i>In vivo</i> | Human     | Plasma                      | Centrifugation and immunoprecipitation             | [162]      | ELISA                                                         | pS129- $\alpha$ -syn was increased in PD-EVs and NfL decreased in female PD-EVs.                                                                                                                                                                                     |

|                 |            |                                |                                                             |       |                                     |                                                                                                                                                                                                                 |
|-----------------|------------|--------------------------------|-------------------------------------------------------------|-------|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vivo</i>  | Human      | Serum                          | Ultracentrifugation and filtration                          | [132] | Multiplex immunoassay               | CD9, CD63, IL9, FGF21, ATP5A, NUDFS3 and SDHB were decreased in PD-EVs. CRP, TNF- $\alpha$ and MIP-1 $\beta$ were increased in PD-EVs.                                                                          |
| <i>In vivo</i>  | Human      | Plasma                         | SEC and L1CAM-based immunoaffinity                          | [121] | LC-MS                               | ATP5F1A, ATP5F1B, CALM3, CALML5, CYCS, GNAI2, HSPA5, PARK7, PSMA1-3, PSMA5-7, PSMB1, PSMB3, PSMB5-6, RPS27A, SLC25A4, TUBB2A, TUBB4B, TXN were increased in PD-EVs.                                             |
| <i>In vivo</i>  | Human      | Plasma                         | Differential centrifugation and filtration                  | [113] | Next-generation sequencing          | mRNAs for AP003068.23, MAP3K7CL, RSU1, ELOVL7, RGS18, TC2N, HIST1H3H, SDPR, BNIP3L, OST4, and KIF2A were decreased in PD-EVs whereas mRNAs for PSME2 and SELENOH was increased in PD-EVs.                       |
| <i>In vivo</i>  | Human      | CSF                            | Centrifugation                                              | [110] | Taqman miRNA arrays, qPCR           | miR-153, miR-409-3p, miR-10a-5p, and let-7g-3p levels were increased and miR-1 and miR-19b-3p decreased in PD-EVs.                                                                                              |
| <i>In vivo</i>  | Human      | Plasma                         | Centrifugation, ultracentrifugation                         | [163] | Nano-scale flow cytometry           | The ratio of A $\beta$ 1-42 in PD-EVs was increased. Also PD-EVs from patients with dementia had higher A $\beta$ 1-42 ratio compared to non-dementia PD.                                                       |
| <i>In vivo</i>  | Human      | Plasma                         | Ultracentrifugation, density gradient                       | [164] | qPCR                                | miR-34a-5p was increased in PD-EVs.                                                                                                                                                                             |
| <i>In vivo</i>  | Human      | Serum                          | Centrifugation                                              | [165] | Western blot, qPCR                  | miR-3147, miR-4497, miR-1915-3p, miR-3960, miR-1665, miR-4787-5p, miR-2861, miR-4488, miR-4745-5p, miR-4466, miR-1469, miR-3940-5p were decreased in PD-EVs. miR-4485-3p and miR-320c were increased in PD-EVs. |
| <i>In vitro</i> | Mouse      | Cell culture                   | Differential centrifugation and filtration                  | [123] | Next-generation sequencing          | miR-210-5p, miR128-1-5p, miR-505-5p, miR-325-5p, miR-16-5p, miR-1306-5p, miR-669b-5p, miR-125-5p, miR-450b-3p, miR-24-2-5p, miR-61516-3p and miR-1291 were increased in PD-EVs.                                 |
| <i>In vivo</i>  | Drosophila | Whole body                     | Centrifugation and filtration                               | [137] | LC-MS                               | Ref(2)P (Drosophila homologue of mammalian p62) and Rab7 levels were increased and ceramide decreased in PD-EVs.                                                                                                |
| <i>In vivo</i>  | Human      | Plasma                         | Ultracentrifugation                                         | [166] | ELISA                               | AChE was decreased in PD-EVs and correlated with disease severity.                                                                                                                                              |
| <i>In vivo</i>  | Human      | Plasma                         | Ultracentrifugation and filtration                          | [114] | Next-generation sequencing and qPCR | SCMH1_0001 and its target genes ARID1 and C1orf115 were decreased in PD-EVs                                                                                                                                     |
| <i>In vivo</i>  | Human      | Plasma                         | miRCURY exosome serum/plasma kit, centrifugation            | [117] | qPCR                                | miR-128 levels were decreased in PD-EVs.                                                                                                                                                                        |
| <i>In vivo</i>  | Human      | Serum                          | Centrifugation, total exosome isolation reagent             | [119] | qPCR                                | miR-19b was decreased and miR-195 and miR-24 increased in PD-EVs.                                                                                                                                               |
| <i>In vivo</i>  | Rat        | Plasma                         | Differential centrifugation                                 | [120] | Spectrophotometer, qPCR, LC-MS      | miR21, miR155 and miR210 were increased in PD-EVs.                                                                                                                                                              |
| <i>In vitro</i> | Human      | SH-SY5Y cells                  | Centrifugation                                              | [122] | MiRCURY Array, qPCR                 | miR-19a-3p was increased in EVs from SNCA-positive cells.                                                                                                                                                       |
| <i>In vivo</i>  | Human      | Urine                          | Centrifugation                                              | [133] | Immuno-blotting                     | pS-1292 LRRK2 levels were increased in idiopathic PD-EVs.                                                                                                                                                       |
| <i>In vivo</i>  | Human      | Serum                          | Centrifugation, ExoQuick exosome precipitation solution kit | [116] | qPCR                                | miR-21-3p was decreased and miR-22-3p and miR-223-5p were increased in PD-EVs.                                                                                                                                  |
| <i>In vitro</i> | Mouse      | Microglia cell line BV-2 cells | Centrifugation and ultracentrifugation                      | [138] | Western blot, flow cytometry        | Surface expression levels of MHC class II molecules and surface TNF- $\alpha$ was increased in PD-EVs.                                                                                                          |

|                 |       |            |                                                                    |       |                                           |                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------|-------|------------|--------------------------------------------------------------------|-------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>In vitro</i> | Mouse | Astrocytes | Ultracentrifugation and filtration                                 | [167] | Small- RNA sequencing, qPCR               | miR-200a-3p levels were decreased in EVs isolated from MPP <sup>+</sup> -stimulated astrocytes.                                                                                                                                                                                                                                                                                                    |
| <i>In vivo</i>  | Human | Serum      | Centrifugation, ultracentrifugation                                | [129] | Mass spectrometry                         | CLU, C1q, AFM, AGT, ApoD, GSN and PEDF progressively increased in EVs from mild to severe PD. Levels of human neuroblastoma full-length cDNA clone CS0DD006YL02, precursor (AA-19 to 113), C1q, myosin-reactive immuno-globulin kappa chain, Ig kappa chain V-III region, immunoglobulin mu-chain and immunoglobulin kappa variable 1 to 33 progressively decreased in EVs from mild to severe PD. |
| <i>In vivo</i>  | Human | Plasma     | Ultracentrifugation                                                | [115] | Next-generation sequencingqPCR            | lncRNAs MSTRG.24001.1 and MSTRG.169261.1; mRNAs ACRBP, CXCL5, and ENKUR were increased in PD-EVs. lncRNAs MSTRG.336210.1 and lnc-MKRN2-42:1; and mRNAs NME4, CD3D, and ECSCR were decreased in PD-EVs.                                                                                                                                                                                             |
| <i>In vivo</i>  | Human | Plasma     | Commercial kit (UR52136, Umibio)                                   | [168] | MALDI-TOF MS and electron multiplier (EM) | CXCL12 related peptides and CXCL4 protein levels were increased in PD-EVs.                                                                                                                                                                                                                                                                                                                         |
| <i>In vivo</i>  | Human | Plasma     | Magnetic microbeads, centrifugation and L1CAM-based immunoaffinity | [169] | qPCR                                      | Linc-POU3F3 and SNCA levels were increased in PD-EVs.                                                                                                                                                                                                                                                                                                                                              |
| <i>In vivo</i>  | Human | Serum      | ExoQuick Kit and L1CAM-based immunoaffinity                        | [170] | Western blot                              | Oligomeric SNCA levels were increased and STX-1A and VAMP-2 were decreased in PD-EVs.                                                                                                                                                                                                                                                                                                              |

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